PSYCHIATRY UPDATE

Psychopharmacology

Editor : Kamal N Kalita
Co-editor : Angshuman Kalita

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Preface

Kamal N Kalita, Angshuman Kalita

To understand how any external agent including psychotropic works one has to know details of the process of healing. Wayne Jonas' in his book 'How Healing Works: Get well and Stay Healthy using Your Hidden Power to Heal' has described many events that help to have broader view of the process of healing and the science involved in it along with a view how little has been known till date. Modern psychopharmacology can be told to be developed serendipitously in 1950s bringing revolutionary changes in treatment of disorders of the mind. Evolving Psychopharmacology changed the conceptualization of most psychiatric disorders in terms of a) their diagnosis and categorization, b) on models for research in the nature of psychiatric illnesses, c) on psychiatric education, d) on methods and standards for experimental therapeutics, and e) on the organization of modern psychiatry as a clinical and academic medical specialty. Consequently a new generation of more biologically oriented psychiatrists came to dominate psychiatry internationally, and to replace their more psychologically minded colleagues in positions of influence. Initial rapid response to medications made us over optimistic and the shift of care for asylums were seen towards community and general hospitals. Thus the economics of health care was a new unfolded chapter in psychopharmacology.

Some scholars like Dr Gardner[1] and Dr Vazquez [2]are critical of recent trends of a growing international inclination toward increasingly brief and routinized clinical encounters, with an emphasis on rapid but superficial diagnostic categorization and initiation of

almost exclusively medicinal treatments. They advocate even if such clinical practices were adequate they require extensive training, experience, knowledge, and judgment to be used effectively and safely. The argument can be made that heavy reliance on medicinal treatments with less emphasis on psychological approaches, and on symptom checklists rather than on thoughtful understanding of each patient has unfolded a chapter involving fundamental changes in the theory and practice of modern psychiatry. These changes involve a tug of war of what has been labelled brainlessness versus mindlessness in psychiatry.

Recent advancement of technology giving birth to neurosciences, neurogenetics, neuroimaging etc with new drug development technologies are not giving any conclusive view in regards to psychiatric conditions. It is expected as most of such conditions are still considered idiopathic. Some scholars criticize the pharmacocentric neurotransmitter related theories to be too simplistic for psychiatric disorders. Baldessarini in his editorial for Canadian Journal of Psychiatry 2014 August issue has even criticized this to e neuromythology. Again over emphasis on statistically significant results with manipulated research methodology and statistical methods influencing the evidence based mental health having different conflicts of interest is a dark chapter unfolded[3].

Global market for psychotropic was estimated to be 88.3 billion USD in 2015 the rise is steeping in last 10 years. But it is interesting that the market for antipsychotic and antidepressant showed declining trend and raising trend for neurocognitive agents, hypnotics, antiepileptics. Similar was the result in India as published in Acta Medica International 2016 vol 3 (GS Poduri). These findings open a different platform for discussion along with the impact of marketing on patient care.

Thus we see Psychopharmacology has unfolded many chapters in Psychiatry and many are yet to be unfolded. In this edition of 'Psychiatry Update: Psychopharmacology' we have tried to give a glimpse into different arena in this regards. To start with

Brahma described about the different nomenclature system of pharmaceutical products. It has become more important when there is ongoing debate of generics Vs branded medicines. To understand how a psychotropic acts we have to know its pharmacokinetics and dynamics. Aziz etal wrote on its emerging concepts while Kalita enumerated roles of drug monitoring. Bhandari etal and Chakravarty described on ethnic differences in psychopharmacology and the changes in PK across life cycle. The article on treatment modalities of Indian System Medicine by Sarma has added a new flavour in modern psychopharmacology.

People seem to be more concerned about side effects of psychotropics than its effects; Deb has seen it from a different angle. Although behavioural modalities remain main treatment options for child and young people there is a growing trend of prescribing psychoactive agents as reflected in market surveys. Behere etal, Linganna etal and Islam etal described use of pharmacotherapy in this age group with various problems. Use of hormonal drugs is still in infancy in psychiatry and Talukdar describes it with brevity.

Sexual disorders still remains a taboo in our society and we see many quack taking advantages of this stigma and ignorance. Manohar etal and Tripathy etal have looked into the use of different agents in this area. Regarding emerging trends in management of anxiety and bipolar depression have been effectively depicted by Ghosh and Chakraborty etal. Chetia discusses the pharmacogenetic factors influencing antidepressant response and this may become pertinent in future patient care approaches.

Psychiatry and psychopharmacology will never be complete if we do not include schizophrenia. But very few volunteered to contribute an article in this regard. We have mentioned about decreasing trend of sale of antipsychotic globally. Perhaps there is transient lack of affinity in this specific illness among the professionals probably due to inherent complicacies associated with this illness with no significant positive news in its care and research.

Pandey etal, Dutta and Borkotoky etal have lucidly narrated specific areas in this regard.

Substance use disorders are getting more emphasis in current psychiatry and the market presence of medications in this area are getting significant attention along with increasing investment in research. Joseph etal, Dutta, Rahman etal, Shantaram etal, and Mukherjee etal have made the chapter on addiction in this edition of 'Psychiatry Update' interesting.

With the world getting more elderly people across different countries the health problems of elderly are getting significant attention. Probably this increased attention is associated with the good response from contributors in this area. Management of cognitive problems have been enumerated by Avinash, Kishore etal, Kumar. Das wrote about use of Z drugs in insomnia of elderly while anxiety management is discussed by Sharma etal. Agarwal etal described the age old problem of delirium along with its management strategies.

Bordoloi etal described the various regulating agencies for Pharma industry in India in their short writing effectively. Das has put forward his view on the emerging trends on different treatment strategies in which agriculture may have significant role. Finally Gogoi deals with a very controversial subject of Polypharmacy fabulously. Defining rationality in an area which is described irrational by conventional textbooks is a daunting task. But polypharmacy has become rule rather than exception. Judicious use is what needs to be learnt and practised till we get better instrument to deal with mental health conditions.

While planning this book we tried for best representation of contributors from different institutions of Assam and a few from outside. Different chapters were planned to ensure coverage of different spectrum of psychopharmacology. The basic research in this area could not be covered well and we apologize for that. Editing this book has been a nice experience and I am grateful to the contributors. I thank Angshuman for his energetic role and the employees of Bhabani Offset & Imaging Systems Pvt. Ltd. for their support and suggestion.

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An Introduction to Drug Nomenclature with Special Reference to Drugs Used in Psychiatric Disorders

D. K. Brahma

ABSTRACT: *The nomenclature of drugs is a complex process. A drug generally has three different categories of names from its discovery to the arrival in the market: chemical name, non-proprietary name and proprietary name. While the chemical name is given when a new chemical entity (NCE) is developed and it describes the substance chemically, the non-proprietary name of a drug is the accepted name by a competent scientific body/authority. As the name suggests, the proprietary name or brand name is the name assigned by the manufacturer(s) and is the sole property or trademark of the concerned pharmaceutical company developing it. The non-proprietary names of newer drugs are kept uniform by an agreement to use the Recommended International Non-proprietary Name (rINN) in all member countries of the World Health Organization (WHO). The system of the INN of drugs was initiated by the WHO and began operating in 1953. The crux of the non-proprietary naming system is the collection of short name fragments called stems. They define the pharmacologically related group to which the INN belongs. The WHO uses its stem classification system in the INN Programme by following a core list to categorize the main activity of pharmaceutical substances. Each category included in the list has an appropriate code consisting of a capital letter and three digits, category, specific stem and appropriate information.*

Keywords: *chemical name, non-proprietary name, proprietary name, INN system*

INTRODUCTION

The term drug nomenclature implies the systematic and scientific naming of drugs. A drug generally has three different

categories of names: chemical name, non-proprietary name and proprietary name. [1]

A chemical name is given when a new chemical entity (NCE) is developed and it describes the substance chemically, e.g. 7-chloro-1, 3-dihydro-1-methyl-5-phenyl-2H-1, 4-benzodiazepine- 2-one for diazepam. It is the name given to drug in accordance with rules of chemical nomenclature established by International Union of Pure and Applied Chemistry (IUPAC).[2] It is useful for chemists or technical personals as it provides the precise arrangement of atoms and atomic groups in the molecule. It is cumbersome and not used to identify the drug in a clinical (prescribing) or marketing situation. A *code name*, e.g. RO15-1788 (later named *flumazenil)* is the name given by the manufacturer for convenience and simplicity before an approved name.

A non-proprietary name of a drug, after its regulatory approval, is the accepted name by a competent scientific body/authority e.g. *British Approved Name* (BAN), J*apanese Accepted Name* (JAN) and *United States Adopted Name* (USAN) etc. [3, 4,] The non-proprietary names of newer drugs are kept uniform by an agreement to use the Recommended International Non-proprietary Name (rINN) in all member countries of the World Health Organization (WHO). [5]

A proprietary name or brand name is the name assigned by the manufacturer(s) and is the property or trademark of the concerned pharmaceutical farm. Thus a single drug may be sold under different proprietary names by different manufacturers. For example, haloperidol is marketed under the brand names of Bezydol-P, Brain-Rest, Cizoren, Depidol, Gendol and Dolcin etc.

The INN name or more popularly known as **generic name** identifies a pharmaceutical substance by a unique name that is globally recognized to varying extent and is public property. We will be restricting our discussion on the different aspects of INN nomenclature.

INN NOMENCLATURE SYSTEM

The system of INN was initiated by the WHO through the *World Health Assembly resolution*

WHA3.11 and began operating in 1953. [6] The first list of international Non-proprietary Names for pharmaceutical substances was published in the same year. Since then, thousands of pharmaceutical substances have been designated as INNs so far and continuously updated. WHO works in close collaboration with the major national nomenclature commissions e.g. BAN *British Approved name*, JAN *Japanese Accepted Name*, USAN *United States Adopted Name* etc.). An International Non-proprietary Name (INN) identifies a pharmaceutical substance by a unique name that is globally recognized and is public property. INNs help to reduce confusion in drug nomenclature and allow us an understanding of the drug even when that individual drug is not known. They are the vital piece of information that is compulsory on medicine labels. INNs are non-proprietary in nature, which implies that the same INN can be used by all manufacturers of that pharmaceutical substance, irrespective of the brand name under which the drug is marketed by each manufacturer. These names are intended to be used in pharmacopoeias, labelling, advertising, drug regulation and scientific literature. The term *approved name* is used until the drug is included in an official pharmacopoeia. The approved name becomes *official name* after its appearance in the official pharmacopoeia.

The procedure of INN selection

Any person or company proposing and requesting an INN needs to apply to the WHO online at http://www.who.int/medicines/services/inn/en/index.html. Applications are also accepted by WHO made through the national nomenclature committee from the applicants where national nomenclature commissions exist. Members of the WHO expert panel on International Pharmacopoeia and Pharmaceutical Preparations or sometimes other panel examine with a formal procedure and select a non-proprietary, *agreed name* based on the information provided. A four-month window period is kept thereafter for any comments or formal objection to the proposed name by any person. If no objection is raised within that period, this *agreed name* is published

as the *recommended* INN.[7] WHO has strictly recommended in 1993 that pharmaceutical companies should not derive trade names from INNs as such practice may frustrate the rational selection of INNs and compromise the patient safety by confusing the drug nomenclature. In India, the trademark registration of words that are declared as INNs or those that are deceptively similar to INNs is prohibited under Section 13 (b) of the Trade Marks Act, 1999.

INN stems

The root of the non-proprietary naming system is the collection of short name fragments called stems. [8] They define the pharmacologically related group to which the INN belongs. Each stem has a meaning connected to a particular drug class or mode of action. The stems and their definitions have been selected by WHO experts and are used when selecting new international non-proprietary names. The naming process itself "is an evolving type of science and therefore the nomenclature process is ongoing and constantly under revision. Definitions of older stems are modified as and when newer information becomes available. An INN generally includes the "common stem" expressing the pharmacologically-related group to which the substance belongs. Names conveying anatomical, physiological, pathological or therapeutic suggestions are avoided while devising an INN. International connotations are also considered while selecting an INN. A name that sounds perfectly fine in English might have bad or even obscene connotations elsewhere. Therefore, to make pronunciation possible in various languages, the letters "h" and "k" are avoided; "e" is used instead of "ae" and "oe", "i" instead of "y", "t" instead of "th" and "f" instead of "ph". Stems are generally used as suffixes but sometimes they are also used as prefixes.

The classification system used by the INN Programme

The WHO stem classification system used by the INN Programme follows a core list to categorize the main activity of pharmaceutical substances while devising an INN. Each category

included in the list has an appropriate code consisting of a capital letter and three digits, category, specific stem and appropriate information. When INNs for substances belonging to a given category include a specific stem, appropriate information is included in the list.

Table - 1: The WHO classification system of stems (example):

Code	Category	Stem	Specific information
A220	Hypnotic sedatives, other	-clone	hypnotic tranquillizers
C100	Anxiolytic sedatives	-azenil	benzodiazepine receptor antagonists/agonists (benzodiazepine derivatives)
C300	Antidepressants	-oxetine	antidepressants, fluoxetine derivatives
C310	MAO inhibitors	-giline	MAO-inhibitors type B
C320	Tricyclic antidepressants	-pin(e)	tricyclic compounds; *dipine*: see --dipine; -zepine: antidepressant/neuroleptic; C.0.0.0 *-apine*: psychoactive; A.3.1.0 *cilpine*: antiepileptic; -oxepin, -oxopine, -sopine, -tepine
G210	Histamine H1-receptor antagonists	-tadine	histamine-H1 receptor antagonists, tricyclic compounds

Source: The use of stems in the selection of International Non-proprietary Names (INN) for Pharmaceutical Substances Geneva, WHO, 2009.

However, different stems may exist under the same code and category, e.g. Tricyclic antidepressants under the code C320 also contains stems *–pramine* and *-triptyline* for the substances of the imipramine group and antidepressants, dibenzo[a,d]cycloheptane

or cycloheptane derivatives respectively. The following Table.2 contains more information on stems used in INN for the drugs used in psychopharmacology:

Table-2: The WHO stems classification system of drugs commonly used in psychiatric disorders

Code	Category	Stem	Specific information
C000	Psychopharmacologics	-piprazole	psychotropics, phenylpiperazine derivatives (future use is discouraged due to conflict with the stem –prazole)
		-racetam	amide type nootrope agents, piracetam derivatives
		-zotan	5-HT1A receptor agonists/ antagonists acting primarily as neuroprotectors
C100	Anxiolytics sedatives	-azenil	benzodiazepine receptor antagonists/agonists (benzodiazepine derivatives)
		-azepam	diazepam derivatives
		-bamate	tranquillizers, propanediol and pentanediol derivatives
		-carnil	benzodiazepine receptor antagonists/agonists (carboline derivatives)
	antipsychotics	-peridone	see *-perone*: antipsychotics, risperidone derivatives
		-perone	tranquillizers, neuroleptics, 4'-fluoro-4-piperidino-butyrophenone derivatives

	hypnotics/ sedatives	-pidem	hypnotics/sedatives, zolpidem derivatives
		-plon	imidazopyrimidine or pyrazolopyrimidine derivatives, used as anxiolytics, sedatives, hypnotics
		-pride	sulpiride derivatives
		-quinil	benzodiazepine receptor agonists also partial or inverse (quinoline derivatives), see -azenil
		-spirone	anxiolytics, buspirone derivatives

Source: *The use of stems in the selection of International Nonproprietary Names (INN) for Pharmaceutical substances Geneva, WHO, 2009.*

CONCLUSION

Today, due to the existence of this system of naming, it is rare that a national generic name for a new pharmaceutical substance is different from the INN. The non-proprietary names of many older drugs now have been modified to be commensurate with rINN. But, it is difficult to do away with some of the well establish old names e.g. lignocaine and lidocaine. The pharmaceutical industry is a rapidly growing one as the number of drug substances being registered is constantly increasing. It requires a vibrant and strong nomenclature system to ensure the identification of each pharmaceutical compound by a unique, universally available and accepted name. The international nomenclature system for pharmaceutical products is crucial for the clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists worldwide. However, challenges do exist till today in the global implementation of the resolution in relation to INNs. For India, Section 13 (B) of

the Trade Mark Act, 1999 prohibits the registration of names of chemical elements or INNn which have been declared by the WHO and notified by the Registrar of Trade Marks. Nevertheless, there were reported incidents of marketing of drugs under the names that are similar to INNs.

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Emerging Concepts in Pharmacokinetics and Pharmacodynamics

Sahid Aziz, Meghali Chaliha, Angelene Brahma

ABSTRACT: *Understanding pharmacokinetic and pharmacodynamic principles is the key to drug development, clinical pharmacology and safe therapeutics. As the importance of patient safety and development of more efficient drugs is growing day by day, scientists from all over the world are trying to explore more advanced and relatively newer entities related to different fields of medical science. Some of the widely explored fields to understand the nuances of drug safety, variation in drug responses in relation to time, demographic or environmental factors are pharmacogenetics, pharmacogenomics, chronopharmacology and chronopharmacokinetics, single cell pharmacokinetics, population pharmacokinetics etc. A proper understanding of these concepts helps in better and efficient drug designing, application of pharmacokinetics and pharmacodynamics principles in therapeutics, designing better treatment protocol and minimisation of the emergence of adverse drug reactions. Hence they contribute to patient safety, improved therapeutic results and better compliance with therapies. This article tries to give a brief idea about these newer fields to the clinicians who are always directly related to patient care and safety.*

Keywords: *Pharmacokinetics, Pharmacodynamics, patient care.*

INTRODUCTION

Pharmacokinetics (PK) is the study of drug absorption, distribution, metabolism and excretion. Pharmacodynamics (PD) is the study of the mechanism of drug action. PK and PD studies are carried out to understand the process of disposition of drugs in humans and the molecular basis of drug actions and their

adverse effects.[1] A proper understanding and application of the pharmacokinetic principles help in achieving the desired therapeutic goal as well as minimizes the emergence of any possible adverse drug reactions (ADRs) and similarly knowledge of pharmacodynamic principles helps in ensuring rational drug use and also designing novel therapeutic agents.[2,3] But certain factors such as demographic features, pathophysiological factors and therapeutical features such as body weight, metabolic and excretory functions and genetic makeup can regularly alter the dose-concentration relationship and eventually the therapeutic outcome.[4] Several new concepts are evolving in recent times for better drug designing, formulating therapeutic protocols and tailoring of personalized treatment. Some of such recent concepts are:

1. Pharmacogenetics.
2. Pharmacogenomics.
3. Chronopharmacokinetics.
4. Population Pharmacokinetics.
5. Single cell Pharmacokinetics.

Pharmacogenetics [5-7]

It is the study of genetic variations in drug responses. Differences or variations in drug response among individuals are known to exist since the early ages but understanding the causes of such variations was always difficult. Varieties of complex factors cause such variations, some of which involve fundamental aspects of human biology. Genetic variation in humans was recognized as an important determinant of individual variability of drug response from clinical observations in the late 1950s. Genetic variations may affect PK of drugs and their PD responses. Pharmacokinetic variations may be at the level of absorption, distribution, metabolism and excretion of drugs due to different genetic polymorphisms; and pharmacodynamic variations are due to variations in drug response proteins, channels or transporters. Table 1 shows some of the pharmacogenetic variations of either type.

Table 1: Pharmacogenetic variations

<table>
<tr><th>Pharmacokinetic variations</th><th>Pharmacodynamic variations</th></tr>
<tr><td>Oxidation:
● CYP2D6: Sparteine/ debrisoquine oxidation polymorphism.
● CYP2C9: Genetic polymorphism.</td><td>Red cell enzyme defects:
● G6PD deficiency
● Glutathione reductase deficiency.
● Methaemoglobin reductase deficiency.</td></tr>
<tr><td rowspan="2">Acetylation
● Fast acetylators
● Slow acetylators</td><td>Malignant hyperthermia</td></tr>
<tr><td>Insulin resistance</td></tr>
<tr><td rowspan="2">Typical and atypical pseudocholinesterase enzyme for
hydrolysis of succinylcholine.</td><td>Resistance to drug effects:
● Vitamin D resistant rickets.
● Coumarin resistance.</td></tr>
</table>

Potential benefits of pharmacogenetic studies are:

- Understanding the basis of variations of drug responses among individuals.
- Development of drugs that maximize therapeutic effects.
- Reduces the likelihood of emergence of potential adverse drug reactions (ADRs)
- More accurate method of determining drug doses.

Pharmacogenomics: [5, 6]

With increasing knowledge of pharmacogenetic variations as a cause of variation in drug responses and the knowledge of human genome had led to the emergence of a new pharmacological entity- Pharmacogenomics. It is tailoring of drug therapy on the basis of an individual's genome. It marks the use of the genome of an individual so as to choose a particular drug therapy for the

responder only. It is different from pharmacogenetics in its initial approach. Pharmacogenetics starts with unexpected drug response and look for a genetic cause. Whereas pharmacogenomics starts by looking for genetic differences within a population that explains the certain observed response to a drug. Benefits of pharmacogenomics are similar to those of pharmacogenetics.

One example of translation of pharmacogenomics into clinical therapeutics is warfarin anticoagulation as a model of individualized therapy. Warfarin is known for a narrow therapeutic index and large individual variations in clinical response and ADRs. Genetic polymorphisms of different enzymes involved in warfarin drug action and pharmacokinetics have been shown to be important in determining individual variability in warfarin therapy. The standard dose of warfarin therapy is 4-6mg/day but may vary from 0.5-30mg/day from patient to patient. The goal of warfarin therapy is to attain optimum therapeutic response without any bleeding risk by adjusting the dose of warfarin according to the need of the particular patient. This dose adjustment is done by measuring prothrombin time of the patient and maintaining the International Normalized Ratio or INR between 2-3. [6]

With all the benefits and future promise of personalized medicine, pharmacogenomics has got certain limitations too. Genomic study of individuals is very difficult, costly and time-consuming. Also, interactions with other drugs and environmental factors are to be determined before any conclusion is made about the genomic influence on how the drug is working. Personalized medicine has got ethical issues involved too as it is likely to be very expensive and may adversely impact on equity and access to drugs.[5]

Chronopharmacokinetics

Chronopharmacology is the branch of science concerned with the effects of drugs upon the timing of biological events and rhythms and vice versa.[8, 9] Chronopharmacokinetics investigates the variation in drug plasma levels as a function of time of day and the mechanisms responsible for time-dependent variations

[10]. It deals with temporal changes in the absorption, distribution, metabolism and excretion and thus takes into account, the influence of time of administration on these different steps. Some of the examples of diseases showing dependence on biological rhythm are: [8]

- Onset of a migraine headache is most frequent in the morning time.
- Symptoms of rheumatoid arthritis are worst during morning time.
- Symptoms of congestive cardiac failure are worse nocturnally.
- Onset and acute exacerbation of peptic ulcer disease is most likely in the late evening and early morning; etc.

Chronopharmacokinetics in the Medical Application

Morning daily dose or alternate day dosing strategy for corticosteroids introduced during the 1960s was the first chronotherapy to be incorporated into clinical practice. Programmed in-time infusion of anti-tumour medications according to biological rhythms has shown in minimization of toxicity and enhanced dose-intensity in cancer treatment. [8]

Calcium channel blockers like nifedipine when administered during evening provide better bioavailability than morning time administration.[10] Propranolol is absorbed more rapidly after morning dosing than after night time dosing in younger hypertensive subjects.[11]

Fuchs et al showed in their study the importance of chronopharmacokinetics of theophylline in the treatment of asthma. They designed liquid sustained release formulation of theophylline and reported that maximum serum levels of drug coincided perfectly with the critical morning dip at 2-4 am. [12] Thus this chrono-tailored therapy takes into account the pathophysiology of chronic asthma.

Population Pharmacokinetics

Population pharmacokinetics can be defined as "a study of

the basic features of drug disposition in a population, accounting for the influence of diverse pathophysiological factors on the pharmacokinetics and explicitly estimating the magnitude of interindividual and intraindividual variability." The aim of population pharmacokinetics is the quantitative assessment of PK parameters; and between individual and residual variability in drug absorption, distribution, metabolism and excretion. [4]

Factors responsible for PK variability in population: [13, 14]

- Demographic factors: Gender, body weight and surface area, age, race etc.
- Environmental factors: Smoking, diet, pollution exposure.
- Pharmacogenetic variations.

Unlike normal individual PK and PD studies, population pharmacokinetic studies are complex in nature. [15] Different types of population pharmacokinetic studies are single sampling design, multiple sampling designs and full pharmacokinetic sampling design. Population pharmacokinetic analysis helps in estimating variability in drug response and also helps to identify the exact source of this variability. This variability is termed as fixed effect such as population average values or random effect. Later this information of fixed and random parameters can be used for developing dosing guidelines and for revising dosing regimens in a specific patient population. [4]

Advantages of population pharmacokinetics are sparse sampling strategy, special populations, a large number of patients, unbalanced study design, and target patient population. Different disadvantages are quality control of data, the timing of analytical results and data analyses, complex methodology, resource allocation, and unclear cost/benefit ratio. [4]

Single Cell Pharmacokinetics

New drug development is a hugely costly affair financially and an average of 13 years of time is required per drug to develop from identification of a hit compound to successful marketing. Despite this huge investment, a large number of potential drug candidates

fail at different levels of the drug development process leading to loss of time and money.[16] One major factor is that, traditional PK/PD studies and compartmental analyses do not consider the heterogeneity of tissue and cellular level.[17] Being the functional unit of life, a cell is self-sufficient to maintain its own physiology.[18] In human settings, PK can be spatially distinct and the cells exhibit heterogeneous phenotype. Therefore newer technologies, especially in vivo techniques, are required to develop to measure cellular pharmacology. Fluorescent drugs or drug analogues can be used to exhibit the heterogeneity of drug presence at tissue, cellular or sub-cellular levels. Use of fluorescent microscopy and PET scan can be used for single cell pharmacokinetics measurement, single cell drug-target engagement measurements and single cell downstream pharmacodynamic measurements.

Integration of conventional and traditional PK/PD studies with measurement of single cell pharmacokinetics and downstream pharmacodynamics help in understanding the rate-limiting barriers to drug efficiency in vivo. [17]

CONCLUSION

Recent and advanced concepts in understanding the PK and PD principles from the level of a single cell to the population can overcome many challenges encountered in the process of new drug development, can lead to the development of more efficacious drugs and better safety related to patient care. The knowledge of PK and PD principles may help for better clinical and functional outcome of the patient.

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Pharmacokinetics across Life Cycle

Pinaki Chakravarty

ABSTRACT: *The movement of a drug within the body is affected with the advancement of age. The increasing age needs adjustment in the requirement of medicines. Dose adjustments with most of the drugs according to the liver and kidney functions need to be considered. Age invites many diseases and polypharmacy itself have many interactions. Adverse drug reactions are common when many drugs are being used concomitantly and restrict the use of drugs in elderly. The knowledge of Pharmacokinetics with the advancement of age may help to use medicines optimally. The geriatric population is increasing worldwide with an increase in life expectancy. Ethical issues may not permit the different clinical trials on drug acting in the elderly. The Pharmacovigilance reporting may help in generating signals of any severe drug reaction in the old. The safety of the drug is a primary concern and if the drug fails to benefit the recipient then by definition it ceases to be called a drug.*

Keywords:*Pharmacokinetics, Age, Drugs.*

INTRODUCTION

Pharmacokinetics is the movement of the drug within the body. Drugs after administration undergo absorption, distribution, metabolized and excreted. During this journey, body tries to flush away the drug. What body does to the drug is precisely called Pharmacokinetics. For obtaining any effect of the drug, it is essential that the drug is absorbed in an adequate amount to reach the threshold concentration. The steady state has to be maintained by adequate dose in an optimum interval using a route through

which drug is administered in a convenient way. The drug after absorption, have to be distributed sufficiently to reach its site of action. Mere reaching the target may not suffice. The concentration of the drug has to be enough to elicit a desired response for a time to benefit the recipient. The drug administered orally has to cross many obstacles before it reaches the site of action. In the process maximum amount is destroyed on the way, which is not the case if a drug is injected IV. The drug being a foreign substance cannot stay within the body. Body subsequently shall metabolize the drug so that it is excreted by a suitable route after a particular time. The liver[1] plays an important role in drug metabolism. Kidneys are essential to flush out the unwanted products out of the body. A little amount comes out in breast milk which may affect the infant suckling the milk. So while prescribing a normal dose of any drug prerequisite to assess the hepatic and renal functions. Dose reductions and adjustments have to be made if there is any problem with the normal physiological system. Ultimately, the drug gets eliminated after a certain time if no further dose is repeated. Plasma half-life determines the time of stay of a drug within the body. Longer the plasma half-life of a drug the longer it stays within the body. The chance of toxicity is more if drug remains inside the body for a prolong period of time. Knowledge of pharmacokinetics is thus essential to prescribe any medicine to a patient by the physician.

Factors Affecting Pharmacokinetics

Pharmacokinetics is modified by many factors. Physiological, pathological and pharmaceutical factors are notably important. The age is a determinant of drug movement in the body[2,]. Infants may metabolize drugs inadequately as the enzymes are not sufficiently present. As age advances the body synthesizes most of the enzymes and coenzymes required to be used in various biotransformation reactions. The ultimate goal is to make the most of the end products water soluble so that it goes out from the body with urine. The absorption of a drug is dependent on the movement of gastric muscles. The peristaltic movement if fast like in diarrhoea may

decrease the absorption due to decreased transit time. The drug has to remain in the GIT for sufficient time to get entry into the system if given orally. Liver being the vital organ to metabolize numerous drugs contains many enzymes. Hepatic injury and abnormal liver function will increase the risk of drug toxicity. While prescriptions are dispensed it is considered that the liver is functioning in its optimum.

Advancing age is characterized by impairment in the function many regulatory processes that provides functional intermigration between cell and organs, therefore, there may be a failure to maintain homeostasis under condition physiological stress[12]. Thereduced homeostatic ability effects different regularity in different subject thus explaining at list partly the increase inter-individual variability occurring as people get older[13]. Important Pharmacokinetic and Pharmacodynamic changeoccur with advancing age[14]. Thepharmacokinetic changes include a reduction in renal and hepatic clearance and increase in the volume of distribution of lipid solution able drug whereas pharmacodynamic changes involve altered sensitivity to several classes of drugssuch as anticoagulants, cardiovascular, psychotropic drug.This review focuses on the main age-related physiological changes affecting different organ systems and their implications for pharmacokinetics and pharmacodynamics of drugsAdvancing age is characterized by impairment in the function of the many regulatory processes that provide functional integration between cells and organs. Therefore, there may be a failure to maintain homeostasis under conditions of physiological stress. The reduced homeostatic ability affects different regulatory systems in different subjects, thus explaining at least partly the increased interindividual variability occurring as people get older. Important pharmacokinetic and pharmacodynamic changes occur with advancing age. Pharmacokinetic changes include a reduction in renal and hepatic clearance and an increase in volume of distribution of lipid soluble drugs (hence prolongation of elimination half-life) whereas pharmacodynamic changes involve altered (usually increased) sensitivity to several classes of

drugs such as anticoagulants, cardiovascular and psychotropic drugs. This review focuses on the main age-related physiological changes affecting different organ systems and their implications for pharmacokinetics and pharmacodynamics of drugs..

Ageing is the progressive accumulation of more or lessrandom changes[33]. This limits the average life expectancy to about 85 years, maximum lifespan to around 122 years, and lowers the ability to cope with external stresses[22]. Moreover, the inter-individual variability in the physiological responses increases with age. Ageing is not a single entity but a collective term representing the sum of cumulative local effects at the molecular, cellular and tissue level. Ageing is the effect of these underlying changes and not the cause. Although an all-encompassing definition of ageing is not possible, several characteristics are recognized. The most consistent is the time-related loss of functional units. These units are the smallest structures still capable of performing the specific physiological activities characteristic of the organ of which they are a part (e.g. nephrons, alveoli or neurons). A further characteristic is the disruption of some of the regulatory processes that provide functional integration between cells and organs. Consequently, there is a failure to maintain homeostasis under conditions of physiological stress. This loss of functional reserve is associated with a decrease in viability and an increase in vulnerability. Ageing is not solely a progression of functional decline but produces anatomical and physiological changes which might lead to decompensation of the relevant system when they progress beyond a threshold. Some important age-related physiological changes are discussed. This is followed by a detailed description of the age-related changes in pharmacokinetics and pharmacodynamics.

Cardiac Structure and Function

Ageing produces major cardiovascular changes, including reduced elasticity and compliance of the aorta and great arteries[6, 8]. This results in a higher systolic arterial pressure, increased impedance to left ventricular ejection, and subsequent left

ventricular hypertrophy and interstitial fibrosis[60]. A decrease in the rate of myocardial relaxation also occurs. The left ventricle becomes stiffer and takes longer to relax and fill in diastole, thus increasing the importance of a properly timed atrial contraction in contributing to a normal left ventricular end-diastolic volume. The isotonic contraction is prolonged and velocity of shortening reduced.

Ageing is associated with a reduction in the intrinsic heart rate and increased Sino-atrial node conduction time. The response to postural changes differs between young and elderly subjects as cardiac output is maintained by increasing the heart rate in the young whereas elderly subjects rely on an increase in stroke volume to compensate. During exercise, the tachycardiac response is reduced. In some subjects, cardiac output is maintained by an increase in stroke volume (relying on the Starling mechanism), in others, no compensation occurs and aerobic capacity is reduced.

Renal System[7, 9, 10]

Renal mass decreases with age. This reflects the reduction in nephrons. Intra-renal vascular changes also occur, consisting of hyalinization of the vascular tuft leading to reduced blood flow in the afferent arterioles in the cortex. No changes in the medullary vasculature are reported with ageing. Both renal plasma flow and glomerular filtration rate decline with age[35]. The decline is not uniform or consistent; however, despite the decline in glomerular filtration rate, there is no concomitant increase in plasma creatinine because of age-related loss of muscle mass. Therefore, creatinine is not a reliable indicator of glomerular filtration rate in the elderly subject. Other markers such as serum cystatin C do not provide significant advantages over creatinine for the measurement of creatinine clearance.

Acid-base balance is maintained under physiological conditions but a reduced response to stress is revealed by the inability to deal with acid loads, which may be due to defective renal tubular secretion

of ammonium ions. The ability to concentrate the urine during water deprivation is reduced. This is probably due to the inability of the declining number of nephrons to deal with an increased solute load or to the increased perfusion of the juxtamedullary glomeruli producing medullary washout. The response to water loading is also impaired but the mechanisms responsible are unclear. Basal vasopressin secretion is probably normal in elderly subjects. However, both normal and reduced responses to water deprivation have been described. Although the ability to conserve salt is maintained, there is a delay in balancing losses. Changes in salt and water regulation also interact with age-related change in thirst mechanisms. Reduced thirst has been reported in elderly subjects during water deprivation, despite considerable rises in plasma osmolality. Possible mechanisms include a reduced sensation of mouth dryness and increased activity of the renin-angiotensin-aldosterone axis.

Gastrointestinal System[4, 5]

Stomach and duodenum

The main changes involve the secretion of hydrochloric acid and pepsin, which are decreased under basal conditions [11, 24]. This may be the direct consequence of changes in the enzyme- secreting cells and organs or hormonal and neural regulatory alterations. By contrast, gastric emptying in elderly subjects is similar to that of young subjects.

Small intestine

Advancing age is accompanied by reduced absorption[41, 45, 51] of several substances (e.g. sugar, calcium, iron) while digestion and motility remain relatively unchanged.

Colon

The studies investigating the relationship between age and colonic motility have shown conflicting results. In one study, elderly subjects had a slower colonic transit time of radio-labelled plastic particles than young subjects. No significant age-related changes in

colonic transit time have been observed in a recent study comparing young and middle-aged subjects.

Pancreas

Some uncertainty exists regarding the effects of advancing age upon pancreatic secretion. Of the major enzymes, some (amylase) [56] remain constant whereas others (lipase, trypsin) decrease dramatically. Secretin-stimulated pancreatic juice and bicarbonate concentrations remain unchanged.

Liver

Advancing age is associated with a progressive reduction in liver volume and liver blood flow[15, 28]. Alteration of hepatic structure and enzymatic functions with ageing is moderate. In the healthy elderly person, routine tests of the liver function involving the metabolism and elimination of specific dyes, radioisotopes, and protein synthesis do not show significant differences between individuals aged 50–69 and 70–89 years.

Neuroendocrine Responses

Ageing is accompanied by changes in neuroendocrine responses to psychosocial or physical stress[25]. In particular, an altered function of the hypothalamic-pituitary-adrenal (HPA) axis has been observed[30, 62]. Excessive HPA activation and hypersecretion of glucocorticoids can lead to dendritic atrophy[43] in neurons in the hippocampus, resulting in learning and memory impairment. Damage or loss of hippocampal neurons results in impaired feedback inhibition of the HPA axis and glucocorticoid secretion, leading to further damage caused by elevated glucocorticoid concentrations. This positive feedback effect on hippocampal neuronal loss is known as the glucocorticoid cascade hypothesis. Thus, glucocorticoids may sensitize hippocampal neurons to cell death and/or functional impairment, indirect effects that are likely to be age-dependent.

Under conditions of chronic stress, there would be insufficient adjustments in HPA axis activity in response to the challenge of

sustained glucocorticoid levels. This might be caused by impaired feedback regulation of the HPA axis activity.

Body Composition

Significant changes in body composition occur with advancing age[27, 29]. There is a progressive reduction in total body water and lean body mass, resulting in a relative increase in body fat.

Pharmacokinetic Implications

Drug absorption

Although earlier studies reported significant apparently age-related effects including reduced gastric acid secretion and gastric emptying[42] reduced splanchnic blood flow, and absorptive capacity of the small intestine[49], probably due to the effects of disease states, more recent reports have not confirmed these findings in healthy subjects.

Pharmacokinetic studies on the effect of ageing on drug absorption have provided conflicting results. While some studies have not shown significant age-related differences in absorption rates for different drugs, the absorption of vitamin B_{12}, iron and calcium through active transport mechanisms is reduced whereas the absorption of levodopa is increased. The latter is probably secondary to a reduced amount of dopa-decarboxylase in the gastric mucosa. Some of the discrepancies in the results obtained from these studies might be due to different methods of assessing drug absorption.

First-pass metabolism and bioavailability

Ageing is associated with a reduction in the first-pass metabolism. This is probably due to a reduction in liver mass and blood flow. As a result, the bioavailability of drugs undergoing extensive first-pass metabolisms such as propranolol and labetalol can be significantly increased. On the other hand, several ACE inhibitors such as enalapril and perindopril are pro-drugs and need to be activated in the liver. Therefore, their first-pass activation might be slowed or reduced with advancing age.

Drug distribution

As a consequence of the age-related changes in body composition, polar drugs that are mainly water-soluble tend to have smaller volumes of distribution (V) resulting in higher serum levels in older people. Gentamicin, digoxin, ethanol, theophylline, and cimetidine fall into this category. Loading doses of digoxin need to be reduced to accommodate these changes. On the other hand, non-polar compounds tend to be lipid-soluble and so their V increases with age. The main effect of the increased Vis a prolongation of half-life. Increased V and $t_{1/2}$ have been observed for drugs such as diazepam, thiopentone, lignocaine, and chlormethiazole. The reduction in V for water-soluble drugs tends to be balanced by a reduction in renal clearance (CL) with little net effect on $t_{1/2,z}$, as shown in the following equation:

$$t_{1/2,z} = \frac{Ln(2) \cdot V}{CL}$$

Where $t_{1/2,z}$= elimination half-life, Ln(2) = natural log of 2 (0.693), V = apparent volume of distribution, and CL = clearance.

Protein binding

Acidic compounds (diazepam, phenytoin, warfarin, salicylic acid) bind principally to albumin[3] whereas basic drugs (lignocaine, propranolol) bind to $_1$-acid glycoprotein. Although no substantial age-related changes in the concentrations of both these proteins have been observed, albumin[44] is commonly reduced in malnutrition or acute illness whereas $_1$-acid glycoprotein is increased during acute illness. However, the importance of such changes remains to be elucidated as the main factor determining drug effect is the free concentration of the drug. Although plasma protein binding might theoretically contribute to drug interactions or physiological effects for drugs that are highly protein-bound, its clinical relevance is probably limited. The reason for this is related to the fact that the initial and transient effect of protein binding on free plasma concentration is rapidly counterbalanced by its effects on clearance.

Drug clearance

Kidney

Reduction in renal function in elderly subjects[19], particularly glomerular filtration rate[21], affects the clearance of many drugs such as water-soluble antibiotics, diuretics, digoxin, water-soluble -adrenoceptor blockers, lithium, and non-steroidal anti-inflammatory drugs. The clinical importance of such reductions of renal excretion[31] is dependent on the likely toxicity of the drug. Drugs with a narrow therapeutic index like aminoglycoside antibiotics, digoxin, and lithium are likely to have serious adverse effects if they accumulate only marginally more than intended[64]. However, a recent study has questioned the importance of age-related reduction in renal function in affecting pharmacokinetics. Although creatinine clearance was slightly reduced in healthy elderly subjects, excretion of atenolol, hydrochlorothiazide and triamterene was similar to young subjects.

Liver

The drug clearance by the liver depends on the capacity of the liver to extract the drug from the blood passing through the organ and the amount of hepatic blood flow, as illustrated by the following formula:

$$Cl_{liver} = Q\frac{[C_a - C_v]}{[C_a]} = QE$$

Where E = steady-state extraction ratio, Q = liver blood flow (sum of hepatic portal and hepatic arterial blood flow), $[C_a]$ = concentration of drug in portal vein and hepatic artery; $[C_v]$ = concentration of drug leaving the liver in the hepatic vein, and CL_{liver} = clearance by the liver. Therefore, the clearance by the liver depends on both the blood flow and the extraction ratio. The latter is dependent on the metabolizing capacity of the liver.

Drugs can be classified into three groups according to their extraction ratio: high (E > 0.7, such as chlormethiazole, dextropropoxyphene, glyceryl nitrate, lignocaine, pethidine, and

propranolol), intermediate (E 0.3–0.7, such as aspirin, codeine, morphine, and triazolam), and low extraction ratio (E < 0.3, such as carbamazepine, diazepam, phenytoin, theophylline, and warfarin). When E is high, CL [57] is rate-limited by perfusion. When E is low,C_v is similar to C_a and changes in blood flow produce little changes in CL. Therefore, the reduction in liver blood flow with ageing will mainly affect the clearance of drugs with a high extraction ratio.

Several studies have shown significant reductions in the clearance of many drugs metabolized by phase-1 pathways in the liver[32]. The main factor is probably represented by the age-related changes in liver size and hepatic blood[50] flow as the activity of drug metabolizing enzymes is preserved. Studies on human liver tissue showed that mono-oxygenase activities are maintained even in advanced old age[39]. These results have been confirmed by in vivo studies using radiolabelled erythromycin breath tests as probes for CYP3A activity[46, 47]. It is unclear whether enzyme responsiveness changes with ageing in man. Some pharmacokinetic studies have reported that factors such as cigarette smoking do not induce drug metabolism in older people to the same extent as in younger people[59]. Other authors reported similar theophylline clearances in old and young smokers. Conflicting reports also exist regarding the inducing effects of various drugs. The evidence regarding enzyme inhibition in ageing is more consistent, most of the human studies showing enzyme inhibition similar to young subjects. Much less effort has been directed into investigating the effects of ageing on conjugative metabolism. In general, studies reported no major effects of ageing in the pathways of conjugation.

Recently, it has been observed that a reduction in renal function may significantly affect not only renally excreted drugs but also drugs undergoing extensive metabolism in the liver. A decrease in liver cytochrome P450 activity, secondary to reduced gene expression, has been observed in renal failure. Therefore, the age-associated reduction in renal function might potentially affect drug metabolism in the liver. Further research is needed to clarify this issue.

Age-Related Pharmacokinetic Changes in Specific Clinical Situations

Congestive heart failure

Studies investigating possible age-related differences in cardiovascular function in patients with congestive heart failure show a progressive decrease in heart rate and an increase in systemic vascular resistance in older patients[17]. This is associated with increased plasma noradrenaline and serum creatinine concentrations. The therapeutic implications of some pharmacokinetic changes involving the main agents used for the treatment of this condition are discussed.

Digoxin

Digoxin is well absorbed in the gastrointestinal tract[16]. However, the time to peak plasma concentrations is prolonged with advancing age from a mean of 38 h in younger subjects to 69 h in elderly subjects[26, 58]. Therefore, the time to reach steady-state plasma concentrations increases from 7 to 12 days in elderly subjects. The volume of distribution is decreased in elderly patients. As a result, loading doses should be reduced by approximately 20%.

Because digoxin is cleared mainly through the kidneys and digoxin clearance is proportional to creatinine clearance, the systemic clearance of digoxin is reduced with age. As clearance is the main determinant of the maintenance dose, the daily dose of digoxin should be reduced. This should be guided by renal function and body weight.

Diuretics

Several studies investigated the effect of ageing on the pharmacokinetics of furosemide administered intravenously[23]. The volume of distribution was similar in older subjects as compared with younger individuals. This was associated with a reduced renal clearance[54] and a prolonged half-life in elderly subjects. The reduced effects of furosemide with ageing seem to be due mainly to a decrease in tubular secretion. The latter may be caused by a reduction in renal plasma flow[48].

A slight reduction in the renal clearance of thiazide diuretics and triamterene, alone or in combination, has also been observed with advancing age. The latter findings have been disproved by a recent study.

ACE inhibitors

Some of the drugs of this class are active compounds (i.e. lisinopril) but most are pro-drugs undergoing activation in the liver (i.e. enalapril, perindopril). This biotransformation might be impaired in patients with severe heart failure and hepatic congestion. Most of the ACE inhibitors are excreted through the kidney by glomerular filtration and tubular secretion. In the presence of renal impairment their plasma concentration increases. Therefore, the dose needs to be adjusted accordingly, especially when the creatinine clearance is below 30 ml min^{-}. Some of the newer ACE inhibitors, such as benazepril, fosinopril, spirapril, and zofenopril, are also eliminated by the biliary route thus potentially compensating for the reduced renal clearance in elderly subjects.

Pharmacodynamic Implications

Some important pharmacodynamic age-related changes are illustrated in Table 1. Since the effect of age on drug sensitivities varies with the drug studied and the response measured, generalizations are often difficult. Studies of drug sensitivity require measurement of concentrations of drug in plasma as differences in pharmacokinetics with increasing age may increase or decrease differences in response to the drug.

Table 1: Selected pharmacodynamic changes with ageing.

Drug	Pharmacodynamic effect	Age-related change
Adenosine	Heart-rate response	↔
Diazepam[40, 52]	Sedation, postural sway	↑

Drug	Pharmacodynamic effect	Age-related change
Diltiazem	Acute and chronic antihypertensive effect	↑
	Acute PR interval prolongation	↓
Diphenhydramine	Postural sway	↔
Enalapril[18]	ACE inhibition	↔
Furosemide	Peak diuretic response	↓
Heparin	Anticoagulant effect	↔
Isoproterenol	Chronotropic effect	↓
Morphine	Analgesic effect	↑
	Respiratory depression	↔
Phenylephrine	α_1-adrenergic responsiveness	↔
Propranolol[61]	Antagonism of chronotropic effects of isoproterenol	↓
Scopolamine	Cognitive function	↓
Temazepam	Postural sway	↑
Verapamil	Acute antihypertensive effect	↑
Warfarin[63]	Anticoagulant effect	↑

↑ = increase; ↓ = decrease; ↔ = no significant change; ACE = angiotensin-converting enzyme.

Anticoagulants

There is evidence of a greater inhibition of synthesis of vitamin K-dependent clotting factors at similar plasma concentrations of warfarin in elderly compared with young patients. However, the exact mechanisms responsible for the increased sensitivity are unknown. By contrast, the relationship between plasma heparin concentration and anticoagulant effect does not change with increasing age.

Cardiovascular and respiratory drugs

Although elderly subjects are less sensitive to the effects of verapamil on cardiac conduction, the effect on blood pressure and heart rate tends to be greater in older than in younger patients. This might be explained by an increased sensitivity to the negative inotropic and vasodilator effect of verapamil as well as diminished baroreceptor sensitivity. The acute intravenous administration of diltiazem causes greater prolongation of the PR interval (dromotropic effect) in young than in elderly subjects.

A reduced β-adrenoceptor function is observed with advancing age. Elderly patients are less sensitive to the chronotropic effect of isoprenaline. The impaired response, however, is due primarily to an age-related reduction in the influence of reflex cardiovascular effects on heart rate rather than reduced β-adrenoceptor sensitivity. On the other hand, both salbutamol (β_2-adrenoceptor agonist) and propranolol (β-adrenoceptor antagonist) show reduced responses with age. This is secondary to impaired β-receptor function due to reduced synthesis of cyclic AMP following receptor stimulation. The total number of receptors seems to be maintained but the post-receptor events are changed because of alterations of the intracellular environment. The responsiveness of α-adrenoceptor, on the other hand, is preserved with advancing age.

Psychotropic drugs

Elderly patients are particularly vulnerable to adverse effects from neuroleptics[55], including delirium, extrapyramidal symptoms[36], arrhythmias, and postural hypotension. Advancing age is also associated with increased sensitivity to the central nervous system effects of benzodiazepines[20, 34, 38]. Sedation is induced by diazepam[37] at lower doses and lower plasma concentrations in elderly subjects. Advancing age is also associated with increased sensitivity to the effects of nitrazepam, flurazepam, and loprazolam[53]. The exact mechanisms responsible for the increased sensitivity to benzodiazepines with ageing are unknown, however.

CONCLUSIONS

The ageing process is characterized by structural and functional changes affecting all organ systems and results in reduced homeostatic capacity. Although the function of a particular system may be maintained during resting conditions, the reduction of the functional reserve is responsible for an increased vulnerability to stress. Changes in body composition, hepatic and renal function are responsible for an increase in the volume of distribution of lipid soluble drugs, reduced clearance of lipid soluble and water soluble drugs, respectively. All these changes lead to a prolongation of plasma elimination half-life. Significant pharmacodynamic changes also occurwhich; in general, tend to increase sensitivity to drugs. The reduced functional reserve itself also leads to an increase in sensitivity by impairing homeostatic compensatory mechanisms. A better understanding of the effects of ageing on the clinical pharmacology of therapeutic agents would enhance the quality of prescribing.

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A Brief overview of Ethnopsychopharmacology

Samrat S Bhandari, Sanjiba Dutta

ABSTRACT: *Pharmacogenomics has given a new insight into the heterogeneity of psychotropic response by defining the genetic polymorphism in the drug metabolizing enzymes. These enzymes belonging to the Cytochrome P450 family not only varies between different races and ethnicity but also among within the group individuals. Dietary practices within a culture and the use of Complementary and Alternate medicine also plays a role in the metabolism of various psychiatric medicines. With the advances in the genetic research and the application of these findings in clinical psychiatry has opened the door for the individualized treatment in psychiatry.*

Keywords*: Pharmacogenetics, Race, Genetic polymorphism,Psychotropic*

INTRODUCTION

Modern psychopharmacology has gone beyond the border of a single country or group representing a single race and ethnicity. However, not much inquisition was entrusted until recently on the differences of pharmacokinetics and pharmacodynamics of psychotropic medications on different ethnic populations or groups with different cultural practices. Almost all the psychotropics have been developed in the Western Countries and on mostly "young white males" and the aim usually is to find the "typical effects" which can be generalized and anything out of usual observations has been discarded as "noise". So even though a number of literatures exist showing the differential response, these are not widely disseminated, and our knowledge remains limited [1].

Pharmacogenomic techniques promise to define this heterogeneity of psychotropic response and correct the error[2]. Psychiatric pharmacogenomics helps to find the genetic variability which affects the psychotropic metabolism, differential neurotransmitter sensitivity, possible adverse effects and drug interactions[3]. The insight gained so far points that the pharmacodynamic and pharmacokinetic process is controlled by genetic factors in a significant way. But it is also seen that the expression of most genes is strongly influenced by the environmental factors. Since the genetic attributes are determined by the ancestral lines (ethnicity) and the environmental factors are determined by the lifestyles, social interactions and behavioural patterns (culture), the importance of ethnicity and culture in governing drug response is obvious [4].

Factors determining drug response

Drug metabolizing enzymes

Biotransformation of drugs is controlled by a limited number of enzymes and among them; the most important is those which belongs to the Cytochrome P450 system.Almost all the psychotropics are metabolized by one or more of the following four cytochrome enzymes: CYP2D6, CYP3A4, CYP1A2, and CYP2C19. Genetic polymorphism results in variation in the activities of these enzymes within and between the populations [1]. The variation in CYP2D6 has been found to be extremely variable as it has more than 50 variants and has four level of activity [5]

Ultra-rapid Metabolizer (UM): They have three or more copies of the active CYP2D6 gene and have extremely high CYP2D6 activity.

Extensive Metabolizer (EM): They are the normal subjects with the typical activity of CYP2D6. They have one or two copies of the functional CYP2D6 gene.

Intermediate Metabolizer (IM): They one non-functional allele and one low activity allele.

Poor Metabolizer (PM): They are the subjects with two non-functional alleles and no CYPD26 in their liver.

People who are UM are usually suspected of non-compliance because of poor response and low serum level of the drug unless they are given a higher dose than the usual. 29% of Ethiopian are UM, followed by Arabs (19%), Spaniards (5%), White Americans (1%-5%) and Swedish (1%) [6]. The mutant alleles have been found to be ethnically specific. In approximately 25% of Caucasians, CYP2D6*4 is found which produces defective protein and is rarely seen in other ethnic groups. This mutation has been found to be mainly responsible for the PM which is seen in 5-9% of Caucasians. Instead of CYP2D6*4, high frequencies of CYP2D6*17 and CYP2D6*10 were found in those of African and Asian origin respectively. These two alleles are associated with poor enzyme activities and slow metabolism of their substrates. The PMs require a lower dose of psychotropics to avoid higher plasma concentrations than therapeutically indicated [7].

Another example which shows variation in drug metabolism among different ethnic groups is the polymorphism in CYP2C19. This enzyme is involved in the metabolism of diazepam and tricyclic antidepressants. Studies have shown that up to 20% of East Asians which includes Chinese, Japanese and Koreans are PM whereas only 3-5% of Caucasians are PM [8, 9]. CYP2C19*2 and CYP2C19*3 are the two unique polymorphism that has been established. Of these two,CYP2C19*3 is exclusively found in East Asians. The presence of CYP2C19*3 and a higher rate of CYP2C19*2 make them PM which explains why they are sensitive to diazepam and other substrates of CYP2C19[8, 10].

Dietary factors

Cultural variation in the diet, as well as intake of many substances, practised in a particular group also affects the efficacy of psychotropics either alone or together with genetic polymorphism. In the 70s, a number of studies were conducted with indicates the change in culture determines the drug metabolism. Studies were done on Sudanese and South Asians before and after migration to England. It was seen there was poor metabolism of CYP1A2

substrates before migration. Once they migrated to London and changed their dietary habits, their metabolic profile for CYP1A2 became indistinguishable from the native Westerners[11]. A number of foodstuffs can induce or inhibit the metabolism of the psychiatric medicines and knowledge about the dietary pattern can make us understand why some drugs work for someone but fail to show any response in others. A high protein diet accelerates drug metabolism through increased oxidation and conjugation. Also, the amount of carbohydrate, protein and fat in a diet along with other micronutrients exerts an important effect on the expression of many drug metabolizing enzymes. The enzyme CYP1A2 is induced by Charcoal broiled beef and cruciferous vegetables such as cabbage, cauliflower and kale. On the other hand, grapefruit juice inhibits its activity significantly if the juice also contains naringin, which usually gives a slightly bitter taste to the juice. CYP3A4 is also inhibited by grapefruit and corn [12]. Not many studies have been done on Indian dietary habits and its effect of drug responsiveness, few studies were done on Indian spices containing essential oil have found that the components in the spices like cinnamon, cardamom, black pepper have an inhibitory effect on Cytochrome enzymes involved in various drug metabolism [13]. Tea which is consumed leisurely or served to the guest has been found to have an inhibitory effect. Black tea has more inhibitory effect when compared to the green one on the action of the CYP3A4 enzyme [14].

Complementary or alternative form (CAM) of treatment

CAM with medicinal herbs has been used since ages in Asian Countries like India and China. During the last few decades, there has been a rapid rise of 'herbal' or 'botanical' supplements in the Western countries[15]. Slowly it is gaining attention that this supplement or alternative treatment which has many phytochemicals is affecting the metabolism of prescription drugs [16]. There is emerging evidence which suggests that the phytochemicals in the herbal medicine can modulate not only the enzymatic action of the Cytochrome family but also the drug transporting protein,

P-glycoprotein (P-gp). Example of such herbal medicine includes St. John's Wort which has been used for its antidepressant property and is readily consumed as a supplement. St. John's Wort affects the pharmacokinetics of many drugs by inducing CYP3A4, CYP2C19, CYP2C9, and the drug transporter protein P-gp [17].

Health and religious beliefs

The response to psychotropics may also have to be considered in the cultural context. The perceived response reported by Asians may differ from their Western counterpart. Many of the Asian population perceive adverse effect as an indirect measure of the biological response of the drug and they may not report any response until they develop the adverse effects [18]. Moreover, Asian population express symptoms somatically and their primary contact is a primary care physician rather than a psychiatrist and they are more likely to contact a faith healer resulting a delay in treatment which may again affect the response[19]. Under our observation, it was found that in few ethnic groups, the modality of drug administration is decided by the family after consultation with the religious head who after assessing the horoscope of the patient suggest the route of drug administration. They believe that the good spirit in the patient may get offended if the drug is administered intravenously as it is painful, and this may have a deleterious effect on the patient.

Recent advances

Several genes have been identified which controls the therapeutic targets' response to psychotropics. These include the genes encoding the transporters and receptors of neurotransmitters which mediate the therapeutic and toxic effects. Genes responsible for synthesis and catabolism have also been identified. Most of these genes show polymorphism specific to various ethnicities[1]. The most studied gene in this regard is Serotonin transporter (5HTT). The serotonin transporter is the principal site of action for most of the antidepressant. Its main action is to transport

back the serotonin neurotransmitter from the synaptic cleft to the neurotransmitter pool. Polymorphism in the transcription encoding region of 5HTT may include insertion [long (L) allele] or deletion [short (S) allele] and this region is named as Serotonin Transporter-Linked-Polymorphic Region (5-HTTLPR). The basal activity of L variant is twice of the S variant and so the individual with the former variant has a better response to Selective Serotonin Reuptake Inhibitors [20]. However one study done in the Eastern part of Asia in which the participants included were Malaysian, Chinese and Indian, the S variant was associated with better response contrary to what was found in the Caucasian population and this study has been planned to be done in a large scale [21]. This difference seen may be because of polygenic factors or the reason that it is difficult to find the homozygous L variant among the Asian population and so it is difficult to associate this variant with the response [22].

Calabrò et al 2017 studied Short Nucleotide Polymorphism (SNP) in the genes involved in antipsychotic's action. The participants were Koreans and Italians. They found a trend of antipsychotic response among Koreans with variants withinCholinergic Receptor Nicotinic Alpha 7 Subunit (CHRNA7) and CAMP responsive element binding protein 1 (CREB 1) genes and variant withinPhospholipase A2 group IVA (PLA2G4A) gene in the Italian sample were nominally associated with the antipsychotic response. Though no significant association was seen, they suggested further investigation [23].

Individualized treatment: The future

'Individualized treatment' conveys the hope to search for 'right treatment for the right person at the right time' and it depends on evidence of enough biological difference between patients which rationalizes specific treatment for individuals. It also depends on the biological difference within each illness (bio-signature) to guide treatment selection and development of drugs which is more effective and less toxic. As there is a continuous accumulation of plethora of evidence showing the biological differences among

patients with psychiatric illnesses, individualized treatment in psychiatry does exist [24]. Assays are available to find the CYP450 genetic variants to individualize the treatment for maximum efficacy and less adverse effects. The United States Food and Drug Administration require pharmacogenetic information in product labelling and have developed guidelines on the incorporation of pharmacogenetic research in drug development [25].

CONCLUSION

Racial and ethnic differences are decisive factors in determining the pharmacokinetics and pharmacodynamics of psychotropics among individuals, inter-individual differences within a race or ethnicity are also there. The progress in pharmacogenomics will help in the choice of psychotropics, plan for titration and predicting the adverse effects and will change the concept of 'one size fit for all' to a more customized treatment.

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Drug Monitoring in Psychiatry-Its Future

Bitupan Kalita

ABSTRACT: *A new wave was given to the treatment approach to diseases by the development of drugs. But, this new development also brought with it new problem, i.e. drug-related side effect. This side effect depends upon the different properties of the drug as well as different factors of the recipient of the drug. Neurotransmitters, receptor and metabolizing enzyme are three important system through which a drug act on the body. There has been a great variability in these systems in different people, because of which a drug can show a variable response in the different individual. So, "individualised treatment" is the need of the hour and monitoring of the drug is the way by which we can provide it. It involves the measuring of the drug concentration in the body fluid and its clinical correlation. Use of drug monitoring in Psychiatry is rare; it may be because of lack of sufficient research in this regard. As we are moving towards biological psychiatry, drug monitoring will be our backbone in the individualised treatment approach.*

Keywords: *Individualised treatment, side effect, drug-monitoring.*

INTRODUCTION

The invention of Drug was one of the revolutionary developments in the medical science. Since then it has changed the therapeutic approach to diseases to a great extent. In the 19th century development of laboratory technique and equipment revolutionized the practice of medicine. By definition, a drug is any substance that when absorbed in the body causes temporary physiological changes in the body. This physiological change

depends upon the different properties of the drug as well as different factors of the recipient of the drug. Most of the psychiatric medicine acts on the brain neurotransmitters and receptors. Variation in the neurotransmitter, receptor and the metabolising enzyme leads to a variable response of the same drug to a different individual. A specific group of people, such as elderly people, children and pregnant women are more important in this regard. So, improving the way the medicine is given to a particular individual is much more important than the total dose. Recent guideline suggests for the optimum treatment.

Therapeutic drug monitoring is a useful procedure for the individualised treatment. It involves the measuring of the drug concentration in the body fluid and its clinical correlation. The Principle behind the therapeutic drug monitoring is that there is a specific correlation between plasma drug level of some drug and their clinical effect. It involves definite steps-identifying the indication, collection of the blood sample, laboratory processing, interpretation of the result and optimizing the therapy. So effective drug monitoring requires teamwork especially the clinician, nurse and laboratory team. [1, 8]

Which Drug Needs Monitoring?

Psychotropic drugs vary widely in their properties. There are a few characteristics that warrant for drug level monitoring. [2]

1. **Narrow therapeutic window**: Drug with narrow therapeutic window has a small difference in the concentration of therapeutic effect and toxic effect. So slight variation in the concentration of these drugs will lead to change in the effect of the drug.
2. **Variation in pharmacokinetics properties**: Pharmacokinetic properties of a drug depend on many factors like the variation in the metabolising enzyme, age, gender, pregnancy, concomitant use another drug. Cytochrome P450 enzyme system is the major drug metabolising system. This enzyme system shows genetic polymorphism to a great extent.

3. **Steep drug response curve**: Drug with steep drug response curve binds rapidly with the receptor. So, a small increase in the dose can lead to toxicity.
4. **Relation of plasma concentration and clinical effect**: Therapeutic drug monitoring is useful if there is a definite relation of the plasma concentration of the drug and its clinical effect.

Indication Of Therapeutic Drug Monitoring

The indication of therapeutic drug monitoring varies with patient and the drug. So, each indication does not apply to every drug. Few of the indications are: [3, 6, 13]

1. **Non-response to a drug**: None response or inadequate response could be either due to poor compliance with drug or inadequate treatment. Drug compliance is an important issue with patients having a psychiatric illness. Studies have shown that patient with antipsychotic medicine took an average of 58% of the prescribed dose. By measuring the plasma concentration of the drug we can assess the compliance of the patient. If the standard dose of the drug has been prescribed but the clinical response is not satisfactory, then we can go for drug monitoring to see the compliance.

   Another reason for poor response to a drug may be inadequate treatment. If the compliance is good, still the patient is not responding well then one should look for the dose of the drug. Therapeutic drug monitoring can help in achieving adequate dosing.
2. **Toxicity and suspected drug abuse**: Therapeutic drug monitoring will help to avoid toxicity and also to diagnose toxicity. For a drug with a narrow therapeutic window like Lithium, it will be of benefit to avoid toxicity. In such cases monitoring the drug level in the initiation of the therapy will help to maintain the drug at the required range.

   In some cases drug toxicity can mimic other diseases, so measuring the drug level can help in diagnosis the toxicity.

3. **Drug interaction:** Most of the psychotropic medicine is metabolised by the cytochrome P450 system. When combined medicine are used which either induces or inhibit the cytochrome enzyme system, then pharmacokinetic interaction will occur. Therapeutic drug monitoring will help in guiding the dose of the medicine.
4. **Organ failure**: Failure of the organ in the body can cause improper metabolism and excretion of a drug from the body. So to prevent side effect or toxicity, drug monitoring will be a useful tool.
5. **Individualised therapy**: Recent evidence suggest for optimized therapy. Each individual varies in the response to a drug, which warrants for individualised dosing. Therapeutic drug monitoring is also very much useful in special population like pregnant and breastfeeding women, elderly patient, children and patient with an intellectual disability. During pregnancy the renal clearance and activity of the different cytochrome isoenzyme changes which can lead to change in the drug level in the body. Similarly, in children, the metabolic process is different from an adult. Whereas in a geriatric patient the function of different organs decreases significantly.
6. **Pharmacovigilance programme**: Here the safety of a drug is examined in a natural situation. In case any adverse event drug monitoring will help in the determining the safety of the drug.

Collection of Sample

The timing of sample collection is very important, as the drug level changes with dose interval [6]. Usually, sampling should be done once the drug achieves steady state i.e. after 4-5 half life. This does not imply in case of overdose or when it is done to establish a dose. Drawing the sample just prior to the next dose i.e. 12hr post dose (24 hr in case of once-daily dosing) is the usual practice. In case of a patient treated with depot preparation of antipsychotics, sample should be collected just prior to the next dose.

Methods of Analysis

Different methods [6, 7,9] are available for analysing a sample. The methods should be able to detect a small amount of the drug, should distinguish between similar compounds and should be unaffected by other drugs. The available methods are-

1. Fluorescence spectroscopy: It involves the use of ultraviolet light to excite the electron of a compound to emit light. But in this procedure sample amount need to be large.
2. Thin layer chromatography: This method needs longer time and also the sensitivity is less.
3. High-performance liquid chromatography: It has high specificity and sensitivity.
4. Radioimmunoassay: It is also a highly sensitive technique. But the use of radioactive material limits its usefulness.
5. Enzyme immunoassay: It has the advantage that here the radioactive material is not used.
6. Fluorescence polarization immunoassay: The principle is fluorescence polarization. The molecule is exposed to polarized light, which then gets excited and emits radiation back.

Monitoring Of Psychoactive Drugs

The utility of therapeutic drug monitoring depends on the drug used and the specific indication. As per the revised guideline of 2004 of 65 psychotropic medicines for therapeutic drug monitoring, there is four level of recommendation. [4, 7]

1. Level 1: Strongly recommended

   Evidence: Definite drug concentration and therapeutic range are established. The controlled trial has shown beneficial effects of therapeutic drug monitoring.

   Recommendation: Monitoring is strongly recommended. Example-Lithium

   Clinical consequences: At therapeutic range highest probability of response and remission. At subtherapeutic range response rate similar to placebo in acute treatment and chance of relapse in maintenance therapy. At supratherapeutic range there is a risk of intoxication.

2. Level 2: Recommended
   Evidence: Reported drug concentration at a therapeutically effective dose. Reports on intoxication at a supratherapeutic range.
   Recommendation: Monitoring is recommended for dose titration and for special indication.
   Clinical consequences: Monitoring will increase the response in the non-responder. At subtherapeutic range chance of poor response and at supratherapeutic range risk of intoxication.
3. Level 3: Useful
   Evidence: Reported drug concentrations were calculated from pharmacokinetic studies. Plasma concentrations related to pharmacodynamic effects are not yet available or based on retrospective analysis, single case report or nonsystemic clinical experience.
   Recommendation: Monitoring is useful for special indication.
   Clinical consequences: Clinical improvement may be attained by an increase of dose in case of non-responders.
4. Level 4: Potentially useful
   Evidence: Plasma concentrations do not correlate with clinical effect due to unique pharmacology if the drug, e.g. irreversible blockade of enzyme or dosing can be easily guided by clinical symptoms.
   Recommendation: Monitoring is not recommended for dose titration but can be used for special indication.Clinical consequences: Monitoring should be restricted to a special indication.

As per literature review, therapeutic drug monitoring was "strongly recommended" for 15 of the 128 surveyed drugs, "recommended" for 52 drugs, "useful" for 44 drugs and "potentially useful" for 19 drugs.

Therapeutic drug monitoring is strongly recommended for typical antipsychotics and atypical antipsychotics like clozapine, olanzapine, risperidone [12]. Clozapine shows a strong relation of its concentration and CNS adverse effect, commonly seizure.

Out of the different antidepressant [11], therapeutic drug monitoring is strongly recommended for a tricyclic antidepressant, specially imipramine, desipramine and nortriptyline. Imipramine shows linear dose-response relationships, whereas desipramine and nortriptyline show curvilinear dose-response relationships. For selective serotonin reuptake inhibitor therapeutic concentration has been established and also the therapeutic window is wide, so therapeutic drug monitoring for SSRI is not useful.

Another group of medicine widely used in psychiatry are the mood stabiliser. Out of different mood stabiliser, Lithium has well established therapeutic concentration and also its therapeutic window is narrow, so therapeutic drug monitoring for Lithium is strongly recommended. For Sodium valproate and carbamazepine, monitoring is recommended to avoid toxicity.

Therapeutic drug monitoring is also used for Methadone, which is used for opioid dependence treatment.

Pharmacogenetics-Future of Therapeutic Drug Monitoring

Interindividual variability in drug response occurs as a result of genetic variability in the drug metabolising enzymes, drug receptor and transporter proteins [5, 10]. This genetic polymorphism results from the variable expression of alleles in the gene. Pharamacogenetics test examines the genetic polymorphism of the drug metabolising enzymes, receptor and transporter proteins. Polymorphism can be determined either by phenotyping or genotyping. In phenotyping, the drug is administered and the metabolic capacity of the individual is monitored. Accordingly, the individual is classified as poor, intermediate or extensive metabolizers, whereas in genotyping the DNA of an individual is examined for polymorphism. Genotyping has an advantage in that it can be performed from saliva, buccal swab or hair root and it gives the information prior to the drug is administered in the body. Information of the pharmacogenetic test is lifelong and the result can be utilised for any drugs.

Situation where pharmacogenetic oriented therapeutic drug monitoring is important-

1. If the polymorphism has a major role in the metabolism of the drug.
2. A drug with a narrow therapeutic index.
3. Drug those are converted to an active metabolite.

Considering the genetic polymorphism, tricyclic antidepressants are an important candidate for pharmacogenetic oriented therapeutic drug monitoring. It has a narrow therapeutic index and there is large interindividual variability in the drug concentration. This interindividual variability occurs due to polymorphism of the CYP2D6 isoenzyme. Another psychotropic drug that can be a candidate for pharmacogenetic oriented therapeutic drug monitoring is clozapine. It has been seen that there is polymorphism of the serotonin receptor 2A and 2C gene that causes a large interindividual difference in the response to clozapine.

CONCLUSION

Psychiatry has developed to a great extent in the 21st century with remarkable development in biological psychiatry. With the advent of newer medications and changing clinical scenario, the therapeutic drug monitoring will provide more knowledge regarding the patient response to therapy. Use of the therapeutic drug monitoring in psychiatry is still very less, it may be due to the lack of knowledge, confidence as well as lack of sufficient evidence. As we are moving towards individualised therapy, therapeutic drug monitoring especially pharmacogenetic oriented therapeutic drug monitoring will have an important role in the near future.

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Treatment Principles and Options for Mental Health Problems in Ayurveda

Bishnu P Sarma

ABSTRACT: *Ayurveda is an ancient healing science that has offered solutions for various diseases afflicting mankind. With the global rise in mental health disorders and considering the multifactorial origin of such disorders,Ayurveda can offer some solutions to prevent as well as treat mental health issues. Drug treatment, diet and lifestyle changes are an integral part of the Ayurvedic management of diseases as it considers the human body and mind to be deeply connected. Various studies have proved the utility of Ayurvedic treatment specially panchakarma therapy like Shirodhara in the management of mental disorders. The need is to accept and explore the various options that this ancient healing science offers.*

Keywords- *'Ayurveda' 'mental health', 'medicinal plants' ,'panchakarma'*

INTRODUCTION

The National Mental Health Survey of India reported a wide prevalence of mental health problems across the states of India.One of the important findings of the NMHS was the finding that the treatment gap for mental health disorders ranged from 70 to 92 % for different disorders. These findings are important from the point of view of providing care to the mentally diseased persons.[1]As mental disorder are chronic and often require lifelong treatment, the need for accessible, affordable and effective treatment cannot be undermined.

AYURVEDA and MENTAL HEALTH

Unlike the western world, the use of complementary and traditional medicine like Ayurveda is widespread in India. Various controlled studies of traditional and complementary medicine have

shown promising results in the areas of mental health problems like anxiety and depression. [2, 3]Ayurveda is one of the most ancient systems of medicine in the world and its antiquity goes back to the Vedas. This unique science has survived and flourished in the present times. Contemporary Ayurvedic psychiatry consists of two components of – rational Ayurvedic psychiatry dealing with clinical conditions where treatment is based on fundamental principles of Ayurveda and Bhutavidya which also deals with psychiatric problems but treatment is based on paranormal or spiritual factors like the doctrine of karma etc.

According to Ayurveda mental health is a state of sensorial, mental, intellectual and spiritual well-being. Any disorder in the mental health problem is brought forth by an unwholesome interaction between the individual and his environment and they operate through three fundamental factors of Kala (time),buddhi (intellect) and indriyaartha (sensorial inputs).

Thus Ayurveda puts three causative factors in any mental illnesses which are –the genetic factors, the personality makeup and the environmental factors.

In terms of the psychopathology of mental disorders in Ayurveda, Charak has mentioned it in details and pointed out eight essential psychological factors to be centrally affected in all psychiatric disorders. The eight factors include

a. Mana(mood ,emotion)
b. Buddhi(thought and decision)
c. Sajna jnana(orientation)
d. Smriti(memory and learning)
e. Bhakti(desire)
f. Sila(habits)
g. Cesta(psychomotor function)
h. Acara(conduct and behaviour)

PRINCIPLES OF TREATMENT

The management of a psychiatric patient in Ayurveda is done through three broad therapies: a) Daivayaprasraya chikitsa (divine

therapy/ use of spirituality),b) Yuktivyaprasraya chikitsa (biological therapy) and c) Sattavajaya therapy (psychotherapy).

The divine therapy here includes the use of meditation, use of spiritual practices like the repeated chanting of various mantras.

Various studies have reported the benefits of using spiritual practices in mental disorders. Koenig in his article on spirituality and mental health reported that more than 100 quantitative studies had examined the relationship between religion and depression and amongst them 93 were observational studies. Two-thirds of these studies found that there are significantly lower rates of depressive disorders or fewer depressive symptoms amongst the more religious.8 RCT found that religious-based psychological interventions resulted in faster symptom improvements. The author concluded that while spiritual beliefs often represent powerful sources of comfort, hope and meaning, at times they can entangle mental and emotional disorders making it difficult to determine whether they are a resource or liability. [4, 5]

In biological therapy or Yuktivyaprasraya chikitsa,Panchakarma along with palliative treatment with drugs,diets and lifestyle changes are used. The patient is also subjected to bio purificatory treatment like panchakarma in order to cleanse and detoxify the body. This is often followed by samsamana therapy or palliative treatment which is through the help of drugs, diet and lifestyle changes. The drugs used in the treatment are medhya or medhya rasayana, which are believed to act as brain tonics and adaptogens.

Some of the commonly used medhya drugs have been found to be clinically effective in alleviation of symptoms in mental illnesses. For example- Brahmi (Bacoppa monnieri)-Brahmi has shown significant improvement in general mental ability and behavioural pattern including cognitive function (Dubey et al 1994,Agarwal et al 2000) have shown the potentiality to regulate the altered level of brain biogenic amines and improve learning abilities. Increasedacetylcholine synthesis is seen after Brahmi supplementation which has improved memory and learning skills, elevated mood, prevent memory loss in ole people.

Shankapushpi (Convolvulus pluricaulis) –it has shown anti-anxiety, hypotensive, and mental function improving property. Shing et al (1977) have studied the beneficial role of Shankapushpi in the management of anxiety and depressive disorders.

Mandukparni (Centella asiatica) Alkaloids and glycoside compound extracted from the plant and it has shown memory enhancing and tranquillizing property in several experiments and clinical trials.

Ashwagandha (Withania somnifera)- it is widely regarded as the Indian "Ginseng" by the practitioners of Indian system of medicine as it possesses properties similar to Korean Ginseng. Singh and Malviya (1978) and Singh and Tripathi (1982) have demonstrated the psychotropic effect of Ashwagandha and found that it is very effective in treatment of anxiety neurosis. One month of treatment showed symptomatic relief as well as a significant reduction in the level of anxiety, maladjustment, mental fatigue and an immediate improvement in memory span.

Jatamansi (Valeriana jatamansi) Valerian – the active compound of Jatamansi has been shown to improve sleep quality and reduce blood pressure (Chevallier 1996)

Amongst Ayurvedic compound medicines Brahmi Vati,Medhya Vati,Smritisagar ras etc. can be used to treat various mental disorders.

Further Panchakarma therapy can also be used in various mental disorders. Shirodhara is an ancient Ayurvedic healing practice performed in India for over 5,000 years. The word Shirodhara breaks down into two ideas: "Shiro," meaning head, and "dhara," which means flow. Together they form a concept that aims to bring physical and emotional balance by rejuvenating the spirit and preserving health. This is achieved through a relaxing technique in which warmed oil is poured over a client's forehead for an extended period of time. Shirodhara has been traditionally shown to help with fatigue, mental exhaustion, anxiety, insomnia, some mental disorders, headache, excessive thinking, nervousness, and many other conditions.

CONCLUSION

Ayurveda has various treatment modalities that can be used to treat and prevent mental disorders. The availability of distinct forms of therapies including drug and panchakarma means it is more likely that an individual will find to which he or she responds well and can be potential areas for further exploration.

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Psychiatric Side Effects of Non-psychotropics

Kunal Deb

ABSTRACT: *Psychiatric disorders are often accompanied by medical comorbidities which require additional pharmacotherapeutic interventions. Drugs, often de novo, may give rise to psychiatric side effects and at times drug interaction may be the contributory cause. Extreme caution has to be exercised in clinical practice, particularly in extremes of ages so as to prevent the side effects.*

Keyword: *Psychiatric, Side Effects, Non-psychotropics*

INTRODUCTION

Physical illnesses are common co-morbidity in patients with psychiatric illness. The co-morbidity is more common as we move towards the extremes of ages. On the contrary, many a time, patients with other physical illness are treated with medications which itself may produce psychiatric side effects. The clinical presentation of psychiatric side effects may resemble psychiatric syndromes. They can occur at usual doses, in cases of intoxication, or during the days following withdrawal of a given treatment. These side effects are at times potentially dangerous and may pose difficulty in recognizing them in everyday clinical practice. A psychiatric side effect differs from spontaneous psychiatric syndromes in duration since side-effect is more linked to the presence or absence of the drug.

MECHANISM OF PSYCHIATRIC SIDE EFFECTS

Pharmacodynamic mechanism

Medications used in the treatment of physical disorders can modify neurotransmitter systems similar to psychotropic

medications. These modes of action can imply a direct influence on neurotransmitters. They may increase circulating concentrations of cytokines such as IL-1β, IL-6, γ-IFN, positive acute-phase proteins and hyper-activate the hypothalamus-pituitary-adrenal axis. [1]

Pharmacokinetic mechanism

Disease states, hepatic enzyme polymorphisms, and drug interactions are the leading cause of the side effects. Many drugs inhibit one or more pathways of hepatic metabolism particularly the CYP 450 enzyme system. [1]

Risk Factors

Patient-related

History of mental illness, extremes of ages, hepatic or renal insufficiency, increased permeability of blood-brain barrier (as in meningitis), stress(e.g. intensive care unit)

Drug-related

Poly-pharmacy, high dose, route of administration (intravenous), a narrow therapeutic index

COMMON MEDICATIONS CAUSING PSYCHIATRIC SIDE EFFECTS (PSE)

1. Antibiotics

Bhattacharya S et al[2] have demonstrated that antibiotics can cause encephalopathy. Antibiotic-induced encephalopathy can be divided into three different types:

Type 1 is characterized by seizures and myoclonus arising within days after administration of the drug (caused by cephalosporin and penicillin)

Type 2 is characterized by psychosis within days of administration caused by fluoroquinolones, macrolides and procaine penicillin

Type 3 is characterised by cerebellar signs and MRI abnormalities

emerging weeks after initiation of the drug caused mainly by metronidazole.

2. Anti-malarials

Mefloquine[3], which is prescribed for the prophylaxis or treatment of malaria, may cause psychosis, delusion, and even suicidal ideation.

Chloroquine[4] also produces psychiatric side effects like agitation, aggressiveness, amnesia, confusion, depression, hallucinations, and mania. Children are at a greater risk of developing psychosis. The possible mechanisms of the side effects are thought to be NMDA antagonism and action at sigma receptors.

3. Antiretroviral agents

Protease inhibitors (ritonavir, saquinavir, indinavir) are found to cause mood changes and anxiety. The NRTIs (lamivudine, zidovudine, stavudine, didanosine) are reported to cause mood changes, sleep disturbances, vivid dreams and at times psychosis. Among the NNRTIs efavirenz is commonly associated with depersonalization, hallucination, suicidality, catatonia and anti-social behaviour. Fosamprenavir, abacavir, nevirapine, delavirdine and tenofovir are considered relatively to have no PSE.

Although the exact mechanism is not known, however, PSE depends on the CNS penetration of the drug. Hence protease inhibitors which lack greater penetration have relatively lesser PSE. Probable mechanisms of PSE are inhibition of mitochondrial DNA polymerase, the presence of cytochrome P 450 2B6 allele, partial agonism at 5HT2C and 5HT2A and activation of AMPA[5,6].

4. Cardiovascular agents

Calcium channel blockers (verapamil, diltiazem, amlodipine) are found to be associated with akathisia, psychosis and delirium. ACE inhibitors (captopril, enalapril) may result in increased psychomotor activity, hallucination and mania. Diuretics (acetazolamide, chlorthalidone) may increase sedation and anxiety.

Digoxin may cause apathy, depression and delirium. Early reports of a major association between propranolol and depression have recently been revised, with a lower occurrence of depression currently suggested. Ophthalmic preparations of β-blockers such as timolol may also induce PSE.Propranolol and metoprolol which are lipophilic may result in PSE as compared to atenolol which is non-lipophilic[1].

The probable mechanism for PSE may be due to increased lipophilic nature, transport by cerebral protein, effect on electrolytes, acidosis and thiamine deficiency, particularly with loop diuretics.

5. Antiepileptic agents

Of the anti-epileptic agents in use, ethosuximide, clobazam, phenytoin, carbamazepine, phenobarbital, primidone have all been associated withthe development of psychotic symptoms. Vigabatrin causes few cognitive side-effects but can result in transient psychosis. Increased risk has been associated with a right-sided epileptic focus and acute suppression of seizures. Topiramate can induce psychosis. The withdrawal of anti-epileptics may cause prominent psychiatric symptoms, including psychosis. This is well recognised for barbiturates and benzodiazepines. However, withdrawal of phenytoin, carbamazepine and valproate has been implicated in the development of psychiatric symptoms.

Female gender and temporal lobe involvement are commonly implicated in PSE[7].

6. Other agents

Aminophylline and salbutamol may induce agitation, euphoria and delirium. Increased IL6 and BDNF may be associated with PSE.

Corticosteroid treatment may lead to many PSEs. The most frequent PSEs are depression, mania, anxiety, insomnia, delusions (paranoia or other themes), hallucinations, agitation and confusional states which probably is due to glutamate-induced neuronal toxicity, decrease levels of corticotrophin, norepinephrine and decrease in hippocampal volume.

Prednisone is the most Implicated corticosteroid, but PSEs were also described with methylprednisolone, dexamethasone and beclomethasone.

Interferons are also implicated to cause PSE. Interferon alpha induces more PSE than interferon beta. Psychiatric manifestations of IFNs are depression, personality disorders, panic attacks, other anxiety states, manic and psychotic symptom, impulsiveness, aggressive behaviour. Suicidal behaviour is an alleged side effect of IFN alpha.

Depression, psychosis and suicide attempts have been reported in patients treated with isotretinoin. The probable mechanism may be decreased neurogenesis and impaired serotonin signalling.

Cases have been reported of indomethacin causing depersonalization, paranoia particularly due to its indolic molecular structure which looks like serotonin and prostaglandin inhibition[8, 9, 10, 11].

CONCLUSION

Drug-induced PSEs may occur with several medications prescribed in internal medicine and that these side effects might be overlooked. A PSE can be a stressful and traumatic life event for patients and their families. Detecting a PSE avoids its confusion with a sign of a psychiatric disease and since spontaneous psychiatric diseases frequently require long-term treatment, the correct diagnosis of a PSE can spare the patient the stigma, distress, and other costs of an unjustified long-term psychiatric treatment. Correct diagnosis of a PSE also enables the prescriber to communicate suspected side effects to the organization responsible for Pharmacovigilance.

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Psychotropic Drugs in Children and Adolescents

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ABSTRACT: *Over the past decades there has been a humongous rise in the number of psychiatric and neurobehavioral disorders in children and with it increase in the number of children for psychiatric consultation. This, in turn, has increased the use of psychotropic drugs in children and adolescent. However, there lies a significant difference between adult and child psychopharmacology. A number of factors other than age separate the practice of psychopharmacology with children from that with adults. As clinicians, utmost care has to be taken in prescribing psychiatric medication in a child or an adolescent. The increasing drug trials and research going on in the field of childhood psychopharmacology has brought about new guidelines and measures to prescribe drugs. This article mainly deals with the precautions we need to take, the side effect profile and the various other issues pertaining to childhood psychopharmacology.*

Keywords: *Psychotropic Drugs, Child Psychopharmacology, Children, Adolescent.*

INTRODUCTION

Child psychopharmacology is still in its infancy stage in the field of psychiatry[1]. Over the past decades there has been a humongous rise in the number of psychiatric and neurobehavioral disorders in children and with it increase in the number of children for psychiatric consultation [2, 3]. This, in turn, has increased the use of psychotropic drugs in children and adolescent. Although there has been a fourfold rise in the use of medications in children, studies have reported that

many a time there is a tendency of overdiagnosis, poor compliance, poor response, and most importantly higher side effects. Research is still scarce in this area of pharmacology [1, 4, 5]. Many of the drugs used are not yet approved by the FDA and they are used as off-label drugs [5]. However pharmacological treatment has become a potent force in controlling the psychiatric symptoms in children and it is now being increasingly used. There are proven advantages that in a way drugs manage the early onset illness, improves quality of life, reduces burden in caregivers and most importantly decreases or alleviates the probability of future mental illness in a child [6]. Lack of efficacy and side effects are frequently cited as reasons for noncompliance in paediatric psychopharmacology [7]. As clinicians, we must have an insight into potential side effects, the nature and intensity of the patient's illness, and the psychosocial concerns. Utmost care is to be taken when prescribing psychiatric medications to children. Long-term side effects on the maturing and developing children may be potentially harmful.Before prescribing a medicine we should be clear about the diagnosis and be mindful of the target symptoms that are focused on treatment.

Differences of Adult & Childhood Psychopharmacology

There lies a significant difference between adult and child psychopharmacology. Differences arise in both the pharmacokinetic and pharmacodynamic properties.

Phelps et al[8] (2001) laid emphasis on major issues that a clinician should follow while treating a child. There area plethora of factors that should be taken under consideration. These mainly include assessing emotional and behavioural problems that may beappropriate for pharmacotherapy; identifying intervention goals;selecting empirically supported psychological interventions to accompanypharmacotherapy; and assessing therapy, readiness for change in case of side effects, family dynamics, maintenance dose, duration of treatment etc.

A number of factors other than age separate the practice of psychopharmacology with children from that with adults.

Physiological Factors

The rates at which medications are absorbed, distributed in thebody, and metabolized by children differ markedly from adults[9]. When considering additional medications, the practitionermust take care to consider any adverse medication interactionsthat may occur from polypharmacy. A number of physiologic and metabolic processes differ when compared to adults. For example, different metabolic pathways predominate in the biotransformation of drugs. Children and adolescents may require larger doses of psychoactive medication per unit of body weight than adults to attain similar blood levels and therapeutic efficacy.As clinicians,we mustpay attention to these physiological factors.

Psychological Factors

Children may not be able to accurately describe their feeling and symptoms. So for accurate diagnosis and proper prescription doctors must take information from all sources like parents, siblings, caregivers and teachers.

Adherence to Treatment

For proper adherence to treatment, both caregivers and parents should be given adequate psychoeducation about the illness, the importance of medication and the need for continuation of treatment. Education regarding the compliance issues should be imparted amongst parents. Parents, as well as the child, should be made aware of the side effects also. Children and adolescents do not always respond to treatment with psychotropic drugs in a similar way compared to adults. Also what is safe for adults might not be the case in children [10].

Diagnostic process of biological therapy[11]

1. Conduct a comprehensive psychiatric evaluation of the child or adolescent, including information from multiple sources, assessment of the family, and family history of psychiatric and medical disorders.

2. Provide careful diagnostic and psychiatric symptom review with the patient and caregivers.
3. Ensure a physical examination.
4. Stress should be made to rule out predisposition to side effects.
5. The parents and caregivers should be made aware of the treatment side effects. They should be made aware of the precautions they should be following.
6. Collect baseline laboratory and physical assessment data where warranted. Consider baseline rating scales of target symptoms.
7. Determine indicated non-pharmacologic interventions for the diagnosed disorder.
8. Consider the risks and benefits of pharmacotherapy.
9. Consider the risks and benefits of specific medications relevant to the disorder.
10. Conduct a formal consent procedure with the parent and youth. Give handouts on medications, where appropriate.
11. As the golden rule states **start low and go slow**

Principles to be followed

American Academy of Child and Adolescent Psychiatry (AACAP)follows certain principles in the treatment of childhood psychiatric illnesses[12]

1. Before Initiating Pharmacotherapy, aPsychiatric Evaluation is completed.
2. Before Initiating Pharmacotherapy, a medical history is obtained, and a medical Evaluation IsConsidered When Appropriate.
3. The Prescriber is advised to communicate with other professionals involved with the child to obtain a collateral history and set the stage for monitoring outcomes and side effects during the medication trial.
4. The prescriber develops a psychosocial and psychopharmacological treatment plan based on thebest available evidence.

5. The prescriber develops a plan to monitor the patient, short and long-term.
6. Prescribers should be cautious when implementing a treatment plan that cannot be appropriately monitored.
7. The prescriber provides feedback about the diagnosis and educates the patient and family regarding the child's disorder and the treatment and monitoring plan.
8. Complete and document the assent of the child and the consent of the parents before initiating medication treatment and at important points during treatment.
9. The assent and consent discussion focuses on the risks and benefits of the proposed and alternative treatments.
10. Implement medication trials using an adequate dose and for an adequate duration of treatment.
11. The prescriber reassesses the patient if the child does not respond to the initial medication trial as expected.
12. The prescriber needs a clear rationale for using medication combinations.
13. Discontinuing medication in children requires a specific plan.

The AACAP stresses that thisapproach is absolutely necessary for safe, effective and proactivetreatment and should help decrease the stigma fromparticipating in psychiatric care. These recommended practices are implemented in an effort to eliminate demoralization experienced by patients and families receiving substandard treatment, "dropping out" of care or not seeking necessary treatment in the future [12].

Indications and Class of Psychotropic Medication
Bipolar Disorder and Mood Stabilizers

Traditional mood stabilizers (i.e., lithium and antiepileptic) have greater benefits in children and adolescents than adults where study findings support greater benefits (i.e., reduction in mania) with second-generation antipsychotics (SGAs).However, SGAs caused more weight gain and somnolence than mood stabilizers in

youth than adults and SGAs caused greater weight gain in youth than adults. Also, the efficacy of combination therapy of two mood stabilizers compared with one antipsychotic agent at the present time is not known. Currently, the FDA has indicated risperidone, Quetiapine and Aripiprazole for use in children aged 10 or older and olanzapine for children aged 13 and older with bipolar disorder (i.e., mania and mixed mania); approved lithium for adolescents aged 12 and older; olanzapine for adolescents aged 13 and older; and Aripiprazole and lithium as treatments to prevent the recurrence of bipolar symptoms in children and adolescents. There is currently insufficient evidence on the treatment of bipolar depression in children and adolescents[13, 14]. Few studies have documented the use of lithium in bipolar disorders in paediatric populations. Lithium therapy has received widespread clinical use. There are in fact several controlled trials suggesting that lithium can be effective in the management of symptoms associated with bipolar disorder in adolescents [15]. Campbell and colleagues [16] have demonstrated the efficacy of lithium in treating aggressive behaviour and conduct disorder; according to their findings, some children showed marked improvement. Anticonvulsants which were used in seizure have been found to be beneficial in controlling mania and aggression in children [17].

The FDA has given approval for use of this class of drugs in seizures and in mania. Sodium Valproate and Oxcarbazepine has nowadays proven efficacy in controlling symptoms associated with mania or hypomania. Large-scale studies have suggested that Oxcarbazepine has proven efficacy for controlling behavioural problems in autism, intellectual disability, and conduct disorder.

Depression and Antidepressant

The NICE guideline suggests and recommends that psychological intervention should be considered as the first line of management in childhood depression. The antidepressants may be divided into several classes, including the tricyclics, the selective serotonin reuptake inhibitors (SSRIs), monoamine

oxidase inhibitors, and the atypical antidepressants. There has been a growing use of this class of drug to subside the features of depression like low mood, anhedonia, lack of sleep, decreased appetite. Tricyclics have not been found to be quite efficacious. There have been incidences of sudden deaths. So this class of drug have not been proposed for use in childhood depression [18]. Among SSRI,sertraline escitalopram and fluoxetine have been found to be favourable while fluvoxamine has been proposed for use in OCD. Paroxetine is the least preferred drug among the SSRIs[19].Bupropion have been found to reduce symptoms of ADHD [20]. The AACAP indicated that depressedpatients treated with selective serotonin reuptakeinhibitors (SSRIs) have a relatively good response rate.The Treatmentfor Adolescents with Depression Study (TADS) comparedtreatments for moderate to severely depressed youthand found that 70% of those who received fluoxetinecombined with weekly cognitive-behavioural therapy (CBT)had better responses [21]. Another important trial, the Treatmentof Resistant Depression in Adolescent (TORDIA) studydemonstrated that for adolescents with depression who donot respond to an initial SSRI (i.e., fluoxetine, citalopramor paroxetine), a switch to another antidepressant(i.e. another SSRI or the selective serotonin andnorepinephrine reuptake inhibitor [SNRI] venlafaxine)combined with CBT should be considered for a betterclinical response[21].

Attention Deficit / Hyperactivity Disorder and Stimulants

Pharmacotherapy remains the primary treatment. Many studies have reported the effectiveness of stimulants. This class is mostly used to treat ADHD mostly the symptoms of inattention, impulsivity and hyperactivity. There use has been steadily rising [17]. Methylphenidate (Ritalin and others), a commonly used stimulant medication, has been demonstrated to exert significant positive effects on measures of attention and academic efficiency for children with ADHD [22]. They also reduce aggression in children of ADHD [23]. The amphetamines and methylphenidate

are stimulant drugs that remain first-line treatments for ADHD with strong demonstrated efficacy in treating the core symptoms. Dextroamphetamine is approved by FDA for use in 3 years and above, while methylphenidate is used above 6-7 years of age. The non-stimulant SNRI drug, atomoxetine, was approved by the FDA to treat ADHD. It is the first non-stimulant to be approved by FDA for use in ADHD. Currently, the alpha agonist like clonidine is also being increasingly used as a combination to treat symptoms of ADHD.

Schizophrenia and Antipsychotics

The atypical antipsychotics form the bulk of treatment of schizophrenia in children. The atypical antipsychotics have replaced the traditional antipsychotics because of their favourable side effect profile. They have also been found to be favourable in treating the negative symptoms. Open-label trials have reported the effectiveness of aripiprazole, olanzapine, risperidone and quetiapine. The FDA approved several SGA agents for use in children and adolescents (aged 13 – 17) with schizophrenia after a wave of new placebo-controlled clinical trials were conducted and demonstrated efficacy in this population. Haloperidol was once the mainstay of treatment but because of the side effect profile, it has been replaced by SGA. Clozapine has been approved as last resort to treat childhood schizophrenia. Risperidone has been found to be the most efficacious drug in childhood psychosis, the behavioural problem associated with intellectual disability and pervasive developmental delay [24, 25, 26].

Autism

Autistic disorders have been associated with impulsivity, inattention ritualistic behaviour and temper outburst. In 2006 the FDA has approved the use of risperidone for use in the behavioural problems. Risperidone has been found to be the most efficacious drug in childhood psychosis, the behavioural problem associated with mental retardation and pervasive developmental

delay [24, 25, 26]. Other drugs used are olanzapine and Aripiprazole. Oxcarbazepine has been proven to be efficacious in sudden mood swings and aggressive behaviour associated with Autism. As in ADHD,clonidine has also been used in autism for control of aggression and irritability. Repetitive behaviour, rigidity, obsessive-compulsive symptoms are being treated with SSRI like fluoxetine, fluvoxamine, citalopram, escitalopram[27]. Beta blockers and mood stabilizers are also increasingly used to control behavioural problems. Stimulants also are helpful to reduce hyperactivity and inattention in children. Studies have reported improvement in children with autism.

Obsessive Compulsive Disorder

The AACAP Workgroup recommends cognitive-behavioural therapy (CBT) as the first line of treatment for mild to moderatecases of OCD. The AACAP specifies that for youth with moderateto severe OCD, medication is indicated in addition to CBT. At the present time, there are four medicationsthat have FDA approval for use in OCD in children andadolescents: the tricyclic antidepressant, clomipramine,for children aged 10 and over, and the SSRIs: sertraline(6 and older), fluoxetine (7 and older) and fluvoxamine (8and older). Clomipramine was found to be more effective than SSRI. Also, it was found in studies that when clomipramine was combined with CBT it gave a better outcome. However, SSRI is more commonly used because of a favourable side effect profile [28, 29]. Sertraline and fluvoxamine are the most preferred drugs that have been reported in studies.

Generalized Anxiety Disorder (GAD) / Separation Anxiety Disorder (SAD) / Specific Phobia:

Although the non-OCDdisorders (i.e., GAD, SAD, and Specific Phobias) are moreprevalent than OCD in childhood, clinical studies onthe efficacy of treatments are far more limited. SSRI again are the mainstay of treatment. Sertraline and escitalopram have proven to be effective. Clonazepam has been found to be effective

in separation anxiety [30].Combination CBT has also been found to be effective.

Disruptive Behavioural Disorders/Aggression and Conduct disorder

Maladaptive aggression has been defined as nonspecific serious symptoms accompanying many childhood disorders i.e. oppositional defiant disorder (ODD), conductdisorder, ADHD and bipolar disorder. Guidelines indicate antipsychotics arethe most studied class of drugs and have demonstratedthe largest efficacy for disruptive/aggressive conditions, particularly risperidone versus placebo [31].Oxcarbazepine and sodium valproate have been effective in controlling the problematic behaviours. When associated with ADHD studies report stimulants are faster acting. However, the combination of mood stabilizers and antipsychotics remain the best treatment option.

Tourette's disorder

Risperidone is found to be effective. Haloperidol was the first choice however due to side effect profile its use is restricted. Recent studies have found clonidine to be equally effective.

Enuresis

Behavioural modification remains the first line of treatment in most cases. However, in pharmacological treatment desmopressin and imipramine have been found to be effective.

Mental retardation

No specific pharmacological treatment is currently available for mental retardation. Specific behavioural techniques, parental skill training and counselling remain the mainstay of treatment. Comorbid disorders like seizures, behavioural problem, and psychosis are treated with specific medicines described as above.

PSYCHOTROPIC DRUG FOR CHILDREN AND ADOLESCENTS [32]

Combination

DRUG NAME	FDA APPROVAL/ INDICATION	PEDIATRIC DOSE	WARNING
FLUOXETINE & OLANZAPINE IN COMBINATION	18 and older N/A:	Paediatric dosing is currently unavailable or not applicable for this drug.	Usage Black Box Warning for fluoxetine/olanzapine combination formula increased the risk of suicidal thinking and behaviours in children and adolescents Possibly unsafe during lactation.

Antipsychotics

* Precautions which apply to all atypical or second-generation antipsychotics (SGA): Neuroleptic Malignant Syndrome/ Tardive Dyskinesia/ Hyperglycaemia/Diabetes Mellitus/ Weight Gain/ Akathisia/Dyslipidaemia

† Precautions which apply to all typical or first-generation antipsychotics (FGA): Extrapyramidal symptoms/Tardive Dyskinesia

DRUG NAME	**FDA APPROVAL/ INDICATION**	**PEDIATRIC DOSE**	**WARNING**
ARIPIPRAZOLE * (SGA)	10 and older for bipolar disorder, manic, or mixed episodes; 13 to 17 for schizophrenia and bipolar; 6 to 17 for irritability associated with autistic disorder	2-10 mg/kg/day	*Black Box Warning for Aripiprazole:* Not approved fordepression in under age 18. Increased risk of suicidal thinking and behaviour
CHLORPROMAZINE† (FGA)	18 and older	0.25 mg/kg tid	May alter cardiacconduction; sedation; Neuroleptic Malignant Syndrome;weight gain. Use caution with renal disease, seizure disorder
CLOZAPINE* (SGA)	18 and older Children	150-300 mg/day in children Adolescents: 200-600mg/day	Agranulocytosis; seizures; myocarditis; other adverse cardiovascularand respiratory effects. (Note: Clozapine is considered a treatment of last resort in children in whom trials of both FGA and SGA agents have failed

HALO-PERIDOL† (FGA)	3 and older	0.15-0.5 mg/kg/ day	*Other precautions for haloperidol:* May cause seda-tion,orthostatic hypotension, photosensitivity, constipation,dry mouth, prolactin elevation.
OLANZAP-INE* (SGA)	18 and older; ages 13 to 17 as second line treatment for manic or mixed episodes of bipolar disorder and schizophrenia 18 and older	2.5 -5 mg	Diabetes Melli-tus/ Weight Gain/ Akathisia/Dyslipi-daemia
PIMOZIDE † (FGA)	12 and older ≤ 12 yrs	0.2mg/ kg/d > 12 yrs: 1-10 mg/ day	*Other precautions for pimozide:* Dyskinesias, drymouth, consti-pation, prolactin elevation, pro-longed QTcinter-val. Possibly unsafe during lactation. Avoid abrupt Withdrawal

QUETIAPINE* (SGA)	13 and older for schizophrenia; 18 and older for bipolar; 10 to 17 for treatment of manic and mixed episodes of bipolar disorder	100-300 mg	Diabetes Mellitus/ Weight Gain/ Akathisia/Dyslipidaemia
RISPERIDONE* (SGA)	13 and older for schizophrenia; 10 and older for bipolar mania and mixed episodes; 5 to 16 for irritability associated with autism	Usually 1-2mg/ day; other recommended doses: 3mg/ day - children; 6mg/day - adolescents	
THIORIDAZINE† (FGA)	2 and older	3mg/kg/day	*Black Box Warning for thioridazine:* Dose-related-prolongation of QTc interval may cause torsade depointes-type arrhythmias and sudden death. Use restricted to schizophrenia resistant to standard antipsychotic drugs

TRIFLU-OPERA-ZINE† (FGA)	18 and older	0.5-10mg/ day	CNS collapse, CNSdepression, blood dyscrasias, bone marrow depression,hepatic impairment. Safety in lactation is un-known.
ZIPRASI-DONE* (SGA)	18 and older Children:	10mg/ day initial dose, maximum dose not estab-lished; 160mg/ day – adolescents	Black Box Warn-ing for ziprasidone: Not approved fordepression in under age 18. Increased risk of suicidalthinking and behaviour. Other precautions for ziprasidone: Prolonged QTc interval

Antidepressants

DRUG NAME	**FDA AP-PROVAL/ INDICATION**	**PEDIATRIC DOSE**	**WARNING**
AMITRIP-TYLINE (TRICY-CLIC [TCA])	18 and older 9-12 yrs	1-3 mg/ kg/day >12 yrs: 50-100 mg/ day	*Precautions for amitriptyline and other TCAs:* General caution for use in patients < 25 yrs; those with bipolar disorder or comorbid schizophrenia or cardiovascu-lardiagnosis.

			Avoid abrupt withdrawal. Do not take if an MAOI was used within the past 14 days. EEG to be done prior to starting of this drug
BUPROPI-ON	18 and older	1-7 mg/kg/day	Anorexia and risk of seizures
CLOMIP-RAMINE (TCA)	10 and older (for OCD only	Used for OCD >10 yrs: Max: 3 mg/kg/ day up to 100 mg/ day in first 2wk; up to 200 mg/day	
DOXEPIN (TCA)	12 and older	N/A	Unsafe in lacta-tion. Significant adverse effects to infant/breast milk production - contraindicat-ed or requires cessation of-breastfeeding.
ESCITALO-PRAM (SSRI)	18 and older; 12-17 (for major depressive disorder)	12-17 yrs: Max: 20 mg/day Taper dose gradually	*Black Box Warning for escitalopram:* As noted aboveplus notes not to be used in children under 12 years ofage.

FLUOXE-TINE (SSRI)	8 and older; 18 and older (for premenstrual dysphoric disorder)	5-30 mg/day	Black Box Warning for ziprasidone: Not approved fordepression in under age 18. Increased risk of suicidal thinking and behaviour
FLUVOX-AMINE (SSRI)	8 and older (for OCD only)	-Children: 200mg/ day Adolescents: 300mg/day	
IMIPRA-MINE (TCA)	6 and older (for bedwetting)	1-5 mg/kg/ day; 150-250 ng/ mL	
SER-TRALINE (SSRI)	6 and older (for OCD only)	200 mg/day	
PAROXE-TINE (SSRI)	18 and older Children:	Adolescents: 10-20 mg/day	*Note:* FDA changed the classification of paroxetine from category C to D for scientific evidence of positive teratogenic effects. Parox-etine should be avoided in pregnancy if possible

Mood Stabilizing and Anticonvulsant Medications

DRUG NAME	FDA APPROVAL/ INDICATION	PEDIATRIC DOSE	WARNING
CARBAMAZEPINE	any age (for seizures)	10-50 mg/kg/day 8-12 mcg/mL (serum level	*Black Box Warning for carbamazepine:* Stevens-Johnson Syndrome (particularly among Asians), aplastic anaemia, agranulocytosis. *Other warnings/precautions:* neutropenia, hyponatremia, induces the metabolism of itself and some other drugs, decreased the efficacy of oral contraceptives, teratogenicity, MAOI use within 14 days

DIVALPROEX SODIUM (VALPROIC ACID)	2 and older	15-60mg/kg/day 50-100 mcg/mL (serum level)	*Black Box Warning for divalproex sodium:* Hepatoxicity, teratogenicity, pancreatitis. urea cycle disorders, multiorgan hypersensitivity reaction, thrombocytopenia,polycysticovaries.
LAMOTRIGINE	18 and older	0.15-5.0 mg/kg/ day (25-200 mg/ day)	Serious rashesincluding Stevens-Johnson Syndrome and aseptic-meningitis. *Other warnings/precautions:* acute-multi-organ failure, withdrawal seizures, blood dyscrasias, hypersensitivity, suicidal ideation

LITHIUM CARBONATE/ CITRATE	12 and older	300-2,400 mg/day 0.5-1.2 mEq/L (serum level)	Toxicity abovetherapeutic serum levels. *Other warnings/precautions:* Renal function impairment, polyuria, tremor, diarrhoea, nausea, hypothyroid, teratogenic effects. Special risk patients include those with significant renal or cardiovascular disease, severedebilitation, dehydration, sodium depletion.
OXCARBAZEPINE	4 and older	5-30 mg/kg/ day (150-1,200 mg/ day)	*Warnings/precautions for oxcarbazepine:* hyponatremia, suicidal ideation

ADHD Medications

DRUG NAME	FDA APPROVAL/ INDICATION	PEDIATRIC DOSE	WARNING
AMPHETAMINE/ AMPHETAMINE	6 and older (XR	40 mg/day max 30 mg/day max	Abuse potential. Risk of sudden death and serious cardiovascular events. May cause hypertension, psychiatric adverse events and possible growth suppression.
ATOMOXETINE	6 and older	Children: 0.5 mg/ kg/day Adolescents: 40mg/	May cause serious cardiovascular events including sudden death, particularly in those with pre-existing structural cardiac abnormalities or serious heart problems; increase in blood pressure and heart rate; adverse psychiatricevents and liver injury.

DEXMETHYLPHENIDATE/ DEXMETHYLPHENIDATE	6 and older	20 mg/day max 30 mg/day max	
CLONIDINE IMMEDIATE RELEASE (IR)/CLONIDINE EXTENDED RELEASE (ER)	IR- not approved for children ER - 6-17 years old	Up to 0.4 mg/day	
METHYLPHENIDATE/ METHYLPHENIDATE ER AND ER SUSPENSION	6 and older	60 mg/day max	

PSYCHOTROPIC DRUGS—SIDE EFFECTS AND TERATOGENIC RISKS [33]

DRUG NAME	SIDE EFFECT	TERATOGENIC RISK	CATEGORY
ANTIPSYCHOTIC MEDICATIONS	• Akathisia and dystonic reactions are seen in childrentreated with SGAs but risk of tardive dyskinesia are small compared to FGAs. • Weight gain is a significant problem with SGAs. Other side effects: constipation, dry mouth, dizziness. • Sedation/cognitive blunting may occur with FGAs and SGAs Adolescent males at much greater risk for dystonic reactions than adults. • A significant drop in neutrophils and increased risk ofseizures with clozapine (should be used as a treatment of last resort).	FGAs: Rare anomalies, foetal jaundice, foetal anticholinergic effects at birth.	FGA : C

		SGAs: Gestational diabetes, large birth weight.	SGA: BC

DRUG NAME	**SIDE EFFECT**	**TERATOGENIC RISK**	**CATEGORY**
ANTIDEPRESSANT MEDICATIONS	· **TCAs**: slowing of cardiac conduction Cardiaclong QT syndrome may be mechanism be responsiblefor sudden death in children. Other effects: Dry mouth, urinary retention, sedation, constipation, weight gain and hypotension	TCAs: Foetal tachycardia, foetal withdrawal, foetal anticholinergiceffects, urinary retention, bowel obstruction.	D-amitriptyline, Imipramine, Nortriptyline C- (other TCAs)
	MAOIs: Daytime sleepiness, dizziness, light-headedness, lowblood pressure, difficulty urinating, dry mouth, alteredsense of taste, nervousnessand muscle aches, insomnia and weight gain.	MAOIs: Rare foetal malformations: rarelyused in pregnancy due to hypertension	**C**

	SSRI side effects: insomnia, sedation, appetite changes (up or down), nausea, dry mouth, headache, sexual dysfunction, Treatment-emergent akathisia from SSRIs may be more evident in paediatric depression associated with bipolar disorder andgreater suicide risk.	SSRIs: Perinataland cardiovascularcomplications, spontaneousabortions. Potential premature-delivery and neonatalpersistent pulmonary-hypertension (PPHN).	**C** **Paroxetine is D**
	SNRIs: nausea, insomnia, sedation, sexual dysfunction, sweating,hypertension and discontinuation syndrome	Potential-premature delivery. Clinical outcome data sparse compared to SSRIs or TCAs.	**C**
	Bupropion:common side effects: headache, agitation, restless insomnia, weight loss, anorexia, sweating, tremor and hypertension	Bupropion: Risks unknown, but not recommended over SSRIs during pregnancy.	**C**

DRUG NAME	SIDE EFFECT	TERATOGENIC RISK	CATEGORY
MOOD STABILIZING AND ANTICONVULSANT MEDICATIONS	**Lithium** common reactions: tremor, polyuria, polydipsia, weight gain, diarrhoea, vomiting, drowsiness, cognitiveimpairment, muscle weakness, impaired coordination,anorexia, nausea, blurred vision, xerostomia, fatigue, alopecia, reversible leucocytosis, acne and oedema.	Lithium: Associated withan increase in birthdefects including cardiac anomalies (esp.Ebstein's anomaly) andbehavioural effects.	**D**
	Valproate Children younger than 2 yrs. are at greatest risk for hepatotoxicity. Common reactions: headache, nausea/vomiting, loss of muscle strength, somnolence, thrombocytopenia, dyspepsia, dizziness, diarrhoea, abdominal pain, tremor	Valproate: Neural tube defects lower IQ measures	**D**

	Carbamazepine: May cause dizziness, drowsiness, unsteadiness, impaired coordination, nausea/vomiting, blurred vision, nystagmus, rash, confusion	Neural tube defects, minor anomalies	**D**
	Lamotrigine: Children are at greater risk for rash thanadults. May cause nausea, vomiting, dizziness, vertigo, visual disturbance, somnolence, ataxia, pruritus/ rash,headache, pharyngitis, rhinitis, diarrhoea, fever, loss ofmuscle strength.	Unknown but there appears to be a high rate of cleft lip and palate	**C**
	Gabapentin: May cause dizziness, somnolence, ataxia,fatigue, peripheral oedema, nystagmus, nausea, and vomiting,-viral infection.		**C**

	Pregabalin: dizziness, somnolence, xerostomia, peripheral oedema, blurred vision, weight-gain, abnormal thinking, impairedcoordination.		**C**

PRINCIPLES FOR USE OF PSYCHOTROPICS:

The following was recommended by Nunn et al [34].

1. Target the symptoms initially and not the diagnosis: treatment should initially target the symptoms. Comorbidity is common and diagnosis might be difficult
2. Begin with less and go slow
3. Multiple medications might be required in severely ill
4. Adequate time must be given for adequate trial
5. Change of drug should be made one at a time.
6. Patient and family psychoeducation holds the key

CONCLUSION

With the increasing use of psychotropic in childhood psychiatric illness has helped to reduce the burden of illness. However, polypharmacy and off-label drugs should be avoided. The increasing drug trials and research going on in the field of childhood psychopharmacology has brought about new guidelines and measures to prescribe drugs. However, the challenge of ensuring that children and adolescents receive evidence-based mental health treatment requires a multi-disciplinary approach where children and families access and accept treatment, providers gain the necessary

skills/knowledge and organizations and funding policies align to support them.

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Rationality of using psychotropics in Intellectual Disability

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ABSTRACT: *Psychotropics form an important part of the management plan for psychiatric co-morbidity and behavioural problems in Intellectual Disability (ID), like self-injurious behaviours (SIBs), Aggression, mood disturbances, anxiety symptoms, sleep disturbances. However, usage of psychotropics in individuals with ID warrants caution because of difficulty in arriving at accurate diagnosis due to atypical and nonspecific presentations. Additionally, there is a higher risk of side effects and lack of randomized controlled trials (RCTs) in this population which pose tough questions for treatment decisions in routine clinical practice. Here we attempt to briefly discuss the context, challenges, approach to using psychotropics in individuals with ID.*

Keywords: *Psychotropics, Intellectual Disability, Behavioral problems, co-morbidity.*

INTRODUCTION

Psychotropics use in individuals with Intellectual Disability (ID) is widely prevalent albeit understudied. This group of patients can be highly challenging to treat because of their cognitive deficits which impair their ability to effectively express and communicate. To complicate the matter, ID is highly co-morbid with neurological conditions as well as psychiatric conditions. Here we are not attempting to give an exhaustive account of all studies related to psychotropics in ID, rather discuss a practical approach and rationale.

Case Vignette

A 15-year-old boy from middle socioeconomic class comes along with his mother with chief complaints of severe aggressive behaviour for one year in the background of mild ID and moderate Autism. Aggression occurs every alternate day lasting for 30-40 minutes. On clarification of the antecedents, it was clear that all aggressive episodes were provoked by the mother in the form of forcing him to obey and follow commands. However, the mother was puzzled that she always interacted with the child in the same way prior to the onset of aggressive behaviour. Child shared a cordial relationship with the mother. The interval period between the aggression episodes is uneventful and the child is euthymic during these inter-episodic periods. No history suggestive of any medical/substance use related causes for aggression. No history of sleep or appetite disturbance. No history of pervasive mood changes or symptoms suggestive of a psychotic process. No history of any anxiety or Obsessive and Compulsive (OC) spectrum disorder. On observation, the child was euthymic and shared a secure attachment with mother. The child was engaged in writing/drawing while the mother was interviewed. However, occasional gestures of purposeful aggression were seen but the child settles down when the mother talks about good and harmful behaviour following which child agrees to resumes the writing work.

The context of using psychotropics in individuals with Intellectual Disability

Cases like the one described in the above vignette can be quite common in developmental disorder clinics. Often cases tend to become more complicated when there is medical/psychiatric co-morbidity like epilepsy/mood disorder or presence of multiple psychosocial risk factors, for example, sexual abuse or death of a parent/caregiver …and so on. Moreover, risk factors seldom operate independently, and co-morbidity is a rule rather than an exception. This brings us to an important approach that needs to be considered in managing individuals with ID who presents with behavioural

or emotional disturbances i.e. A Multidisciplinary evaluation; supplemented with longitudinal observation and interpreting psychopathology from a developmental perspective, especially in children and adolescents.

Evaluation of psychosocial factors in a given case is of paramount importance as this leads to a good case formulation which in turn leads to better management. Overprescribing and indiscriminate use of psychotropics can be avoided with this approach. Many times,the severity of behavioural problems reported may be a function of the tolerability threshold of caretakers[1]. Parental mental illness can easily contribute to an increase in behavioural problems in children/ adolescents[2]**.** Negative experiences at school/vocational Centre can be the triggering factor. Caregiver's response to these adversities can maintain and perpetuate problem behaviours.Therefore, a better understanding of the emergence and evolution of symptom with a thorough behavioural analysis within the developmental framework needs to supplement routine psychiatric assessment and management practice. With a holistic picture of psychopathology, we can provide a meaningfulexplanation to parents aboutdiverse options such as psychotherapy or behavioural intervention strategies along with psychotropics.

In the above vignette, it is important to consider the developmental perspective; emerging adolescence is known to have higher aggressive tendencies[3],the need for autonomy and identity. With a newly emerging sense of social acceptance and partial understanding of complex evaluative emotions such as envy/ embarrassment, coupled with lack of adequate ways of managing and expressing needs and emotion makes children/ adolescents highly vulnerable to be labelled to be having a psychiatric illness[4], which may very well applicable to young adults as well.

Another aspect of pharmacological management of individuals with ID is compliance. Many parents/caregivers discontinue medication due to fear of adverse effects, although most of their concerns may be genuine. Therefore, prior sensitization and

explanation of the rationality and expected benefits is a must. Many times, parents/caregivers assume that the psychotropics are going to cure the developmental disorder and my child will become completely normal, only to be disappointed later. This may lead to lack of trust in medication and clinician.

Due to the nature of developmental disabilities it is challenging to arrive at an accurate diagnosis and because of the vulnerability of individuals with ID, it is imperative for a psychiatrist to put in extra effort to be as accurate as possible, therefore, below are some questions that can help in clinical decision making. Although these questions are routinely asked, we have restated it as it has proved to be of immense help in our practice.

1. Evaluation of behaviour within the context and developmental age (rather than chronological age).
2. Is there an onset for the problems or has it existed since early childhood?
3. Is there a clear change from the premorbid state?
4. Is there any periodicity or have the symptoms been progressive?
5. Is there clear impairment/distress? This may be evident for example child not going to school/excessive crying/irritability. In adults, they may refuse to engage in activities that they earlier engaged in.
6. Are there any behavioural equivalents like refusal to go to school/self-injurious/non-specific aggressive behaviours may be indicator or mood disorder/ anxiety disorder. Behavioural equivalents provide observable indices for underlying psychopathology[5].
7. Are there disturbances in biological functions?
8. Stress levels of parents/caregiver.
9. Level of environmental stimulation received by the individual.
10. Whether prescribing psychotropics will benefit enough considering the risk-benefit ratio (financial implication, side effect profile, lack of robust evidence for existing psychotropics, availability of expertise in nonpharmacological approaches)
11. If required brief period of in-patient care can be considered

for observation of patient as well as for evaluation of caring practices of parents/caregivers, then admissions can be considered.

The practical difficulty in many centres in our country could be due to lack of trained allied mental health professionals to deal with psychosocial aspects, compounded with clinician's inherent inclination totowards prescription padwhich may be premature at times. Unfortunately, our understanding of neurodevelopmental disorder is not to an extent of directly targeting the pathophysiology of the neurodevelopmental disorder, therefore there is a greater need to rely on psychosocial and symptomatic management. The picture is not so gloomy, for example, some of the targeted treatment has been of interest especially in Fragile x syndrome, Tuberous sclerosis etc. [6]

Precautions and challenges

1. Diagnostic overshadowing- Misattributing symptoms to be part of ID rather than a possible co-morbidity. On the contrary, there can also be a tendency to overdiagnose and overtreat. For example, a child with ID with aggression can be overdiagnosed witha mood disorder, wherein, aggression could be a part of Challenging Behavior (CB). Such overdiagnosis results in unnecessary long-term exposure to psychotropics. Hence, balancing and minimizing both kinds of errors is required.
2. Diagnostic uncertainty- for children/adults with a severe disability, it may be very difficult to establish the components such guilt, worthlessness, or suspiciousness, or exact nature of fears which are some of the core features to diagnose psychiatric illness. A child with ID/ASD may avoid situations due to the sensory issues rather than anxiety. Or a psychologically traumatic event may manifest as bowel/bladder incontinence. Factors such as atypicality in presentation, limitations in the expression of thoughts and feelings compounded with lack of reliable and valid

diagnostic tools for this population contributes to diagnostic uncertainty.

3. Many times, parents report challenging behaviours existed premorbidly; therefore clarifying the clear change in the form of worsening or new onset behaviours can be helpful in avoiding unwanted medications. In practice, many times it may be difficult to categorize into a diagnosis, but the symptoms may be severe enough to warrant treatment. In such cases, short-term use of psychotropics may be indicated and to revise the situation periodically for the need for continuation of psychotropics.
4. In general, the individuals withan ID may be more sensitive to side effects.For example,individuals with downs syndrome are more sensitive to anticholinergic side effects, a seizure can be easily precipitated by drugs such as clomipramine. There is a higher risk of Tardive Dyskinesia in individuals with ID population.[7] As a group ID is heterogeneous with numerous genetic loci implicated, understandably resulting in differences in associated features as well as the vulnerability for side effects. Syndromes such as PraderWilli Syndrome (PWS) can have obesity in adolescence/adulthood but poor weight gain in early childhood, similarly there can be syndromes like William syndrome with cardiac anomaliesand associated electrolyte abnormality thus the risk for cardiac arrhythmias with psychotropics. An individual with Downs syndrome have a higher incidence of thyroid abnormalities which has well-known association with psychiatric disorders, so drugs like Lithium needs caution.Associated Gastrointestinal abnormalities ranging from hypomotility to malrotation to severe anomalies occur as a part of ID syndrome which can logically affect the pharmacokinetic profile. Numerous metabolic derangement (In-born errors of metabolism) is linked with ID, thus pharmacokinetic interaction is a definite plausibility. Therefore, genetic aetiology, medical co-morbidity needs to direct the choice of psychotropics in individuals with ID.

5. Drug to drug interactions is a critical area which needs consideration in this population, for example, an individual on Carbamazepine (CBZ) for seizures may interact with other psychotropics initiated for any other purpose.

General principles of using psychotropics in ID

1. Through evaluation of both biological and psychosocial contextual factors.
2. To be aware of common behavioral phenotypes that are relatively specific to certain syndromes like social anxiety in Fragile X Syndrome (FXS), Obsessive Compulsive behaviors in PraderWilli Syndrome (PWS), Mood lability in Downs syndrome, severe aggression in Angelman and smith magenis Syndrome, helps in recognizing behavioral problems early and managing better.[8]
3. Risk-benefit analysis
4. Clear targets that can be monitored
5. Parental/caregiver education and consent
6. Start low with slow titration
7. May require more frequent monitoring for side effects depending upon the aetiology and severity of ID and comorbidity, compliance.
8. Integrated psychosocial interventions will reduce the need for medications
9. Any causative agents can be withdrawn if behavioural side-effects are severe for example withdrawingphenobarbitone or levetiracetam can reduce behavioural problems (can be substituted with other suitable Anti-Epileptics), Drug-induced hypothyroidism related mood symptoms can reduce ifdrugs like lithium are taken out, or overactivation, irritability, mood instability, insomnia due topsychostimulants are reduced if the dose of stimulants are reduced or switched to Non-Stimulants like Atomoxetine..
10. Involvement of a multidisciplinary team

A brief overview of Psychotropics used in ID

In general, the effect size of pharmacological trials is less in ID population[3], to complicate the process,most of the trials on efficacy and effectiveness of pharmacological agents exclude individuals with ID. However, small but consistent evidence exists for use of pharmacological agents in Attention Deficit Hyperactive Disorder (ADHD) as well as for aggressive behavioural problems in ID. In view of paucity of evidence in this population, it is reasonable to extrapolate from non-ID population, although ID group seems to be heterogeneous with higher co-morbidity and presence of neurological conditions.Polypharmacy is not uncommon;however, adhering to the basic principles outlined above will greatly reduce polypharmacy. Below is the brief description of psychotropic classes tried in ID.

Antipsychotics are the most commonly prescribed class of psychotropics in the ID population. Used for a wide range of indications such as psychosis, anxiety disorders, and challenging behaviours (CB). In a countrywide audit for patterns of prescribing antipsychotics in ID population of UK, Paton C et al (2011) found Risperidone (0.5mg-14mg), Olanzapine (2.5mg-30mg), Chlorpromazine(7.5mg-1000mg), Quetiapine (25mg-800mg) were the common antipsychotics prescribed orally. In 50% of cases with severe ID, challenging behaviours without concomitant psychiatric co-morbidity was the indication for prescribing antipsychotics[9]. Higher risk for Tardive Dyskinesia, sedation and weight gain can be worrisome in the younger population. [7] Other antipsychotics like clozapine have been tried in a small number of subjects. Overall, regular review of dose, side effects andevaluating the need for continuation of antipsychotics is warranted.

Antidepressantsuse in ID parallels use in the non-ID population. In acentre-based chart review of antidepressant use in ID populationby Rai et al (2010) showed antidepressants were commonly prescribed for indications such as depression, anxiety disorders, Obsessive-compulsive disorders as done in non-ID population. Most common antidepressants used was SSRIs followed by Mirtazapine (15-45mg). Among SSRIs Citalopram(8-40mg)

was prescribed in more than 40% of individuals. Most common side-effects reported were related to Gastrointestinal, behavioural activation and seizures. [10] Another off-license usage for aggression and impulsivity has been tried with doubtful effectiveness. If self-injurious behaviours have a compulsive nature, then it is worth trying SSRIs. fluoxetine, paroxetine, sertraline, trazodone, and clomipramine have been reported with favourable results but involving a small number of subjects.[7]A specific concern in this population can be the risk of precipitation of hypomania.[11]

Mood stabilizers: In a review of studies from 1990-2006, related to use of Mood Stabilizer and Antiepileptics in ID by Deb S et al (2007), showed some evidence for lithium (0.5-1.2mmol/l) (supported by one RCT) and antiepileptics like Valproate (900-1300mg), and Topiramate(200mg). However,Carbamazepine (25-26microgram/l) showed no difference from placebo[12] Similarly, Lamotrigine was not found to be convincing.[1]However, agents like Lithium and Valproate (as add-ons) has been shown to improve cyclical mood disturbance and help in reducing challenging behaviour in our clinical experience.In an 8-week open-label trial of Topiramateon 3 adults with PraderWilli Syndrome (PWS) had shown to reduce skin picking behavior.[13] Overall, Lithium appears to have better evidence for SIBs and aggression[1], however, to be cautious of cognitive dulling which can be associated with Lithium.[7]

Benzodiazepines: In a review by Kalachnik et al (2002) related to benzodiazepine side effects in ID population showed benzodiazepines is prescribed for four key areas of use, vizbehavioural/psychiatric, epilepsy, other medical conditions like cerebral palsy, and for dental/medical sedation.Range of benzodiazepines has been used namely Chlordiazepoxide (upto 60mg), Clobazam(upto 40mg), Clonazepam(upto 12mg), Diazepam(upto 100mg),Lorazepam(upto 16mg), Midazolam(upto 10mg) Oxazepam(upto 60mg).This review reported behavioural side effects like paradoxical heightened agitation, impulsivity or disinhibition in 11-25 % of individuals[14] Short-term use and checking for past history of abnormal reactions has been advised.[7]

Other medications: Stimulants can be helpful to treat co-morbid ADHD; however, there are higher chances of paradoxical responses in the form of emergent motor tics and emotional lability. With respect to sleep disturbance melatonin has been helpful.[1]

To the best of our knowledge, there are no ID specific guidelines regarding dosage, duration of use of psychotropics or monitoring. It is sensible to use psychotropics for indications as practised for non-ID population albeit with the awareness that there is a paucity of evidence and vulnerability to adverse effects in ID population on a case to case basis. And it is reasonable to start at low doses with gradual up-titration, and to monitor for side effects, be aware of existing medical problems like epilepsy. Clinicians need to be updated about latest evidence base and for any newer therapeutic agents.

Side effects can emerge or exacerbate as a function of underlying syndromic causes. For example, derangedmetabolic parameters can be seen in syndromes like Down, Turner, Angelman, Prader-Will syndromes, needing caution and greater monitoring while using psychotropics such as Second-Generation Antipsychotics (SGAs). Epilepsy can be central to syndromes like Tuberous sclerosis, Rett syndrome, therefore prefer using psychotropics that has less risk for lowering seizure threshold can be preferred.[15]If not competent to diagnose syndromic causes of ID, it is recommended to take help from peadiatrician/clinical geneticist to evaluate for any medical problems that may interact with psychotropics.

Special circumstance

Many times, individual with an ID may be accommodated in a residential care centre. Therefore, history may be inadequate, and monitoring and finances will be deficient. Which needs to be considered before prescribing.

Psychotropics asTargeted treatments in ID

Great strides in understanding molecular mechanisms involved in the disruption of neuronal development haveled to targeted treatments. Models like Fragile X Syndrome (FXS), Tuberous

Sclerosis (TS) have providedan opportunity to test pharmacological agents. Molecular mechanisms of such syndromes are fairly delineated, for example in TS loss of *TSC1* or *TSC2* results in dysregulation of the rapamycin (mTOR) pathway which is targeted by agents like Vigabatrin.[16]Similarly, metabotropic Glutamate receptors are affected when FMR Protein is the deficit in FXS, thus agents like Fenobam, Lithium, Ampakines are considered potential agents[17]. Psychotropics hold immense potential as treatments in ID population, however, what needs to be seen is,whether these agents have a sensitive period during development when they are most effective, what is dosage and duration of treatment using these agents?

Some relevant questions worth asking in this area would be

1. Whether there are any clinically significant pharmacokinetic/ pharmacodynamic differences between ID population and non-ID population? Or any variation as a function of severity of ID/Gender?
2. Whether individuals with ID respond any differently to psychotropics in comparison to non-ID psychiatric individuals?

With respect to children, non-ID children respond better to Methylphenidate (MPH)[18]**(Pearson et al., 2004**) and tolerability of MPH is less in individuals with ID[19](**Handen, Feldman, Goslong, Breux, & Mcauliffe, 1991**). The evidence from studies at molecular/ cellular and at the level of the brain has shown that there is clear biological difference both structurally and functionally, however it is not clear, how different classes of psychotropics interact withunderlying pathophysiology of ID.

CONCLUSION

Usage of psychotropics in the ID population is more similar than dissimilar to the non-ID population. However, it is important to acknowledge that there is a lack of RCTs and practical difficulties in delivering the psychosocial intervention.

Judicious use with due consideration to risk-benefit, interaction, side effects, parental education and psychosocial interventions, psychotropics can be very useful to improve the wellbeing of individuals with ID.

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Treatment Strategies in Children with OCD

Nahid S Islam, Sumi B Choudhury

ABSTRACT: *OCD in children is found to be quite common with a lifetime prevalence of around 1.9% to 3.3%. Childhood OCD is associated with significant functional impairment and if left untreated or inadequately treated will severely disrupt normal development, impair functioning and extend into adulthood. In general, the symptoms of OCD are similar to those in adults with obsessions on the theme of contamination, damage to self or others, symmetry or moral issues common and compulsions like washing, checking and repeating. Clinical presentation is at times complicated by the child's developmental immaturity. CBT (Cognitive Behaviour Therapy) is considered a safe first-line therapy for children with OCD irrespective of the level of severity according to NICE guidelines. The most common form of CBT for OCD is Exposure and Response Prevention (ERP). A high level of parental involvement is essential for the success of such therapy. In the pharmacological treatment, SSRIs are the drugs of choice with fluvoxamine, fluoxetine and sertraline being FDA approved for the treatment of OCD. Augmentation strategies are often required for about 40% to 50% of the patients with OCD who do not respond to adequate trials of SSRIs with an addition of antipsychotics like risperidone, aripiprazole or haloperidol being most commonly used strategies. Current evidence from the Paediatric OCD Treatment Study (POTS) showed combined treatment proved superior to CBT alone or to an SRI (sertraline).*

Keywords: *OCD, Children, adolescent, ERP*

INTRODUCTION

OCD, a chronic and often disabling disorder in adults and once considered rare in children, have been found to be a common cause of distress in childhood too. Recent advances in the diagnosis and treatment of the disorder havedocumented the condition being observed in children as young as age 2 but more typically begins later in childhood or early adolescence[1]. OCD in childhood is associated with a significant functional impairment which may compound over time and hamper the acquisition of other important developmental milestones. If left untreated or if inadequately treated, young children have an increased likelihood that OCD will severely disrupt normal development, impair functioning and extend into adulthood.

Epidemiological studies of OCD focusing on children and adolescents indicates a lifetime prevalence of around 1.9 to 3.3%[2] and in few other studies it has been found to be in the range of 0.7% to 2.9%[3]. This is affected by certain diagnostic issues like continuity with normal development which makes the boundaries of diagnosis complex. Individual habits that are typical of OCD are extremely common across populations and much ritualistic and magical behaviour are part of normal development[4]. Moreover, secrecy appears to be a hallmark of childhood-onset OCD. Children often recognise their symptoms as nonsensical and are embarrassed by them, so they go to great lengths to hide them which influence recognition and diagnosis of OCD in children.

Symptoms of OCD

In general, the symptoms of OCD in children are similar to those in adults. Obsessions on the themes of contamination, danger to self or others (such as fears that parents will be harmed), symmetry or moral issues are common, typical compulsions include washing, checking and repeating – particularly until the child experiences a feeling of " getting it just right" [5]. Clinical presentation is at times altered by the child's developmental immaturity.

Very early onset OCD because of certain unique features have been thought to represent an important subtype of the disorder. They seem to represent a more familial form of the disorder[6] as well as frequent association with tics and/ or Tourette's disorder [7, 8]. Another association of a subgroup of paediatric OCD has been found with post-streptococcal infection, identified by the acronym PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections)[9]in which the onset of symptoms is unusually abrupt with neuropsychiatric and behavioural manifestations and a response to immunotherapy.

Epidemiological studies indicate that over 50% of adults with OCD report that their symptoms started during childhood or adolescence, with males generally having an earlier onset than females [10]. Sometimes there may be a prodromal phase where parents reported that their children had displayed "micro-episodes of OCD "(excessive rigidity and repetitive rituals, albeit briefly) years before developing full-blown symptoms. The clinical course of the disorder often shows some developmental influence with the obsessions and compulsions changing over time. Most begin with a single obsession or compulsion which is continued for months and years, and then gradually acquire a different obsession or ritual (e.g. from counting to washing and then checking). Childhood OCD is often associated with various comorbidities like Tic disorders, major depression, attention deficit disorders, various anxiety disorders and phobias. The outcome is often a waxing and waning course with some studies reporting a spontaneous remission in about one-third of patients[11]

OCD is a highly heritable disorder when it has a childhood onset and the genetic contribution to OCD is increased when there is comorbid tic disorder. Apart from the genetic basis, abnormal activities or dysfunctions in the CSTC (cortico striato thalamocortical) loops have also been found in children with OCD in various models[12], although there are still inconsistencies in the findings. Neurochemically, monoaminergic neurotransmitters which extensively project from the brain stem to regions within the

fronto striato thalamic circuitry may contribute to the pathogenesis of OCD

Treatment Strategies

Three types of intervention are available for reducing obsessive-compulsive symptoms of paediatric OCD.

Psychological treatment

Pharmacological treatment

Combined treatment

Again Maudsleys' treatment guideline for treatment of OCD in child and young people advises stagewise treatment options as per the functional impairment as shown in Fig1.

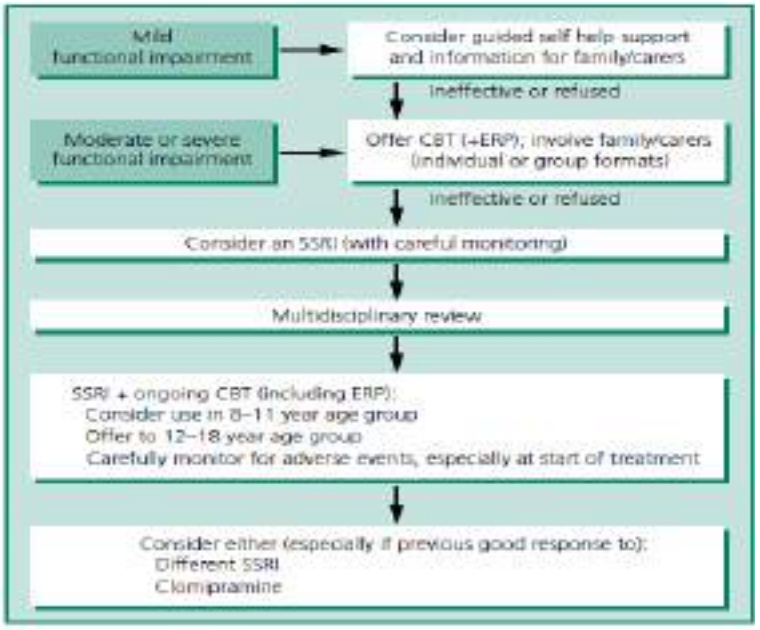

Fig 1. Treatment options in children and young people with OCD. Adapted from The Maudsley Prescribing Guidelines in Psychiatry. 12th Edn. Pg.376

Psychological treatment

Cognitive Behaviour Therapy (CBT)is considered a safe first-line treatment for children with OCD irrespective of the level of severity according to NICE guidelines[15]. The most investigated type of CBT for OCD is graduated exposure with response prevention (ERP). In a study [13], there was a 50% reduction in symptoms which was sustained for atleast 18 months. The conventional treatment modality is around 14 sessions with one session per week. Storch et al [14] (2007) compared the efficacy of a shorter-term, intensive treatment (90-minute psychotherapy sessions held 5 days a week for 3 weeks) and found the results at par with the conventional mode. In clinical practice usually, ERP is usually combined with other behavioural techniques such as anxiety management training and extinction (e.g., instructing parents not to give reassurance when a child compulsively seeks it). Frequently cognitive components are added, such as normalizing intrusive thoughts and reappraising notions of personal responsibility.

When treating younger or more developmentally immature children, ERP may be intimidating and outstrip their cognitive abilities for abstract reasoning and self-observation. In addition, for children with OCD, there appears to be a direct correlation between the extent to which their parents make accommodations (such as assisting the child in carrying out rituals or facilitating avoidance of situations that evoke anxiety) and greater functional impairment and treatment resistance. Thus,a high level of parental involvement is essential in the success of such therapy and the therapist should provide the child and family coping techniques for managing future problems. Parents can actively participate, on the one hand, in the assessment and reporting of more objective data and information to the therapist and on the other hand, in the treatment implementation, reducing accommodation to symptoms, applying exposure at home and modifying beliefs and attitudes towards OCD. Several studies have shown greater efficacy of ERP for children when modified with direct parental involvement with up to 60% improvement and 40% remittance. A review of the

research and the treatment guidelines on CBT for OCD highlights two characteristics that strongly influence treatment efficacy. CBT must closely adhere to an established manual that includes ERP elements. Also, efficacy is correlated with clinicians' depth of training in CBT for OCD and their experience with it.

Pharmacological treatment

The NICE guidelines[15] also state that an SSRI should be added when the patient prefers an SSRI, or when CBT is not effective, is not accepted, or is not adequately complied with.However, the American Academy of Child and Adolescent Psychiatry (2012) Committee[16] on quality issues recommends the combination of SSRI and CBT from the start for patients with moderate to severe OCD which is still a subject of debate.

It is widely known that a variety of agents that inhibit serotonin reuptake appear to be useful in the treatment of OCD. Reliable studies have shown only 40% to 50% of drug naïve patients experience a reduction of 25% to 40% severity of symptoms.

Comorbid psychopathology should be kept in mind when choosing medication. Coexisting panic disorder, psychotic or schizotypal features, depression, or Tourette's disorder might steer towards those classes of drugs with demonstrated efficacy in these conditions and with OCD.

Determining whether a patient has responded to a medication requires that sufficient doses be given for a sufficient duration which is at least 4 weeks of the maximum tolerated dose. Drug adherence is particularly important in determining the efficacy and family accommodation plays an important role here. Gradual dose reductions are essential to avert withdrawal reactions when discontinuing those medications. The most studied medications in the treatment of OCD are potent SSRIs. Fluvoxamine, Fluoxetine and sertraline are FDA approved agents for the treatment of OCD.

Studies have shown that the hoarding group was less likely than other subtypes to respond to SSRIs. The other factor groups were found not different from one another in their responsiveness

to SSRIs [17]. A meta-analysis of 12 studies of paediatric OCD employing SSRIs or clomipramine concluded that response rates among the SSRIs were comparable, and clomipramine was superior by a significant margin [18]. But the side effect profile possibly cardiac arrythmogenic effects and tolerance for clomipramine continue to place it outside consideration as the first line pharmacologic treatment for paediatric OCD.

Augmentation strategies

About 40% to 50% individuals with OCD do not respond to adequate trials of SSRIs. The failure of response to one SRI agent does not predict failure or response to another and side effects from one agent do not predict side effects from another. For this reason, it is important to offer adequate doses for a sufficient period of at least two and even three agents before moving on to augmentation strategies.

While the use of polypharmacy is generally to be avoided, an augmentation strategy may become necessary. In adults showing suboptimal response to an SRI, adjunctive haloperidol or risperidone and also aripiprazole show significant reduction of obsessive symptoms. These augmentation strategies can be applied to children also keeping in consideration the side effect profile for each agent particularly the risk of tardive dyskinesia with haloperidol, metabolic side effects with risperidone, or other antipsychotic agents. A trial comparing aripiprazole versus risperidone added to existing medication for children with tic-related OCD showed both drugs were equally beneficial. Studies do not show significant benefits with olanzapine or quetiapine [19, 20]

Recent double-blind studies of N-acetylcysteine (NAC), an antioxidant precursor to glutathione, have shown significant benefit using 1200-2400 mg/ day in adult patients with OCD, as well as with trichotillomania or skin picking [21]. The mechanisms are poorly understood but NAC has been shown to alter neurotransmitters including glutamate. No studies have been done in children with OCD.

Inspite of major advances in drug treatment, at least 10% of the OCD population remain severely affected. Neurosurgical procedures for

extreme cases in adult OCD which are aimed at disrupting the CSTC loops either through creating a permanent lesion by excision or by repetitive deep brain stimulation are held not appropriate for children. Less invasive alternatives like transcranial magnetic stimulation remain of doubtful benefit for adults and areuntested in children.

Maintenance treatment

OCD is frequently a chronic disorder and long-term maintenance therapy should be anticipated with the current recommendation being a minimum treatment period of 6 months following full remission.

Combination Treatment

Current evidence from the Paediatric OCD Treatment(POTS multicentre study, 2004) [22] showed combined treatment proved superior to CBT alone or to an SRI (Sertraline). Overall, it is clear that while medication alone is an effective and generally safe and well tolerated, CBT may have the edge in term of first-line treatment, particularly when combined with an SSRI or clomipramine.

Adaptive Treatment Strategies (ATS)

ATS consists of a set of decision rules based on clinical characteristics and time-sensitive outcomes to inform a sequence of evidence-based treatments. A study [23] suggests that provision of treatment for childhood OCD could be tailored according to the availability of local resources. Considering the scarcity of mental health services, especially in low and middle-income countries, flexibility in the provision of treatment for childhood OCD seems relevant to clinicians and policymakers dealing with limited financial and human resources. Group CBT offers a low-cost choice for treatment of OCD in youth. Depending on the resources available, beginning treatment with an SRI or CBT and switching to or adding the other treatment for nonresponders revealed to be equally effective treatments.

Immunomodulatory Treatments

Some children, who suffer from an autoimmune based form of OCD following infection with GABHS, are seen to benefit from such treatments. Controlled treatment trials using intravenous immunoglobulin and plasmapheresis were found effective in lessening of symptom severity for children with infection triggered OCD and tic disorders. Penicillin or azithromycin prophylaxis of sufficient intensity to decrease streptococcal infections was also found to decrease neuropsychiatric symptom exacerbation among children in the PANDAS subgroup.

CONCLUSION

For paediatric OCD, the general consensus that emerges is of a less severe disorder than was reported before 1990. 60% of children will improve to a level that they no longer meet the criteria for the disorder and roughly two-thirds of those will recover(40% overall). Although this is certainly encouraging for the majority, those with co-occurring disorders, earlier onset, longer duration of symptoms, and poor psychosocial functioning are not as likely to recover. Poor response to medication, the presence of tics, and parental psychopathology also predict a poor outcome.

Too many persons with OCD continue to suffer in secrecy due to lack of awareness about the illness. Too few clinicians are schooled in CBT techniques. Vigorous effort to inform the public and primary care physicians in recognition of OCD is still needed. Training clinicians in effective treatments, extending treatment and neuroscience research, and improving outreach and public education are the greatest challenges now.

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Hormonal Drugs in Psychiatry-an overview

Binita Talukdar

ABSTRACT: *Nervous system and endocrine system are two different entities but these two systems maintain the internal homeostasis of our body. When there is a problem in one system it may affect other system or vice versa. Role of hormonal drugs in psychiatry is very important. Researches were done and still going on.*

Keywords: *Endocrine, Estrogen, Progesterone, Psychiatric disorder.*

Introduction:

Hormones are the soluble messengers of the endocrine system, and these are classified into steroids, peptides, and amines [1]. Nervous system and endocrine system are two different entities but these two systems maintainthe internal homeostasis of our body.When there is a problem in one system it may affect other system or vice versa [2].Recently much research was going on the importance of the psychological aspect of the endocrine condition [3]. In the 19th century much literature published which contained several presumptions about the pathophysiology of mood disorders in women and endocrine dysfunction. By late 1920 and early 1930 gonadal steroids were isolated and later they were used in much medical illnesses. Many a time it has been seen that gonadal steroids are used in women to treat involutional melancholia, premenstrual syndrome and postpartum depression [4].

Hormones and Psychiatric Disorder:

Role of hormones in psychiatric disorder is very important. Psychological distress is often seen to persist in much endocrine disorder [5]. A list of the psychiatric disorder associated with the endocrine disorder is given below-

Hormones	Endocrine disorder	Psychiatric disorder
Thyroid hormone	Hyperthyroidism	MDD, Anxiety[3]
	Hypothyroidism	MDD[2], paranoid symptoms and cognitive disturbances may be present[3]
Parathyroid hormone	Hyperparathyroidism	Depression and cognitive symptom[3]
Adrenocorticosteroid	Hypocortisolism(Addison's disease)	Depression[3]
	Hypocortisolism	Depression /mania [2]
Gonadal stimulating hormone and sex steroids	Amenorrhea	Anorexia nervosa[2]
		Postpartum depression[3]
		Premenstrual dysphoric disorder [2]
Growth hormone, prolactin		Mental retardation, drug induced hyperprolactinemia[3]

When we look into the neurobiology of psychiatric disorder, it has been found that the mechanism of the different hormone causing such illness is different. Hypothalamus is one of the brain structures which serve a major link between endocrine and nervous system. Major output pathways from the hypothalamus reach the pituitary gland and convert neural signals into endocrine signals[2].

It is seen that thyroid hormones have a profound influence on the human brain and behaviour, and the interrelationship between thyroid dysfunction and psychiatric disturbances has always been well documented. Patients with thyroid disturbances can present with a variety of neuropsychiatric symptoms, including depressed mood, mania, acute psychosis, anxiety, and dementia [6]. T_3(Triiodothyronine) is available in peripheral organs and T4 (Tetraiodothyronine) is available in brain.T_3 acts as a neuromodulator by enhancing γ-aminobutyric acid (GABA) release and calcium influx, which subsequently facilitate neurotransmitter release. It has been shown that to predict relapse in unipolar depression T_3 levels is measured, and exogenous T_3 supplementation appears to potentiate or accelerate the antidepressant response [7]. Although most depressed subjects have normal T3, T4 and TSH (Thyroid stimulating hormone) circulating levels, there is evidence of altered activity of the HPT (Hypothalamic-pituitary-thyroid) axis in some cases of depression including [8].

On the other hand,Corticosteroid receptors are abundant in limbic regions such as the hippocampus and the amygdala, and excessive corticosteroids can be cytotoxic to thehippocampus. A stress-mediated chronic hypercortisolemic state is supposed to be depressogenic due to its toxic effect on the hippocampus.There is stress induced hyperactivity of HPA axis and release of CRF and ACTH and this isone of the causes of depression [2].

Though the gonadal steroids have more roles in causing mood disorder, it is seen that it has also played a very important role in causing psychosis. Psychiatric conditions like schizophrenia and mood disorder exacerbate during the menstrual cycle and it is due to the fluctuation of estrogen level [9]. Gonadal steroids regulate the functions of central neurotransmitters such as serotonin, dopamine, norepinephrine and GABA [10].In premenstrual (late luteal) phase level of Estrogen, progesterone and levels of their metabolites decrease and it remains low inthe menstrual (follicular) phase [11]. It is seen that there is Increase of increase in psychotic symptoms in schizophrenia during the luteal phase of the menstrual cycle

and hypothesis says that it is due to increase estrogen sensitivity in dopaminergic receptors [12]. In functional MRI studies, it was shown that due to estrogen reaction response to stress decrease and this indicates that psychotic findings triggered by stress may be due to a decrease in estrogen levels [13].

The antidepressant effect of estrogen is due to its serotonergic activity.In one animal study, it has been found that estrogen increases genomic expression of tryptophan hydroxylase and decrease the activity of monoamine oxidase and it increases serotonin level. Estrogen appears to increase the sensitivity of post-synaptic 5-HT1a receptors and to decrease the sensitivity of pre-synaptic 5-HT1a autoreceptors. It has also an antidopaminergic effect. On the other hand, progesterone appears to decrease 5-HT1a binding potential and to downregulate the formation of NMDA synapses in the hippocampus [2].

Hormonal Drugs Used in Psychiatric disorder

1. Hormone replacement therapy: HRT is used in mood disorder of perimenopausal and menopausal women [14]. It is not only used to alleviate depressive symptom but also as an augmenting agent of the antidepressant [15]. It is used in the form of a transdermal patch to reduce the risk of thromboembolism. The main idea of using such drugs is that it has serotonergic, adrenergic, dopaminergic effect on brain [16, 17].

   Estrogen can also be used Alzheimer's disease because of its effect on the cholinergic system. Estrogen promotes the growth and survival of cholinergic neurons, increases cholinergic activity, has antioxidant properties, and promotes the nonamyloidogenic metabolism of the amyloid precursor protein [18].
2. Oral contraceptive pill: It can be used in menstruation related exacerbation of affective disorder and to treatthe comorbid premenstrual dysphoric disorder.
3. Tamoxifen: Tamoxifen is a selective estrogen receptor modulator. Though it's used in non-psychiatric treatment

is more, many studies shows that it can be used in mania. However,Tamoxifen-induced depression is also seen in some cases [19, 20].

4. Testosterone: it is a male gonadal hormone used in depression and it not only improves mood, energy but also libido in men [21, 22]. It can be used as a monotherapy or adjunct to antidepressants [23, 24]. Because of the side effect such as hypertension, gynecomastia, polycythemia and treatment-emergent paranoid symptoms and prostate cancer, the use of such hormone is limited [25, 26].
5. Oxytocin: Oxytocin is the hormone secreted from the pituitary gland and many studies shows that it can be used in schizophrenia, post-traumatic stress disorder (PTSD) and anxiety, and improve social abilities among those with autism. One hypothesis shows that oxytocin dampens the activity of the brain's fear centre, the amygdala, thereby easing stress and anxiety [27].
6. Thyroid hormone: it can be used as an augmenting agent in the treatment of treatment resistant depression and as a mood stabilising agent in rapid cycling bipolar disorder[28].
7. Melatonin: Melatonin is the secretory hormone from the pineal gland and it regulates circadian rhythm [29]. It can be used in insomnia, jet lag, and difficulties associated with shift work and both in seasonal and non-seasonaldepression [30]. Agomelatine is a melatonergic agonist which acts both on melatonin-1 and melatonin-2 receptor and it is used as an antidepressant [31].
8. Adrenal axis hormone: due to the release of CRH,there is hypersecretion of cortisol and hypercortisolism is one of the causes of depression. Antiglucocorticoid drugs have been studied in depressed patients: including cortisol synthesis inhibitors such as metyrapone, aminoglutethimide, and ketoconazole. Mifepristone (RU486), the glucocorticoid receptor antagonist has also been examined mostly in psychotic depression [32, 33].

CONCLUSION

As the nervous system and endocrine system maintain the homeostasis of our body,knowledge of both this system is important in treating a psychiatric disorder. Psychoneuroendocrinology is a new branch in psychiatry and more research on hormonal treatment in psychiatric disorder is required to further elucidate and clarify the precise neurobiological mechanism in such disorder. This will not only help us to find out the aetiology but also to treat psychiatric illness.

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Pharmacotherapy of Sexual Dysfunctions

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ABSTRACT: *The essential feature of sexual dysfunctions is an inability to respond to sexual stimulation or the experience of pain during the pleasure. Sexual dysfunctions are diagnosed only when they are a major part of clinical picture. It can be lifelong or acquired, generalised or situational and results from psychological factors, physiological factors, combined factors and numerous stressors. Sexual dysfunctions are frequently associated with other mental disorders. If the dysfunction is largely attributable to an underlying psychiatric disorder, only the underlying disorder should be diagnosed. Pharmacotherapy is not the ultimate answer for them. Combination treatment is a better option.*

Keywords:*Desire disorder, Arousal disorder, Orgasm disorder, Androgens*

INTRODUCTION

Humankind is in constant search for that "magical" potion with sexual properties for ages. Most outrageous claims have been made with most unlikely substances. Oysters, raw meat, tiger penis, snake soup, rhinoceros horn, deer antler marrow, ginseng, vanilla bean are some of the examples which are included in the menu with the claim of improving sexual functioning. Some extreme substances like Spanish fly (Cantharides) which is a poison,causing urinary tract irritation and may even lead to death have also been tried. The whole concept of aphrodisiac has been a suspect; even traditional medicine has not played a meaningful role.

Chemicals favouring sexual functionality do exist. Basically, these are the drugs that were developed for other medical purposes and their usefulness in sexual functionality was incidental. Clarity regarding the mechanism of action of these drugs in sexual functioning is not very clear. Dose-response in some drugs in terms of sexual functioning is paradoxical. There is a gradual accumulation of evidence that medicine can improve sexual functioning has attracted a lot of scientific research. Like other medicines, drugs which are claimed to be sexually effective, may or may not be useful in all, and even so to various degrees. These drugs are valuable adjuncts to sex therapy, but cannot replace sex therapy. However, in some cases, they will be the difference between a successfulor failed therapy and also with regard to the duration of therapy. [1]

Sexual Response Cycle

Without briefing about the sexual response cycle, treatment of sexual dysfunction would be incomplete to discuss. Robinson and Helen Kaplan proposed the DEOR model. Here 'D' stands for the 'Desire phase' which is influenced by sexual drive and fantasies and is the conscious desire to have sex.[2] This phase depends on the psychological makeup and the biological characteristics of the individual. The 'Excitation phase' begins with psychological and/or physiological stimulation and leads to penile tumescence and enlargement of testes in males. In females, it is characterized by vaginal lubrication, hard clitoris, the formation of an orgasmic platform (vagina becomes barrel-shaped with a constriction in outer 1/3rd), thickening of labia minora and an increase in breast size. Nipple erection occurs in both sexes during this phase[3]. There is an increase in heart rate, respiratory rate and blood pressure. In the 'Orgasmic phase', sexual pleasure peaks and there is a rhythmic contraction of perineal muscles and reproductive organs; inevitable ejaculation triggers orgasm in males whereas involuntary contractions of the uterus and lower third of vagina is seen in females.

Resolution phase is characterized by disengorgement of blood from the genital organs, along with a general feeling of well-being and muscular relaxation rapidly following orgasm. However, if orgasm does not occur, resolution may take upto 6 hours and may be associated with irritability.

Human sexual response cycle is mediated by Neurotransmitters like serotonin, acetylcholine, nitric oxide and hormones like testosterone acting in specific brain structures like hypothalamus, limbic system and cortex.[3]

Aetiology of Sexual Dysfunction

Aetiology of sexual dysfunction is multifactorial. Psychological causes include both sociocultural and individual factors. Sociocultural factors include attitude, cultural norms, religious beliefs, incest and sexual abuse. Individual factors include performance anxiety, guilt, communication difficulty and anger. Psychiatric disorders and psychotropic medications have a significant impact on sexual functioning. Psychosomatic disorders like diabetes mellitus, hypertension, cardiovascular diseases, neurological disorders and their treatment also cause impairment in sexual function. Recent studies have suggested impairment in penile blood flow causing erectile dysfunction, predicts major cardiovascular adverse events in patients free of clinical atherosclerosis.[4]

Classification of Sexual Disorders

Detailed classification is beyond the scope of this article, yet it is necessary to understand the treatment of sexual disorders.DSM-5 classifies sexual disorders into:

- Male Hypoactive Sexual Desire Disorder
- Female Sexual Interest/ Arousal Disorder
- Premature (Early) Ejaculation
- Delayed Ejaculation
- Erectile Disorder
- Female Orgasmic Disorder
- Genito-Pelvic Pain/ Penetration Disorder[5]

Treatment of Sexual Disorders

Male hypoactive sexual desire disorders

DSM-5 describes male hypoactive sexual desire disorder as persistently deficient or absent sexual thoughts or fantasies and desire for sexual activity. The age and socio-cultural factors are taken into consideration. The symptoms are present for a minimum period of 6 months and cause significant distress.[6]

Treatment

Psychiatric comorbidities like depression, anxiety and psychosis are the main concern with respect to pharmacological treatment of male hypoactive sexual desire disorders. Successful treatment of depression has been well-established to reverse its effect on sexual desire. Antidepressants themselves have been associated with side effects like anorgasmia and to certain extent low desire. This can be minimized by use of certain antidepressants like Bupropion and Nefazodone.Duloxetine has been shown to have lesser side effects than selective serotonin reuptake inhibitors by some studies.

It is a well-known fact that a psychotic disorder like schizophrenia is associated with low libido. Successful treatment with antipsychotics may help to restore libido, though they may have their own sexual side effects.Evidence suggests that prolactin sparing antipsychotics have a lower incidence of sexual dysfunction. Dopamine agonists like Cabergoline and Bromocriptine help to lessen the side effect burden of antipsychotics.

Treatment with testosterone is beneficial as hypogonadism and low testosterone levels contribute to low desire. It is less clear that treatment with testosterone in eugonadal men is beneficial. [6]

Female Sexual Interest/Arousal Disorder

Significantly reduced or absence of sexual interest or arousal which may include any 3 of the following: (1) Absent/Reduced interest, (2) Absent/reduced erotic thoughts, (3) Absent/reduced initiation of sexual activity or no response to partner's attempt to initiate the same, (4) Absent/Reduced sexual excitement in 75-

100% encounters, (5) Absent/reduced response to erotic cues, (6) Absent /reduced genital or non-genital sensations during sexual activity in 75-100% encounters.[5]

Symptoms mentioned above must be present for a minimum period of 6 months and cause clinically significant distress.

Specify- Lifelong v/s Acquired; Generalized v/s Situational; Mild, moderate or severe**.**

Treatment

Esterified estrogen: Esterified estrogen has shown to improve sexual interest as well as genital sensitivity according to some published reports. [7]

Promising results in improving sexual desire as well as genital sensitivity were also seen with Methyl testosterone. [8]

Improvement in sexual desire, as well as frequency of satisfying sexual activity, has been shown with 300microgram/day of transdermal testosterone. [9]

Flibanserin is a dynamic compound that affects serotonin dopamine and norepinephrine with affinity to 5HT1A,5HT2A,5HT2B,5HT2C and D4 receptors. It is the first US FDA approved molecule to treat desire and arousal disorders in females. In animal studies, it was found to decrease serotonin and increase dopamine and norepinephrine in the prefrontal cortex. Trials on flibanserin in depressed individuals, despite its promise in animal studies,did not show good results, but sexual functioning improved in women who had a low sexual desire with depression. Its effects on neurotransmitters in limbic system contributed to the improvement in sexual functioning. It is a potential non-hormonal treatment option for desire disorders in a female in doses of 50-100mg once or in two divided doses. [10]

Bupropion, a norepinephrine dopamine reuptake inhibitor has shown promising results in antidepressant-induced desire disorders. Off-label use of bupropion in desire disorders has been reported. [11] Buspirone;an Azapirone has potential off label use in desire disorder due to its favourable profile in terms of sexual functioning. [12]

In females with desire disorders showing minimal benefits, off-label use of PDE 5 inhibitors has been studied. [13]

Premature (Early) Ejaculation

According to DSM-IV premature ejaculation is defined as "persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it." Several pharmacotherapies are used for the treatment of premature ejaculation, which includes topical local anaesthetics (LA), selective serotonin reuptake inhibitors (SSRIs), tramadol, phosphodiesterase type 5 (PDE5) inhibitors, and alpha-adrenergic blockers. [14]

Off-label treatment with daily SSRIs

Selective serotonin reuptake inhibitors like paroxetine 10-40mg, fluoxetine 20-40mg, and sertraline have been tried to delay ejaculation with significant success in terms of effectiveness, safety and tolerability. Temporary effect of the ejaculatory delay is seen in 5-10 days, but sustained and full therapeutic effect will be achieved in two to three weeks. Adverse effects occur in the first few weeks of treatment, but are rare. These include yawning, nausea, diarrhoea and sedation. Hypoactive desire and erectile dysfunctionare other significant adverse effects of Paroxetine, which arerarely reported. On-demand treatment with SSRIs 4-6 hours prior to intercourse is moderately efficacious but less effective when compared to daily use. [15, 16, 17]

Off-label use of Dapoxetine

Dapoxetine, a selective serotonin reuptake inhibitor is the first compound developed specifically for the treatment of premature ejaculation. It has a half-life of 1.4hrs-2hrs and elimination half-life of 19hrs, and a rapid decline in plasma level – 5% of C_{max} level reached in 24hrs.Used in doses of 30-60mg one to two hours before intercourse, there is 2.5-3.0 fold increase in intravaginal ejaculatory latency time from the first dose itself.Abrupt withdrawal does not cause any symptoms. [18]

PDE5 Inhibitors

PDE5 inhibitors are mostly used in erectile dysfunction and their use in premature ejaculation without erectile dysfunction is speculative and is only based on cGMP/nitric oxide signal transduction mechanism.[19] Several reports on the use of PDE5 inhibitors either alone or in combination with SSRIs are available.

Other drugs used in premature ejaculation

Tramadol has a nociceptive and anaesthetic effectand is also a weak reuptake inhibitor of GABA, serotonin and norepinephrine. Studies suggest on-demand use of tramadol increases intravaginal ejaculatory latency time by 2.49 times. [20]

Off-label use of alpha 1 adrenergic antagonist like alfuzosin, terazosin and silodosin has shown a three-foldincrease in intravaginal ejaculatory latency time. [21]

Delayed ejaculation

Off the male sexual dysfunction, delayed ejaculation is the least common, least understood and least studied type.DSM-5 defines delayed ejaculation as a marked delay of ejaculation; infrequent or absence of ejaculation. More objective definition of delayed ejaculation is an absence of ejaculation even after 20-25 minutes of intravaginal ejaculatory latency time associated with adverse consequences. It can be lifelong or acquired, and may be situational or general. Loss of erection, exhaustion, irritation or request by the partner is usually the reasons for stopping intercourse.

Treatment

There are no approved drugs for the treatment of delayed ejaculation by regulatory agencies. Pseudoephedrine, an alpha 1 adrenoceptor agonist, 120mg taken one to two hours prior to intercourse has been tried with minimal success while, noradrenaline reuptake inhibitors like Reboxetine, 4-8mg given one to two hours prior to intercourse have shown mild to moderate efficacy. There are anecdotal reports suggesting the efficacy of Cyproheptadine,

2-16mg, a central serotonin antagonist taken either on demand or on a regular basis in the treatment of delayed ejaculation. There are some reports suggesting the efficacy of Amantadine, 100-200mg given either on demand or regular basis also being effective in the treatment of delayed ejaculation. Drugs like Bromocriptine, Cabergoline, bupropion, and buspirone is seen to be useful to some extent in the treatment of delayed ejaculation according to some reports. A recent case report suggestsadministration of oxytocin intranasal spray, intracoital to be effective. [22, 23, 24]

ERECTILE DISORDER

DSM-5 defines erectile disorder as marked difficulty in obtaining an erection during sexual activity or maintaining an erection during sexual activity or marked decrease in erectile rigidity.

Treatment

PDE-5 inhibitors are the first line drugs for the treatment of erectile dysfunction as suggested by all published guidelines. Phosphodiesterase (PDE)-5 inhibitors (Sildenafil,Tadalafil, Vardenafil) act on the nitric oxide mechanism.PDE-5 inhibitors block the enzyme Phosphodiesterase (PDE) – 5, which hydrolyses cGMP (cyclic guanosine monophosphate) in the corpora cavernosa. This causes the accumulation of cGMP, which leads to smooth muscle relaxation and increased arterial blood flow, compressing the subtunical venous plexus and increases penile erection. Sexual stimulation is still required to facilitate erection.[25, 26]

Sildenafil (launched in 1998) is rapidly absorbed after oral administration. However, fatty food causesprolonged absorption, hence reducing the efficacy. Efficacy is measured based on the sufficiency of the erection for vaginal penetration; peak plasma concentrations are reached about an hour later. The terminal half-life is 3-5 hrs. Sildenafil should be given with extra care in elderly, severe renal insufficiency patients and in those suffering from a hepatic disease as clearance is reduced in them. It has been shown to be effective irrespective of the cause of the erectile dysfunction

(ED). Individuals with ED due to psychogenic causes, diabetes mellitus, post-prostate surgery and spinal cord injury have all shown improvement. Patients have been benefitted irrespective of age and baseline severity of symptoms. The magnitude of the benefit however varies. Sildenafil improves not only the strength and duration of erection, but also the number of times that the erection is satisfactory. It is available in doses of 25, 50 and 100 mg, though the recommended starting dose is 50mg, which can be titrated depending on the patient's response. Efficacy can be maintained for upto 12 hours.There are reports of patients tolerating doses upto 1300 mg of sildenafil with minimal side effects. [27]

Common side effects include headache (12.8%), flushing (10.4%) and dyspepsia (4.6%), while nasal congestion, dizziness and abnormal vision may be seen in 1-2% of cases.These are usually mild and transient, lasting a few minutes to a few hours after drug administration. [28]

Tadalafil has a longer duration of action (36 hours), but begins acting 30 minutes after administration. [29] Its absorption is not affected by food. 10 mg and 20 mg doses are used for on-demand treatment of ED; though the recommended starting dosage is 10 mg. Tadalafil has been found to be useful in patients who have been difficult to treat. Adverse effects include headache (14.5%), dyspepsia (12.3 %), back pain and myalgia (5 to 7 %), flushing and nasal congestion (~4 %), and dizziness. The European Medicines Agency (EMA) has approved Tadalafil, 2.5 and 5 mg for daily treatment of ED since 2007.The recommended dose is 5 mg taken at almost the same time of the day. The long-term effects of chronic Tadalafil therapy have been shown to be an improvement in endothelial function which is sustained even after its discontinuation. [30, 31]

Vardenafil is effective 30 min after administration but, absorption is reduced by fatty food. The available doses are 5, 10 and 20 mg tablets, with recommended starting dose being 10 mg for on-demand treatment of ED and titrated as per the response. Side effects include headache (16%), flushing (12%), nasal congestion

(10%), dyspepsia (4%), and dizziness and abnormal vision (2%). Orodispersible tablets are available in a few countries.It was demonstrated that there was no increase in myocardial infarction rates in patients receiving sildenafil, tadalafil, and vardenafil compared to expected rates in age-matched male populations. PDE-5 inhibitors are contraindicated in patients on concurrent organic nitrates as they both act on the same mechanism and they may potentiate the hypotensive action of such drugs. Nitrates should be avoided for a period of 24 hours if the person is on sildenafil and vardenafil and 48 hours in case of tadalafil, if the person develops angina. Other drugs should be used during this time period. It should be used with caution in persons with anatomical deformities of the penis, and in patients at risk for priapism (e.g. patients with sickle cell anaemia). PDE-5 inhibitors are relatively safe in combination with antihypertensives. Although, a combined use of PDE-5 inhibitors and α-blockers may cause hypotension. On concurrent use with CYP3A4 inhibitors like ketoconazole, erythromycin, increased levels of PDE-5 inhibitors might be seen in the blood, whereas with CYP3A4 inducers like rifampicin, phenytoin, carbamazepine higher doses of PDE-5 inhibitors may be required. [30]

Intracavernous injections: Alprostadil (dose of 5-40 μg), was the first and only drug approved by European Medicines Agency (EMA) for use as an intracavernous injection in the treatment of ED. The onset of action is within 5 to 15 minutes, though the duration of action depends on the dosage. Even with an efficacy rate of more than 70% in ED population, compliance has been found to be poor. Complications include pain, priapism, prolonged erections and fibrosis. Papaverine (40 to 80 mg) and phentolamine may be used in combination to achieve better results. Prostaglandin EI is also an effective agent. [32, 33]

FEMALE ORGASMIC DISORDER[34, 35]

Marked delay, infrequent, reduced intensity or absence of orgasm.In terms of pharmacological interventions, it is valuable to consider two different etiologies of female orgasmic disorders;

whether it is due to organic conditions or substance induced. Use of Sildenafil in the dose range of 25-50mg has shown mixed results in nonorganic female orgasmic disorders. Nutritional supplements have been proposed to improve orgasm, L-arginine, Gingko biloba, damiana leaf, vitamins and minerals have been tried with no significant results

Androgen replacement therapies like testosterone, oral testosterone with estrogen, DHEA and methyltestosterone have been studied, but studies also included women with desire disorder, so it is difficult to interpret results. Orgasmic difficulty secondary to hormonal imbalance may benefit with androgen replacement therapy, but hormonal therapies should be considered cautiously. Tibolone- a synthetic steroid having estrogenic, androgenic, progestagenic property has shown to improve orgasmic dysfunction. [36]

In case of medication-induced female orgasmic dysfunction, clinicians consider reducing in the dosage, changing the medication, waiting for spontaneous remission over time, brief drug holidays and adding an antidote.

Adding dopaminergic substances like amantadine or phosphodiesterase-5 inhibitors are the most common choices in treating SSRI induced orgasmic dysfunction. Studied suggest that more than 50% of people developed tolerance to SSRIs and sexual side effects reduced in a span of six months.In some cases switching to a different SSRI was a better option. Agomelatine, amineptine, bupropion, moclobemide, mirtazapine has lesser orgasmic dysfunction. [37]

SEXUAL PAIN DISORDERS

Persistence of any of the following symptoms: (1)Difficulty in vaginal penetration (2)Significant pain during vaginal intercourse/ penetration (3) Fear/anxiety or pain in anticipation during vaginal penetration 4) Significant contraction of pelvic floor muscles during vaginal penetration attempt.

The symptoms are present for a minimum period of 6 months and cause significant distress.

Treatment

Topical medications with anaesthetic property have been recommended for superficial dyspareunia and vaginismus. Topical lidocaine has shown promising results. Botulinum toxin which is a neurotoxin has been used for the treatment of provoked vestibulodynia and vaginismus with some promising results. Tricyclic antidepressants and anticonvulsants like gabapentin have shown some improvement in vaginismus. [38]

CONCLUSION

Drugs are not the ultimate answer for sexual dysfunction. Ignorance, cultural taboos, poor communication skills, myths and misconceptions all can lead to sexual dysfunction. Education, improving communication skills contribute significantly in treatment success of sexual dysfunction. Redefinition of success and removal of performance pressure does a world of good for helping people with sexual dysfunction.

Failure of pharmacotherapy for sexual dysfunction happens due to various reasons, which includes comorbid medical conditions like diabetes, hypertensionand psychiatric illness like anxiety, depression and psychosis. Until medical and psychological conditions are controlled or stable, sexual functioning will not improve. Drugs used to control medical or psychiatric comorbidities themselves can cause sexual dysfunction; also drug drug interactions with medications used to treat sexual dysfunctions also can lead to failure of pharmacotherapy in sexual dysfunction.

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Current Treatment Strategies and Future Directions for Premature Ejaculation

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ABSTRACT: *Premature ejaculation (PE) is one of the commonest complaints about the men seeking treatment for sexual problems. Lack of a standardized definition of PE and the absence of an objective measure of the ejaculation time hampered a truly scientific approach to investigate the efficacy of drugs in delaying ejaculation. Waldinger et al. introduced in 1994 the intravaginal ejaculation latency time (IELT) as a standardized measure of the ejaculation time and also introduced a new classification to better study and treat PE. A variety of pharmacological and nonpharmacological treatment options are available now to successfully treat patients. Although, some form of treatment existed for management of PE, it is the introduction of SSRIs in 1990, the treatment of PE has been revolutionized. Among pharmacological treatment, Selective Serotonin Reuptake Inhibitors (SSRI) is the first line method of treatment. Dapoxetine and other SSRIs are used and are successful in improving the clinical situation. Both the strategies of daily treatment and on-demand use have been utilized to cater the different subtypes and needs of the clients. Other pharmacological treatment used for the treatment of PE includes tramadol and topical anaesthetics. Nonpharmacological treatments of PE are used for quite some time and can be very effective if used in properly selected patients and are applied correctly. This article summarises current treatment methods and future possible strategies to manage PE.*

Key words: *Premature ejaculation, Selective Serotonin Reuptake Inhibitors, Dapoxetine, intravaginal ejaculation latency time.*

INTRODUCTION

Premature Ejaculation (PE) is one of the commonest sexual problems.[1] Despite being recognized in medical literature for a long time, its epidemiology was relatively unknown. This was due to a combination of various factors such as the use of different definitions to define the problem and sensitive nature of the problem which led to variable reporting of the problem. Over the years, standardization of diagnostic criteria has enabled us to have a greater insight into the magnitude of the problem as well as the issues related to its causation and treatment. The exact aetiology remains unknown as till date no biological factor has been consistently shown to be the causative factor in a majority of PE cases. However, psychological, behavioural and physical components are likely to be associated in men presenting with premature ejaculation. Premature Ejaculation leads to loss of sexual confidence and erosion of quality of sex life. Interpersonal difficulties and adverse effects on quality of life have been consistently reported by men having premature ejaculation.

There are various treatment options available to treat PE but they can be basically classified into Pharmacological and Psychological methods. In this article, we will be dealing briefly with each of the treatment options and be reviewing the available evidence regarding its efficacy. The purpose is to guide the reader in choosing the best suitable strategy to achieve maximum benefit for the patient.

PHARMACOLOGICAL THERAPY

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) AND TRICYCLIC ANTIDEPRESSANTS (TCAs)

Waldinger et al proposed that premature ejaculation could be due to hyposensitivity of 5HT2C and/or hypersensitivity of 5HT1A receptors.[2]Premature ejaculation can be treated with on-demand use or daily dosing regimen of SSRIs and TCAs. We will be discussing the evidence-based results of commonly prescribed drugs of the above class.

Dapoxetine

It is approved for use in many countries worldwide and is best suited for "on demand" uses due to its rapid onset and short half-life. Yue et al conducted a meta-analysis of Randomized Controlled Trials (RCTs) and found that Dapoxetine was effective in the treatment of men with PE and could prolong IELT significantly regardless of the dose 30 or 60 mg. Patients receiving Dapoxetine reported improved outcomes such as increase in Intravaginal ejaculatory latency time (IELT), increased ejaculatory control, decreased distress, and increased satisfaction. It was consistently more effective than placebo, regardless of the profile of a patient. Dapoxetine 60 mg showed more improvement than Dapoxetine 30 mg on-demand. So, if the effects are not seen with 30 mg on-demand, the dose can safely be increased to 60 mg on-demand or once daily.[3] Dapoxetine was found to be effective both in men with lifelong and acquired PE. Side effects are uncommon and include nausea, headache and dizziness. A study was conducted on Asia-Pacific men to evaluate the efficacy and safety of dapoxetine 30 and 60 mg. In this study, flexible dosing of Dapoxetine (30 and 60 mg) appeared effective in the treatment of PE. It was well tolerated and adverse effects were generally mild.[4]Contraindications include severe heart ailments, and is not recommended in severe hepatic and renal impairment.

Other SSRIs and TCAs

Twosingle-blind placebo-controlled crossover studiesreported that ejaculatory control achieved with Paroxetine as needed is significantly better if patients are initially treated with the drug daily.[5]A daily dose of 10-40 mg/day is usually effective in delaying ejaculation.[6] On demand administration was effective but had less effect than that of daily treatment. However, a randomized, double-blind fixed-dose study with 20mg Paroxetine found no clinical relevant ejaculation delay in with an IELT of less than 1 minute.[7] Clomipramine is also effective as an off-label use in the dosage of 12.5-50mg/day.[6] On-demand treatment with 25mg/day also

achieved clinical relevant delay with a mildly annoying side effect of nausea.[7]

Sertraline also delays ejaculation in the daily dosage of 50-200mg/day.[6]A single-blind placebo-controlled crossover study conducted by Mcmahon in 1998 with 50mg of Sertraline resulted in significantly greater ejaculatory latency time.[8] A later study also confirmed this finding by studying the effects of as needed use of Sertraline (50/100mg) after an initial daily dosing of 50mg/day and found it to be beneficial.[9]A Double-Blind Placebo-Controlled Study conducted by Kara et al found Fluoxetine to be effective in the dosage of 20-40 mg/day.[10]

The decision to choose between on demand and daily dosing may depend upon the clinical profile of the patient and sometimes on the requirement of the patient. However, it can be conclusively being said that SSRIs and TCAs have proven to be effective in the treatment of PE and remain the most commonly used drugs to treat PE.

Tramadol

Tramadol has also been tried in the treatment of premature ejaculation although the mechanism is not clearly understood. It is thought to act through inhibition of serotonin and noradrenaline reuptake.[11] Safarinejad et al conducted a double-blind, placebo-controlled, fixed-dose, randomized trial to study the effect of tramadol on PE. A sample of 64 men was taken who were randomly assigned to receive 50 mg tramadol 2 hours before planned sexual activity, for 8 weeks. Significant results were seen in terms of improvement of IELT and satisfaction.[12]Bar or et al studied the efficacy of two doses (62 and 89 mg) of tramadol given 2–8 hours before engaging in intercourse in a double-blind, placebo-controlled multicenter study. Significant improvement was seen in both doses although safety profile of 62 mg was better.[13] Easa and El-Shazly also studied the efficacy and safety of tramadol in PE and found that using low doses (25 and 50 mg) improves IELT.[14] Tramadol although appears to be effective, it

should be tried after other modalities have failed due to addiction risk and side-effects.

TOPICAL LOCAL ANESTHETICS

Men with penile hypersensitivity are more prone for PE.[15] This may be due to the spinal reflex arc for ejaculation.[16] Also, men with PE might have a greater cortical representation from glans penis.[17]

Busato and Galindo reported a significant increase in IELT after using a mixture of lidocaine-prilocaine.[18] These results were further replicated in a study using a eutectic mixture of lidocaine and prilocaine applied 5 minutes before intercourse.It was well tolerated in comparison to other topical anaesthetic agents which cause penile hypo-anaesthesia and possibility of transvaginal absorption, resulting in reduced satisfaction.[19] The efficacy of prilocaine-lidocaine mixture has been well established and offers a promising solutionfor PE.

PSYCHOLOGICAL AND OTHER APPROACHES

Psychological interventions can help men with PE by resolving sexual myths and beliefs, reducing anxiety and increasing self-confidence. Couple therapies might help in resolving any interpersonal or relationship issues precipitating the problem. There have not been many studies evaluating the efficacy of these measures; the ones that have been conducted have not been conclusive enough due to a variety of limitations.

The most commonly used approach is are Behaviour Therapy (BT) which includes squeeze or stop-start technique. There have been conflicting results regarding their efficacy as compared to the pharmacological approaches.[20] More research is needed to conclusively establish the efficacy of psychological measures however it should be offered to the patients as they definitely help in bettering sexual skills, address relationship issues and develop self-confidence.

The other methods that have been experimented with but are not routinely used include use of Anti-Oxytocin drugs that have

been used in rats to inhibit sexual behaviour but results were not replicated in the human study.[21,22]Ablation and modulation of dorsal penile nerve has also been tried which has resulted in an increase of IELT but it is an invasive procedure and safety profile needs to be assessed before it can be used.[23]

CONCLUSION

Sexual complaint especially PE among men has been always been a matter of grave concern and distress. Due to the sensitive nature of the problem, many shy away from seeking treatment. However, with increasing awareness and better research, the treatment of PE has been evolving. Over the years, many different modalities have been tried for treatment of PE. The ever-improving understanding of neurobiology has been the main reason behind this. Although each of the treatment approaches appears to be promising and offering positive results, SSRIs remain the preferred choice due to robust and well-established evidence. A combination of pharmacotherapy and psychological therapy may provide a holistic treatment to many. Newer and novel methods which have been experimented upon may give us a variety of options in the future but they need further research to establish their efficacy.

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Newer Agents in the Management of Anxiety

Prosenjit Ghosh

ABSTRACT: *Anxiety disorders are very much prevalent all over the world and affect all sections of the society across all age groups. Most of the agents available for the treatment of anxiety disorders have sedating properties. So, there is a need for newer anti-anxiety drugs with better efficacy and fewer side effects. APubMed search was done with the keyword Newer Anxiolytics in between June 15th and June 20th 2018 with the inclusion criteria of PHASE I,II and III clinical trials and Benzodiazepine group of drugs. The newer anxiolytics in various stages of development are discussed.*

Keywords*: Anxiety Disorders, Newer Anxiolytics, Unwanted side effects, Discontinuation syndrome.*

INTRODUCTION

Anxiety usually means excessive worry or fear about something. At times anxiety may be normal, as for example, when a person is confronted with a real-life threat it is quite normal to feel anxious and either fight or flight. But most often anxiety is maladaptive and causes significant distress.

Data collected from the Anxiety and Depression Association of America (ADAA) suggests that more than 40 million adults are affected by anxiety. It is approximately 18% of the United States population Among the 40 million adults who are affected by anxiety, it is estimated that approximately: 19 million suffer from specific phobias; 15 million suffer from social anxiety disorder; 7 million suffer from generalized anxiety disorder (GAD) and 7.7 million suffer from post-traumatic stress disorder; and 2.2 million suffer from obsessive-compulsive disorder (OCD).

ERA OF TRANQUILISERS

The discovery that ushered in the era of tranquillizers and other anxiety medications was Frank Berger's discovery of meprobamate[1]. Frank Berger, M.D, was a microbiologist of Czech origin working in the United Kingdom during World War II. Shortly after Florey and colleagues' purified penicillin, Berger was looking for a substance that would preserve penicillin by inhibiting penicillinase-producing bacteria. He and his co-workers synthesized a few hundred carbamates and Meprobamate seemed to be "the best one." Meprobamate became extremely popular during the 1950s and opened the market to other "tranquillizing" drugs (e.g., Chlordiazepoxide). Meprobamate relieved anxiety, relaxed muscles, and induced mild euphoria and "inner peace." Berger is an example of an alert observer and an astute researcher from the golden era of serendipity in psychopharmacology research, along with R. Kuhn, J. Delay, P. Deniker, and others.

It seems that psychopharmacology may be well on its way toward the goal of developing new anxiolytic drug(s) that are fast acting and free from the unwanted effects associated with the traditional benzodiazepines. Depending upon the rational targeting of those receptors which are linked with the neurobiology of anxiety several specific candidates exist. Some of the partial agonists at the benzodiazepine receptor, such as alpidem, abecarnil, and bretazenil, have highly promising preclinical profiles. They also have some useful preliminary results in clinical testing of anxiety disorder subjects. Neurosteroids are another set of pharmacologic agents that target the benzodiazepine receptor. They also have a preclinical anxiolytic profile, and now need to be tested in clinical populations.Various serotonin (5HT) receptor subtypes are also an active area of current research for novel anxiolytic agents. 5HT3 receptor antagonists have an anxiolytic profile, but results are preliminary and need more validation. One novel idea is to develop new drugs that act at 5HT1A, 5HT2A, or 5HT2C receptors. It has even been proposed that targeting of both 5HT2A and 5HT1A receptors at the same time may result in robust anxiolytic agents that will have a more

immediate onset of action than currently available 5HT1A receptor acting drugs. Neuropeptide receptor agonists and antagonists with anxiolytic properties may be one of the most striking new classes of potential anxiolytic drugs, but it still requires considerably more systematic clinical testing. Nevertheless, preclinical studies, as well as early clinical studies, suggest that at least three neuropeptide receptors are potential targets for novel anxiolytic agents: antagonists for CCK-B receptors, antagonists for CRF receptors and agonists for neuropeptide Y receptors[2]. Rational development of new drugs based upon targeting receptors for those neurotransmitters that regulate the neurobiology of anxiety promises to bring forth a number of exciting therapeutic agents for the treatment of anxiety disorders in the future.

There are lots of anxiolytics in the development phase, including Tonmya (low-dose cyclobenzaprine), SRX246, Aloradine, NBTX-001, and JNJ-42165279. Most of these agents exhibit unique mechanisms of action when compared to current-market anxiolytics. Examples of novel mechanisms of anxiolytic action include vasopressin receptor modulation (by SRX246); NMDA receptor modulation (by NBTX-001); and FAAH inhibition (by JNJ-42165279).

The greater the total number of anxiolytics with novel mechanisms of action (that are safe and effective enough to survive clinical trials) – the better it will be. At present, the treatments for anxiety include serotonin modulators (SSRIs, SNRIs, TCAs etc.) and GABAergic modulators (e.g. benzodiazepines). These have some common problems with these interventions, including unwanted side effects (sexual dysfunction, weight gain, etc.), long-term effects (benzodiazepines are linked to dementia), and discontinuation symptoms (most have harsh withdrawal symptoms). Off-label use for anxiety may include antihypertensive medications (i.e. beta blockers for anxiety – including clonidine or hydroxyzine, ion channel modulators (e.g. gabapentin for anxiety), or psychostimulants (e.g. Adderall for anxiety).Even then persons with treatment-resistant or refractory anxiety disorders may not

respond at all to any of the conventional interventions – and desperately needs new therapies.

NOVEL AGENTS

AVN 101:- Mechanism:Serotonin receptor modulator. Status: Phase II clinical trials

AVN-101[3] is a substance undergoing trials by Avineuro Pharmaceuticals as a treatment for anxiety disorders – and Alzheimer's disease. AVN-101 is intended to be a safe, orally bioavailable, multi-target medication aimed to treat generalized anxiety disorder– and CNS diseases associated with cognitive dysfunction. It is believed that the serotonergic action of AVN-101 will enable a therapeutic anxiolytic effect while simultaneously reversing cognitive deficits.

Investigators speculate that AVN-101 might also combat depressive symptoms and as a neuroprotective agent by counteracting neurodegeneration. It is structurally similar to the drug Latrepirdine, an antihistamine medication used primarily in Russia with neuroprotective properties. Pharmacodynamically, AVN-101 shows the highest affinity for the 5-HT7 receptor, but also interacts with other serotonergic receptors, including 5-HT6; 5-HT2A; and 5-HT2C.Moreover, AVN-101 exhibits a high affinity for H1 histamine receptors and adrenergic receptors (2A; 2B; 2C). Preliminary results from the phase I clinical trials indicate that it is very well-tolerated at dosages up to 20 mg per day and that it possesses an excellent toxicology profile.

JNJ-42165279:- Mechanism: FAAH inhibitor. Status: Phase II clinical trials

JNJ-42165279[4] is a substance developed by Janssen Research & Development (a subsidiary of Johnson & Johnson) for the treatment of anxiety disorders. It functions as a selective inhibitor of the enzyme known as FAAH (fatty acid amide hydrolase). By Inhibiting FAAH enzymes it may generate rapid anxiolytic (anti-anxiety) effects by inducing long-term depression (LTD) at prefrontal

cortex-basolateral amygdala synapses which leads to the suppression of basolateral amygdala neurons. Till date, there were no serious adverse effects observed among users of JNJ-42165279 to date.

NBTX-001 (Xenon):- Mechanism: NMDA receptor antagonist. Status: Phase I clinical trials

NBTX-001 is a medication developed by Nobilis Therapeutics[5]. It contains the noble gas xenon as its primary active ingredient. Xenonis very safe and is devoid of psychotomimetic properties. It has been utilized extensively in imaging technology, and is occasionally administered some places for general anaesthesia. Preliminary data indicates that NBTX-001 is highly bioavailable and rapidly absorbed. After ingestion, the xenon atoms within NBTX-001 interact with aromatic amino-acid residues on NMDA receptors to exert a highly selective and controlled antagonist effect.

It appears to decrease excitatory neurotransmission via blockade of AMPA, nACh (Alpha-4-beta-2), 5-HT3, Ca2+ ATPase – yet increases inhibitory neurotransmission via stimulation of GlyR1 and TREK-1 potassium channels. It also decreases inflammation via downregulation of cytokines (TNF-alpha, IL-beta) and upregulates growth factors (e.g. BDNF and IGF), possibly yielding neurogenesis.

Aloradine (PH94B):-Mechanism: GABAA receptor modulator. Status: Phase III clinical trials

Aloradine (PH94B) is a synthetic pheromone. It is being developed by Pherin Pharmaceuticals[6] for the treatment of social anxiety disorder. It is formatted as a nasal spray to be administered on an "as-needed" basis to help reduce symptoms of social anxiety, primarily in women. Its effect on men is unknown. Pharmacodynamic evaluations of Aloradine indicate that it activates vomeronasal receptors and functions as a positive allosteric modulator of the GABAA receptor.

It is postulated that GABA-A receptor modulation is probably the mechanism of action by which Aloradine attenuates anxious

symptoms.It will be interesting to see if Aloradine treatment results in rapid tolerance onsetand/or severe withdrawal symptoms. If it is associated with rapid tolerance onset, then there is a chance that it may be abused. Moreover, withdrawal symptoms from Aloradine,as a result of GABA-A modulation, could be severe among frequent users

SRX246:-Mechanism: Vasopressin (1A) receptor antagonist. Status: Phase II (PTSD), Phase I (anxiety) clinical trials

SRX246 (also known as API-246)[7] is a molecule being developed by Azevan Pharmaceuticals for the treatment of PTSD and anxiety disorders. Preliminary proof suggests that SRX246 functions centrally as a highly-selective vasopressin-1A (V1A) receptor antagonist. It may prove efficacious in the treatment of PTSD, generalized anxiety disorder, and intermittent explosive disorders.

As of 2018, SRX246 is in Phase II clinical trials for PTSD, Phase I clinical trials for generalized anxiety, and Phase II clinical trials for adults with the intermittent explosive disorder. It is supposed that SRX246's action upon V1A receptors may counteract stress or anxiety-induced dysregulation of neural circuitry, particularly in the limbic system and cortex.It will be administered orally and is highly bioavailable. In animal model and neuroimaging research, SRX246 decreases aggression, anxiety, depression, fear, and stress. Thus far, it has been well-tolerated and successfully met all of its primary endpoints in clinical trials.

Tonmya (Cyclobenzaprine):-Mechanism: 5-HT2A; Alpha-1; H1 receptor modulator. Status: Phase III clinical trials

Tonmya is under development by Tonix Pharmaceuticals [8] for the treatment of PTSD (post-traumatic stress disorder). The medication is formatted as small, rapidly-disintegrating sublingual tablets that contain 5.6 mg cyclobenzaprine hydrochloride – and is intended to be administered once per day before bed. Tonmya is also formatted with a lower 2.8 mg dose that may prove helpful for insomnia, sleep disturbances, and other forms of anxiety.

The FDA considers Tonmya to be a "**breakthrough therapy**" such that its development may be fast-tracked through Phase III of clinical trials. In preliminary trials it significantly reduced CAP-5 scores, indicating that it decreased symptoms of PTSD. Additionally, it is safe, well-tolerated and enhances deep sleep among persons with military-related PTSD.

According to the developer, Tonmya targets and treats irregular neural activation implicated in sleep disturbances and nightmares. Researchers speculate that restoration of deep stage sleep (e.g. delta brain waves) might aid in natural recovery from severe trauma and reverse hyperarousal. The low-dose cyclobenzaprine in Tonmya: inhibits 5-HT2A receptor (to enhance sleep); inhibits Alpha-1 adrenergic receptor to counteract trauma-related nightmares, and inhibits H1 receptors to reverse stress-induced rapid eye movement (REM).

Travivo (Gepirone ER):-Mechanism: 5-HT1A selective partial agonist. Status: Phase II clinical trials

Travivo (or extended-release Gepirone) is being developed by Fabre-Kramer Pharmaceuticals for the treatment of depression and anxiety disorders – as well as comorbid anxiety and depression). As of January 2018, the medication is in a pre-registration phase for a major depressive disorder. Travivo is currently in Phase II clinical trials for the treatment of generalized anxiety disorder. As a 5-HT1A selective partial agonist of the Azapirone classification, Travivo is believed to reduce anxiety, enhance mood, and improve sexual function (possibly reversing sexual dysfunction associated with SSRIs).Though similar to the medication buspirone, it exerts a stronger effect upon 5-HT1A receptors and minimal interaction with D2 receptors.

Rexulti (Brexpiprazole):-Mechanism: 5-HT1A; D2; D3 partial agonist. Status: Phase II (PTSD) clinical trials

Rexulti (Brexpiprazole) is a medication that's been FDA[9] approved for the treatment of schizophrenia since 2015. It functions as a partial agonist at various receptor sites, including: 5-HT1A (serotonin); D2 (dopamine); and D3 (dopamine) receptors. It

is considered to be like an upgraded version of Aripiprazole with fewer severe side effects and greater therapeutic efficacy.

Though it functions primarily as an antipsychotic, it is believed to exhibit antidepressant, anxiolytic, and anti-aggressive properties. It is being investigated as a potential treatment for PTSD and agitation associated with Alzheimer's disease. Rexulti is currently in Phase II clinical trials for PTSD and Phase III clinical trials for Alzheimer's-related agitation.

Atrial Natriuretic Peptide:-

Preclinical evidence exists for the anxiolytic activity of the atrial natriuretic peptide[10]. It is released during lactate-induced panic attacks. The atrial natriuretic peptide is synthesized by atrial myocytes and released into the circulatory system. It is also found in the neurons of different brain regions in which specific atrial natriuretic peptide binding sites. The atrial natriuretic peptide is released in patients with panic disorder when panic attacks are experimentally induced. This endocrine response possibly serves as a humoural feedback signal to mute overshooting anxiety. Preclinical data have given further evidence for the anxiolytic activity of the atrial natriuretic peptide.

Andreas Ströhle et al studied the antipanic activity of Atrial Natriuretic Peptide in 10 patients with the induced panic disorder. The effects of 150 µg of atrial natriuretic peptide and placebo on panic attacks induced by cholecystokinin tetrapeptide (CCK-4) (25 µg) were studied in 10 panic disorder patients. The panicogenic activity of CCK-4 was measured with the Acute Panic Inventory. Pretreatment with atrial natriuretic peptide resulted in significantly lower Acute Panic Inventory scores than pretreatment with placebo.

CONCLUSION

Compared to benzodiazepine anxiolytics, novel anxiolytic drugs are supposed to have a comparable efficacy, but a better safety profile (e.g. abuse liability, rebound effects, cognitive impairment, sedative effects) [11]. Methodological issues concerning

the development of new anxiolytic drugs are numerous. Anxiety disorders, while being heterogeneous, often occur in combination with each other or with depression. Anxiety appears to be a ubiquitous component of most psychiatric disorders. Most of the studies on newer anxiolytics are double-blind, randomized, parallel-group studies. Usually, the reference drugs remain benzodiazepine anxiolytics. It would be interesting to develop trials comparing new anxiolytics with each other and with non-pharmacological therapeutics, to improve therapeutic strategies in anxiety disorders.

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Pharmacogenetics of Antidepressant Response

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ABSTRACT: *Personalized medicine, if ever it becomes a reality in Psychiatry is likely to tremendously reduce disability and disease burden. Depression, being one of the leading contributors of Global burden of disease needs attention in research aimed at rapid treatment response. Unfortunately, nearly half of the patients do not respond to first line therapy. Identification of predictors of antidepressant response is therefore a necessity. A varied range of such indicators exist in literature. Though not predictive in the literary sense, many of these parameters are early indicators of possible treatment response. Such measures include neuroendocrine, neuroradiological, electrophysiological and inflammatory mediator assays. As of today, although the science of genetics has made rapid progress, in the area of the utility of translating genetic information into useful clinical aids, the situation is far from satisfactory. However, significant data has been gleaned by researchers across the globe. The following is a brief summary of what we know of the utility of genetic data as predictive parameters of treatment response in depression.*

Keyword: *depression, antidepressants, gene, metabolism*

INTRODUCTION

Globally, depression is an illness with a profound clinical outcome. Aside from the fact that it is among the leading contributors of the global burden of disease, on a more individual level for the sufferer, it spells a period of unbearable pain that erodes the sufferer's social, occupational and emotional standing. About 30 to 50 per cent of sufferers of depression do not respond to initial treatment with available antidepressants, thereby necessitating the

use of second or third or subsequent medications, chosen mostly on a trial and error basis. A reasonably good fraction of these patients will respond to subsequent medications. Any evidence, if available, that can predict possible response to a chosen therapeutic agent will go a long way in guiding a clinician in the choice of molecules for first-line depression management.

The problems with the results of genetic studies are twofold. Results so far indicate that all observed gene variations (SNPs/Allele types) do not reach the putative 50% of variance explained by genetic factors in antidepressant response. It is noted that in net logistical models, only about 36% of the variance can be attributed to genetic factors in assessing the predictability of treatment response [1]. In addition, false positive findings in genetic studies can be as high as 96%. The evidence of the predictive value of genetic variations is therefore perpetually open to debate.

Table 1(modified from Cynthia Reyes Arron et al, 2016) is a depiction of genes that have aroused the interest of researchers in the quest to find a reliable genetic predictor of treatment outcome in depression.

Mechanism / Related Physiology	**Genes of Interest**
▪ Pharmacokinetics	▪ Cytochrome P450; ABCB1 gene
▪ Pharmacodynamics	▪ Monoamine metabolic enzymes; Tryptophan hydroxylase; Catechol-O-methyl transferase; Monoamine oxidase A
▪ Monoamine transporters	▪ Serotonin transporter; Norepinephrine transporter; Dopamine transporter
▪ Monoamine Receptors	▪ Serotonin 1A; Serotonin 2A; Serotonin 3A and 3B; Serotonin 6; B1 adrenoceptor; Dopamine receptors

▪ Intracellular signal transduction pathways	▪ G protein B 3 subunit
▪ HPA axis and stress hormone system	▪ Corticotropin-releasing hormone receptor 1; Glucocorticoid receptor
▪ Angiotensin-converting enzyme substance P system	▪ Angiotensin-converting enzyme
▪ Endogenous circadian locomotor output cycles kaput system	▪ Circadian locomotor output cycles kaput
▪ Other relevant genes	▪ Nitric oxide synthase; Interleukin-1; Brain-derived neurotrophic factor; Glutamatergic receptors

A discussion on the evidence of all these genes of interest will be too voluminous. The following discussion is limited to the evidence related to seven of these genes only – those that have aroused maximal interest in tune with current understanding of the biology of depression.

CYP450 Genes and Drug Metabolism:

The Cytochrome P450 (CYP) enzyme system is involved in the metabolism of drugs and other xenobiotics[2]. It was first discovered by Klingenberg in course of his work on steroid hormones in 1954. Subsequently, a host of similar enzymes have been discovered, and these are classified based on the similarity of gene sequences. The activity of relevant CYP enzymes is known to influence drug metabolism as well as drug interactions. As a result, polymorphism in genes regulating the CYP has been a major area of interest for genetic researchers. CYP2C19 and CYP2D6 have received maximal attention, these being the two enzyme systems that are related to the metabolism of a majority of drugs

including psychotropic medications. The genes for these enzymes are located on Chromosomes 10 and 22 respectively (Ch10q23.33 and Ch22q13.1-13.2). The CYP2C19 gene itself has more than 30 allelic variations while the CYP2D6 gene has more than 100 allelic variations [3]. However, as is to be expected, the prevalence of various alleles is different in different ethnic groups.

Based on polymorphisms, the phenotypic representation of individuals may be classified into four types. Poor metabolizers having decreased enzymatic activity, intermediate metabolizers who carry either two partially defective alleles or one defective allele, extensive metabolizers with normal enzymatic function, and ultra-rapid metabolizers with augmented enzymatic activity. Poor metabolizers are likely to experience higher side effects, while ultra-rapid metabolizers are likely to have worse outcomes with antidepressant treatment [4, 5].

ABCB1 and Drug Transport

The ABCB1 gene codes for the ATP-binding cassette, sub-family B (MDR/TAP) member 1 P- glycoprotein (ABCB1) [6]. It is expressed in the luminal layer of brain capillary endothelial cells, and is involved in the transportation across the blood-brain barrier and therefore influences the concentration of therapeutically administered antidepressants.

It is located in Chromosome 7 (Ch7q21.12-21.12) and shows substrate-specific effects. Antidepressants the act as substrates for this protein include Citalopram, Venlafaxine, Desipramine, Paroxetine, and Amitriptyline [7]. Two SNPs – rs2032583 and rs2235015 in this gene are associated with a favourable response. The C allele of rs2032583 (common in Caucasians and African Americans) and the T allele of rs2235015 (common in African Americans) of the ABCB1 gene lead to better rates of remission [8,9]. Another SNP rs1045642 (T allele) is seen to reduce the dose of Escitalopram required for remission though it does not seem to alter treatment efficacy. Three more SNPs in this gene (rs3842, rs17064, rs1128503) are associated with treatment response in Mexican

Americans. It can be expected that in particular ethnic groups, ABCB1 genotyping may provide pointers to possible treatment response.

FKBP5 and the Hypothalamic-Pituitary-Adrenal Axis

The FK506 binding protein 5 gene (FKBP5) located in Chromosome 6 (Chr6 p21.31 - p21.31) codes for a protein that regulates glucocorticoid receptor sensitivity and intracellular molecular pathways. Its expression is regulated by a glucocorticoid mediated feedback loop. Binding of the protein to the glucocorticoid receptor complex results if increased affinity for cortisol, thereby altering the activity of the HPA axis [10]. Therefore, polymorphism in this gene is likely to result in the disruption of hormonal stress response, which is a core feature of most psychiatric illnesses. It is observed that certain polymorphisms in this gene are associated with improved antidepressant response, irrespective of the therapeutic agent used. Four SNPs within this gene have emerged as potential candidates for pharmacogenetics: rs1360780, rs3800373, rs4713916, and rs352428 [11]. Of these rs352428 worsens the response to antidepressant treatment in Caucasians [12]. Polymorphisms rs1360780 and rs3800373 correlated with improved outcomes in Caucasian but not in the Asians populations [13, 14]. Also in the Caucasian population, the rs4713916 polymorphism was shown to be associated with good response [15].

BDNF and Neuroplasticity

Brain-derived neurotrophic factor (BDNF) is one of the several nerve growth factors. It is induced by cortical neurons and essential for the survival of striatal neurons. It is involved in neuronal protection and neuroplasticity and plays a critical role in the reversal of hippocampus atrophy during antidepressant treatment. There is evidence of reduction of BDNF levels in serum and leukocytes of persons suffering from depression and levels are reversed with successful treatment [16]. BDNF is also believed to be involved in memory and various functions of the hippocampus. The gene for

BDNF is located on Chromosome 11.

Several studies have demonstrated a significant association of rs6265Val66Met polymorphism with antidepressant response [17]. The rs6265Val66Met polymorphism, which impacts hippocampal BDNF levels, is related to good treatment response in Asians. The Val/Val allele has been shown to be associated with SSRI response in Caucasians as opposed to the Met/Met allele, which is linked to response to SNRIs [18, 19]. If replicated across different ethnic groups, genotyping the BDNF gene may provide guidance on choice of SSRI vs. SNRI vs. TCAs.

GNB3 and the Signaling Cascade

GNB3 (Guanine nucleotide binding protein, beta polypeptide 3) is one among several G proteins which are essential for signal transduction between a receptor and its effector proteins. These proteins are responsible for intracellular signalling and function as molecular switches. The G-proteins are physiological targets of approximately 30% of pharmaceuticals on the market [20]. The protein itself has three subunits (α, β, and γ) which dissociate to initiate intracellular signalling cascade. One polymorphism of the β subunit gene (C825T) results in augmentation of function and increased signalling. This polymorphism is also linked to treatment response in Asians [21, 22].

HTR2A and the Serotonin Signal

Although Serotonin has been at the forefront in the biological explanation for the genesis of Depression, results from serotonin regulatory genes have been equivocal. One of the more often studied is the 5HT2A receptor. This receptor is a postsynaptic receptor for serotonin, and is coupled to the G-protein signalling cascade that is found throughout the central nervous system. The gene coding for the 5-Hydroxytryptamine (Serotonin) Receptor 2A (HTR2A) gene is located on Chromosome 13 (Chr13 q14.2 - q14.2) [23]. As with other genes, the association with disease or treatment parameters varies across different ethnicities. Two significant associations

are pointed out in a meta-analysis of studies examining these correlations. There is a significant association of rs7997012 G>A and rs6313 T>C with good responses to treatment with SSRIs or SNRIs in Caucasians. However, no such association could be found in Asian subjects. Incidentally, both polymorphisms are fairly common in Caucasians (frequency: 35.6% for rs7997012 and 54.3% for rs6313) when compared to Asian population (frequency: 21.9% and 48.9% respectively)

SLC6A4 and Serotonin Transport

Many of the antidepressants are thought to be effective because they prevent the reuptake of serotonin from the synaptic cleft. Reuptake is mediated by a sodium-dependent membrane protein on the presynaptic membrane. Because of the mechanism of action of SSRIs and other antidepressants, this receptor and the gene coding for it has been the target of a large volume of research. The gene coding this protein is referred to as the SLC6A4 gene [The Solute Carrier Family 6 (Neurotransmitter Transporter) Member4].

The SLC6A4 gene is located on Chromosome 17 (CH17q11.2-q11.2). It is highly polymorphic. One specific polymorphism in the promoter region of the gene 5-HTTLPR (a 44 base pair insertion/deletion), deserves mention. The long allele (L/L) arising out of this polymorphism was associated with better response and remission with SSRI treatment in the Caucasian population [24].

However, when examined with a mixed bag of antidepressant in the Asian population, the association though present was not as robust. The frequency of the L/L allele is 60% in Caucasians and only 23% among Asians. Several SNPs may affect the expression of 5-HTTLPR. The rs25531- G allele is seen to reduce SCL6A4 expression. On the other hand, L allele carriers with rs25531A polymorphism are seen to be associated with better response to SSRI treatment [25], whereas L allele with rs25531G polymorphism showed no improved response even with higher serum concentrations [26]. A variable number terminal repeat

(STin2) within the intron correlated with improved response to SSRIs in Asian populations [13].It is possible that with refinements and more data, SLC6A4 typing may guide the clinician in dose titration with SRIs.

Apart from the genes discussed above, a few other findings need mention. A 2013 publication, by the authors of three major studies that looked into predictive value of Genetic polymorphisms (American Journal of Psychiatry, 2013;170:207-17). This study combined data from MARS (Munich Antidepressant Response Signature), STAR*D (Sequenced Treatment Alternatives to Relieve Depression) and GENDEP (Genome-Based Therapeutic Drugs for Depression). The authors tested 1.2 million SNPs for common variations that may be associated with symptom relief at the end of 12 weeks of treatment. Despite the increased statistical power of the meta-analysis, no reliable predictors of antidepressant response could be found, although the modest influence of genetic variables in antidepressant response was found.

As part of the GENDEP study, blood mRNA expression of 15 candidate genes across three biological systems (GR complex, inflammation, and neuroplasticity) was analyzed to differentiate baseline predictors from longitudinal (aspects that change during treatment) genetic measures. Out of the 15 genes tested, higher levels of the three inflammation-related genes, IL-1β, MIF, and TNF-α, reliably-predicted non- response to antidepressants. The successful antidepressant response was not associated with a reduction in the levels of expression of these genes. However the authors noted that successful antidepressant response is associated with a reduction in the levels of the IL-6, and of the GR-associated gene, FKBP-5; as well as an increase in the neuroplasticity-associated genes, VGF and BDNF.

Based on Genome-wide microarray analysis of mRNA expression in antidepressant therapy, the association of a few other genes in predicting treatment response has been highlighted.. These include Interferon Regulatory Factor (IRF), Cell Adhesion molecule L1 like (CHL1) and Integrin beta 3 (ITGB3)

CONCLUSION

As it stands now, no reliable genetic biomarkers exist that can reliably predict Antidepressant treatment response. The difficulty is not only because of the fact that research finding has not been replicated often enough, but also the fact that false positive results are pretty high. Also, the frequency of a favourable allele varies widely across different geographical regions, making it impossible to come up with a generalizable statement on response predictors to a particular molecule. As noted [1], the available genetic factors can account for only 36% of the variance in logistic models. Therefore, as of today, successful personalized medicine is hence a far cry from reality.

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Treatment Strategies for Bipolar Depression

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ABSTRACT: *Bipolar depression is one of the most challenging clinical conditions for a practising psychiatrist. Episodes of bipolar depression are, compared to unipolar depression, more rapid in onset, more frequent, more severe, shorter and more likely to involve delusions and have reverse neuro vegetative symptoms such as hyperphagia and hypersomnia. Most of the guidelines recommend Lithium, lamotrigine, quetiapine, lurasidone, olanzapine and fluoxetine combination in acute bipolar depression. But combination treatment is often required. Maintenance treatment is usually recommended for preventing relapse and to modify the gradual deteriorating course. Generally, medications that have been found to be effective in the acute phase should be continued during the maintenance phase even if it is lower down in the hierarchy. Lithium, lamotrigine, quetiapine, and olanzapine have been found to prevent depressive relapse. Long-term use of antidepressants is not recommended, especially in the light of concerns about the potential risk of manic/hypomanic switch and mood instability. Psychosocial therapies should be used as an adjunct whenever possible. However, one plan doesn't fit for all. One has to individualise the treatment protocol depending on the psychiatric and medical co-morbidities.*

Keywords: *Bipolar depression; mood stabiliser; antipsychotics; antidepressants*

INTRODUCTION

The DSM-5 criteria for bipolar depression is characterized by a minimum of 2 weeks of depressed mood and/or anhedonia and at least four other symptoms that include changes in sleep, appetite/weight, energy, psychomotor activity, concentration,

thought content (guilt and worthlessness), and suicidal intent. For many patients with bipolar disorder (BD), the depressive polarity is often more pervasive and more debilitating than manic states, with estimates that depressed mood accounts for up to two-thirds of the time spent unwell, even with treatment. [1] Subsyndromal depressive symptoms, which persist despite treatment, are particularly common and a major source of functional impairment in these patients. [2] Hence, they should be treated aggressively.

DSM-5 includes several specifiers that may accompany depressive episodes: anxious mood, mixed features, rapid cycling, melancholic features, atypical features, mood-congruent or mood-incongruent psychotic features, peripartum onset, and seasonal pattern.

Bipolar depression is a common and debilitating disorder which shares the same diagnostic criteria for a major depressive episode of a unipolar disorder but may differ in severity, time course, and liability to recurrence and response to drug treatment. Episodes of bipolar depression are, compared to unipolar depression, more rapid in onset, more frequent, more severe, shorter and more likely to involve delusions and have reverse neuro vegetative symptoms such as hyperphagia and hypersomnia.[3] Around 15% of people with bipolar disorder commit suicide.[4] A statistic which reflects the severity and frequency of depressive episodes. Bipolar depression also poses a greater socio-economic burden on the family than either mania or unipolar depression. [5, 6]

Patients with depression occurring in the context of BD are frequently misdiagnosed as having MDD, since the presence of mania or hypomania (particularly mild or moderate episodes which do not require hospitalization) may be challenging to establish retrospectively. This is especially true in the absence of a comprehensive diagnostic interview or collateral information, as patients may often lack basic knowledge of what hypomania/mania is, and/or has limited insight into these symptoms; and thus may not disclose this information unless specifically asked. Alternatively, patients who will ultimately present with hypomanic or manic

episodes may only have experienced episodes of depression. Thus, clinicians must be vigilant for a diagnosis of BD, and routinely ask for symptoms of a previous manic/hypomanic episode in every patient presenting with a major depressive episode. A diagnosis of MDD should be made only after excluding the possibility of BD. In addition to overt manic/hypomanic symptoms, there are numerous features that increase the likelihood of a diagnosis of BD in depressed individuals. These include earlier age of illness onset (before 25 years), brief, highly recurrent depressive episodes, a family history of BD, depression with psychotic features, atypical features such as reverse vegetative symptoms of hypersomnia and hyperphagia, leaden paralysis, psychomotor agitation, postpartum depression or psychosis, and antidepressant-induced irritability, manic symptoms or rapid cycling.[7] Individuals with depression who are at high risk for BD, particularly those with a strong family history of BD, should be closely monitored for the emergence of manic or mixed symptoms. Therefore, while devising the treatment strategies for bipolar depression, all the above-mentioned factors should be taken into account. In this review of treatment strategies for bipolar depression the authors will restrict themselves in presenting the available clinical data in the form of meta analyses, randomised controlled trials and various guidelines by professional bodies so that the readers can make an informed choice when encountered with a patient in the clinical setting.

Data search methodology

The data search strategies used included electronic databases as well as hand-search of relevant publications or cross-references. The electronic search included PUBMED, Google Scholar, PsychINFO, etc. Cross-searches of electronic and hand search key references yielded other relevant material. The search terms used, in various combinations, were bipolar disorder, bipolar depression, management, treatment, novel, molecules, drugs, clinical, and trials.

A. MOOD STABILIZERS

1. Lithium

The evidence for the efficacy of lithium monotherapy in treating acute bipolar depression is sparse. A more recent large double-blind placebo-controlled parallel design study found that, lithium was not different from placebo in improving depressive symptoms in bipolar I and bipolar II patients.[8,9] In maintenance treatment a number of active comparator studies support the use of lithium. The effective serum lithium level was 0.8-1.2mEq/L. Lithium decreased the frequency and/or severity of the depressive episode. [10] In a 6-month single-blind trial, Lithium was as effective as Quetiapine in preventing relapse. [11]

A meta analysis of clinical trials concluded that lithium reduced the risk of both attempted and completed suicide by 80% in patients with bipolar illness and large database studies have shown that lithium treated patient are less likely to complete suicide than patients treated with other mood stabilising drugs. [12, 13]

2. Divalproex and Valproate

A meta analysis of four small RCTs concluded that valproate is effective in bipolar depression with a small to medium effect size although, a large more convincing study is required. [14]

3. Lamotrigine

Lamotrigine is approved for prophylaxis of depressive mood episode in bipolar I disorder by FDA. Lamotrigine appears to be effective both as an acute treatment for bipolar depression and as prophylaxis against further episodes but it only has marginal efficacy in preventing a manic episode. Lamotrigine does not induce switching or rapid cycling. [15]

A recent trial suggested the robust efficacy of Lamotrigine when combined with Quetiapine. Addition of Lamotrigine showed both an early effect on depressive symptoms compared with placebo and important benefits for remission, sustained to 1 year of follow-up. [16] The addition of Lamotrigine to lithium

proved effective in bipolar depression in an independent European study. [17] Treatment is somewhat complicated by the small risk of rash, which is associated with the speed of dose titration. Other risk factors for skin rash include younger age, a prior history of rash with another drug, and taking lamotrigine in conjunction with valproate. Rash commonly occurs within the first few weeks of therapy. The necessity for titration may limit clinical utility. A further complication is the question of dose: 50 mg/day has efficacy, but 200 mg/day is probably better.

4. Carbamazepine

Carbamazepine is primarily used as an anticonvulsant in the treatment of grand mal and focal seizures and treatment of bipolar illness in patients who do not respond to lithium.

Open studies suggest that carbamazepine monotherapy has some efficacy in bipolar depression. [18] Carbamazepine may also be useful in unipolar depression, either alone or as an augmentation strategy. [19, 20] Carbamazepine is occasionally recommended in bipolar depression but the database is poor and the effects are modest. It may be useful when added to other mood stabilisers. [3]

5. Topiramate

There are no placebo-controlled trials of Topiramate in the treatment of bipolar depression, but several trials have suggested its efficacy as an add-on therapy. An add-on study of Topiramate and sustained-release bupropion in depressed patients with bipolar I or bipolar II disorder found that, both the groups had significant baseline-to-endpoint reduction in 17-item Hamilton Depression Rating Scale (HDRS) and Clinical Global Impression (CGI) improvement scores, with no difference between the two groups. [21]

B. ANTIPSYCHOTICS

1. Quetiapine

Quetiapine, a dibenzothiazepine derivative, is an atypical antipsychotic initially introduced for treatment of schizophrenia

which causes fewer adverse effects, in terms of an abnormal electrocardiogram, extrapyramidal effects, abnormal prolactin levels, and weight gain. [22] At present, Quetiapine is recommended as first-line treatment for acute bipolar depression by some guidelines. [23] Quetiapine acts as an antagonist at 5-hydroxytryptamine (5-HT) 1A, 5-HT2A, dopamine D1, D2, and histamine H1 receptors, as well as at adrenergic α1 and α2 receptors. The mechanism by which Quetiapine ameliorates depression may include 5-HT2A antagonism, 5-HT1A receptor partial agonism, α2b receptor antagonism, and D2 receptor antagonism. While the common side effects of Quetiapine are somnolence, postural hypotension, dizziness, and dry mouth, some serious side effects include elevated blood glucose levels, diabetic coma, and ketoacidosis. [22]

Quetiapine can improve depression within 8 weeks of treatment, as demonstrated by a greater reduction of depression severity as well as higher response and remission rates and lower dropouts due to inefficacy, compared with placebo. Quetiapine is also associated with an improved clinical global impression, quality of life, and quality of sleep, anxiety, and functioning. Five large RCTs have demonstrated clear efficacy for doses of 300 mg and 600 mg daily (as monotherapy) in bipolar I and bipolar II depression. [24]

A later study in Chinese patients demonstrated the efficacy of Quetiapine 300 mg/day in bipolar I depression. Quetiapine was superior to both lithium and paroxetine. [25] Quetiapine also prevented relapse into depression and mania and so is one of the treatments of choice in bipolar depression. It appears not to be associated with switching to mania. [26]

2. Olanzapine

Olanzapine has an affinity for dopamine D2, serotonin 5-HT2A, muscarinic and histamine receptors. A large RCT showed that olanzapine had a weak antidepressant effect in bipolar I depression compared with placebo.[27] A second study was pooled with the original data and also supports modest efficacy

for olanzapine. [28] A relapse prevention study against placebo also supported the efficacy of olanzapine against depressive relapse. [29] Olanzapine has both lower recurrence rate and longer time to recurrence of a depressive episode.

Combination of olanzapine and fluoxetine is more effective than both placebo and olanzapine alone in treating bipolar depression. [30] Olanzapine alone was effective when compared with placebo, but the combination with Fluoxetine was more effective. Olanzapine–Fluoxetine combination was more effective than Lamotrigine also. [31] Olanzapine has been relegated to a second-line treatment option for bipolar depression because of safety issues such as metabolic syndrome. [28]

3. Aripiprazole

Aripiprazole is a partial agonist at D2 and 5-HT1A receptors. In two 8-week monotherapy studies in bipolar depression, it failed to separate from placebo at the pre-specified 8-week endpoint, although separation at earlier times was evident.[32] It fails to demonstrate efficacy on the depressive pole in the existing relapse prevention study. In treatment-resistant unipolar patients, two trials of adjunctive Aripiprazole suggested antidepressant efficacy. [32, 33)]

4. Cariprazine

Cariprazine is a highly selective dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors. Its mechanism of action is therefore novel and of potential interest for the treatment of bipolar depression. One RCT suggests that Cariprazine at 1.5 mg/day is effective in bipolar I depression. Evidence for efficacy in bipolar depression has been published. [34, 35]

5. Lurasidone

Lurasidone is an antagonist at D2, 5-HT2A, and 5-HT7 receptors, and a partial agonist at 5-HT1A receptors. It has a lower binding affinity for α2C and 5-HT2C receptors. It has been demonstrated to show efficacy in two short-term studies in bipolar

depression: one as monotherapy and the other as add-on to lithium or valproate. [36, 37] Lurasidone has a low subjective adverse reactions burden and produced minimal changes in weight, blood lipids, or glycaemic control. The commonest reported adverse reactions are akathisia and somnolence. At present, it did not have a licence for use in bipolar depression in Europe, but has an indication for schizophrenia. In the US it has a licence for the acute treatment of bipolar depression as well as schizophrenia.

C. ANTIDEPRESSANTS

Antidepressants are commonly prescribed for people with bipolar depression. Their use is controversial because of lack efficacy in bipolar depression or because they destabilize mood and cause the switch to mania. [38] One exception is fluoxetine in combination with olanzapine, which has shown individual efficacy versus placebo and, modestly, Lamotrigine. Unfortunately, studies are very less to make an evidence-based recommendation. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) showed that continuation of antidepressant therapy was associated with a trend toward less depressive symptom burden without increasing manic/ hypomanic symptoms. Further, the time to the depressive episode was significantly delayed in antidepressant continuation group. There was no evidence of an increase in the manic episode.

1. Fluoxetine

Fluoxetine was compared with imipramine and placebo in 89 patients with bipolar depression. The response rate with fluoxetine was significantly better than that of both imipramine ($p<0.05$) and placebo ($p=0.005$). [39]

2. Paroxetine

Efficacy of paroxetine was evaluated in three trials as add-on therapy (compared with imipramine, venlafaxine and Li+ Valproate combo). It was found to be equally effective as comparators and superior to placebo. Switch rate with paroxetine was 2-3 %. [40-42]

3. Citalopram

Citalopram was used as an add-on treatment. The response rate was 64% and most of the patients continued to improve through the 16-week continuation phase. [43]

4. Bupropion

Two controlled studies compared Bupropion with Desipramine and Idazoxan (selective α2 antagonist). No significant difference was found between the groups. Switch rate was low in Bupropion group. [44, 45] One open-label study showed Bupropion was good as an add-on therapy in depressed BD-1 with cocaine dependence. [46]

5. Venlafaxine

Two open-label studies with venlafaxine in BD II depressed patients found significantly greater reductions in HDRS score. [47, 48]

6. Tri-Cyclic Antidepressants (TCAs)

Evidence is available for Imipramine and Desipramine. TCAs were equivalent to or poorer than that of the active comparator (e.g. tranylcypromine, fluoxetine, paroxetine, bupropion yet superior to placebo). TCAs have equal rates of efficacy in the two forms of depression i.e. Unipolar and Bipolar. [49] In aggregate, response rates to TCAs have been about 50 to 70%. [50] One prospective randomized study of TCAs in bipolar disorder indicated higher switch rates than reported with other classes of antidepressants. [51]

D. NOVEL TREATMENTS

1. Ketamine

Ketamine is an NMDA (N-methyl-D-aspartate) receptor antagonist, to be an important addition to treatment options in major depression [52]. This is particularly the case in relatively treatment-resistant cases. A single IV dose of 0.5 mg/kg is effective in refractory bipolar depression. Dissociative symptoms are common but brief. [53]

2. Modafinil

Modafinil has some antagonist affinity for the dopamine re-uptake site and perhaps acts as a partial agonist at the dopamine D2 receptor. It elevates histamine concentrations in the brain. One positive RCT is available with Modafinil as an adjunct to a mood stabiliser. The dose is 100–200mg/day. There is one positive RCT with armodafinil (dose 150 mg/day) as well. [54]

3. Pramipexole

Pramipexole is a dopamine D2 & D3 receptor agonist. Two small placebo controlled trials suggested useful efficacy in bipolar depression. The effective dose of Pramipexole averages around 1.7 mg/day. Both studies used Pramipexole as an adjunct to existing mood-stabiliser treatment. Neither study detected an increased risk of switching to mania/ hypomania but data are insufficient to exclude this possibility. [55]

4. Thyroxin

There is limited evidence of the efficacy of thyroxin as an augmenting agent. The dose is around 300 mcg/d. [56]

5. Omega 3 Fatty Acid

There is one positive RCT (1 g/2 g a day) and one negative (6 g a day). [57]

6. Riluzole

Riluzole shares some pharmacological characteristics with Lamotrigine. The database is limited. Only one case report is available. [58]

7. Mifepristone

There is some evidence of mood-elevating properties of mifepristone in bipolar depression. It may also improve cognitive function. The dose is 600 mg/day. [59]

8. Zonisamide

Use of Zonisamide is supported by several open-label studies. The dose is 100–300 mg/day. [60]

E. NONPHARMACOLOGICAL TREATMENT

1. Somatic treatment

a) Electro-Convulsive Therapy (ECT)

ECT was found to be as or more effective than MAOIs, tricyclic antidepressants, or placebo. ECT is a viable option for patients with severe bipolar depression, especially if psychotic features are present. [61] ECT was equally effective for bipolar and unipolar depression. ECT may be helpful for individual patients with a severe bipolar illness who are unable to tolerate or do not respond to maintenance pharmacotherapy.

b) Repetitive Transcranial Magnetic Stimulation (r-TMS)

r-TMS was found to be effective as an augmenting agent during the acute and maintenance treatment of bipolar depression. Right DLPFC is the preferred target. [62]

2. Psychosocial treatment

Psychoeducation, Family Focused Therapy (FFT) and Cognitive Behavioural Therapy (CBT) are the first lines of psychosocial intervention in bipolar depression [23] .On average; adjunctive psychosocial treatments reduce recurrence rates by about 15%. Therefore, adjunctive psychosocial interventions are an important component of the management of BD and should be offered to all patients.

a) Psychoeducation - It is the only first-line psychosocial intervention for the maintenance phase. Additional second-line options include CBT and FFT, and third-line options such as Inter-Personal and Social Rhythm Therapy (IPSRT) and peer support should be offered based on individual strengths and needs. [28]

b) **FFT**- Components of FFT are Psychoeducation, communication skills training and problem-solving. It acts better as an adjunct to pharmacotherapy.[63]

c) **CBT**- Efficacy of cognitive-behaviour therapy (CBT) for the treatment of acute unipolar major depression is well-documented, there is almost no data evaluating its utility in the treatment of bipolar depression. But CBT as an effective psychosocial intervention for depression in bipolar patients already receiving ongoing mood-stabilizing pharmacotherapy.[64]

d) **IPSRT**- It is an empirically-supported adjunctive psychotherapy for adults with bipolar disorder which has been shown to help delay relapse, speed recovery from a bipolar depressive episode, and increase occupational and psychosocial functioning in adults with bipolar disorder.[65]

SUMMARY

Treatment of bipolar depression is no doubt a challenging task for the practising psychiatrists. There are many complexities inherent to the disease process and co-morbidities these patients usually have. Researchers have tried to find molecules that suit most of the patients suffering from bipolar depression but more often than not clinicians have no choice but to adopt a trial and error method. Most of the guidelines recommend Lithium, Lamotrigine, Quetiapine, Lurasidone, olanzapine + fluoxetine combination in acute bipolar depression. But combination treatment is often required. Maintenance treatment is usually recommended for preventing relapse and to modify the gradual deteriorating course. Generally, medications that have been found to be effective in the acute phase should be continued during the maintenance phase even if it is lower down in the hierarchy. Lithium, Lamotrigine, Quetiapine, and olanzapine have been found to prevent depressive relapse. Long-term use of antidepressants is not recommended, especially in the light of concerns about the potential risk of manic/hypomanic switch and mood instability. However, in the subgroups of patients who have

Table 1: A comparison of different guidelines [31, 66-69]

Guidelines	ISBD CANMAT, 2018 Acute Bipolar Depression	Maintenance treatment Lithium, Quetiapine, Divalproex, Lamotrigine	BAP, 2016	APA, 2002	Maudsley, 13th ed.	WFSBP, 2010
1st line agents	Quetiapine and Lithium (as monotherapy), Lamotrigine and Lurasidone (as both monotherapy and adjunctive therapy)	Olanzapine, Risperidone, Carbamazepine, Paliperidone, Ziprasidone as adjunctive therapy	Quetiapine, olanzapine+ fluoxetine, Lurasidone	Lithium, La, Li+AD	Olanzapine +fluoxetine, valproate, Quetiapine, Lurasidone, olanzapine	Lithium, Lamotrigine, Valproate, Carbamazepine, Quetiapine, Olanzapine, or Mood stabilizer + SSRI
2nd line agents	Divalproex (as monotherapy) SSRI, Bupropion with lithium/Divalproex/ atypical antipsychotics (as adjunctive therapy) ECT	Aripiprazole+lamotrigine, Clozapine, Olanzapine+-Fluoxetine, Gabapentin	Lamotrigine, antidepressants (SSRI >SNRI>T-CA) ECT in resistant cases	Various combinations of 1st choice agents, ECT	Aripiprazole, carbamazepine, SSRI and Various combinations of 1st choice agents, augmentation strategies	Various combinations of 1st choice agents, clozapine, ECT
3rd line agents	Aripiprazole, Armodafinil, Asenapine, Carbamazepine, Ketamine, Olanzapine, Pramipexole, Repetitive transmagnetic stimulation, SNRIs NOT RECOMENDED Antidepressant monotherapy					

responded to combination treatment and are stable, preliminary evidence suggests that withdrawal of antidepressants may contribute to destabilization. Among antidepressants best evidence is for paroxetine, which should be used as an adjunct. Bupropion may be a good alternative. CT and r TMS are promising but should be tried only in treatment-resistant cases. Psychosocial therapies should be used as an adjunct whenever possible.

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Factors Influencing the Choice of Antipsychotics in Schizophrenia: A Global Perspective

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ABSTRACT: *Though guidelines are available for prescribing antipsychotics in schizophrenia individual needs and response of patients to antipsychotic medication are much varied and several factors come into play while making the decision of the antipsychotic of choice for an individual patient of schizophrenia in. Also, a better understanding of the various factors which influence the choice of antipsychotic will help in improvising the guidelines and better policy formulation with regard to this illness. This article reviews some of the widely studied factors and other factors where more studies are needed which has an influence on the decision making with regard to antipsychotics.*

Keywords: *Schizophrenia, antipsychotic agents, global*

INTRODUCTION

Schizophrenia is one of the most disabling diseases in psychiatry and is characterized by the presence of psychotic symptoms persistently severe to disrupt the psychosocial functioning of the individual, to this impairment also contributes the cognitive dysfunction that accompanies the disease. Schizophrenia can affect people of any age group gender race and a region with no exceptions. Our understanding about the disease has significantly increased in the past few decades. Several models have been proposed to explain the symptoms of schizophrenia. However, it is still very difficult to find the exact neural mechanism which interferes so extensively with broad cognitive functions that occur in schizophrenia. The current clinical research in schizophrenia focuses on the pathophysiology

of dimensions of dysfunction identifying mechanism for it and exploring treatment options.[1]

According to DSM-V Schizophrenia is diagnosed by the presence of delusions, hallucinations, disorganized speech (e.g. frequent derailment or incoherence), grossly disorganized or catatonic behaviour, negative symptoms (i.e. , diminished emotional expression or avolition) , two of the aforementioned symptoms (one of which must be delusion, hallucination or disorganized speech) must be presence for at least 1 month in six month duration of continuous illness leading to functional impairment and not explained by any other mental or physical illness and substance use. [2]

ICD-11 has identified schizophrenia as a disease characterized by disturbances in multiple mental modalities, including thinking (e.g., delusions, disorganization in the form of thought), perception (e.g., hallucinations), self-experience (e.g., the experience that one's feelings, impulses, thoughts, or behavior are under the control of an external force), cognition (e.g., impaired attention, verbal memory, and social cognition), volition (e.g., loss of motivation), affect (e.g., blunted emotional expression), and behaviour (e.g., behaviour that appears bizarre or purposeless, unpredictable or inappropriate emotional responses that interfere with the organization of behaviour). Psychomotor disturbances, including catatonia, may be present. Persistent delusions, persistent hallucinations, thought disorder, and experiences of influence, passivity, or control are considered core symptoms. Symptoms must have persisted for at least one month in order for a diagnosis of schizophrenia to be assigned. The symptoms are not a manifestation of another health condition (e.g., a brain tumor) and are not due to the effect of a substance or medication on the central nervous system (e.g., corticosteroids), including withdrawal (e.g., alcohol withdrawal). [3]

Treatment with antipsychotics is the mainstay of treatment of schizophrenia. Today many antipsychotics with a wide range of actions are available and there also exist a number of inter-individual differences in response to antipsychotic agents. It is important to identify the right antipsychotic for an individual to treat the disease

and prevent its disabling consequences. It is therefore important to consider all the important factors while prescribing a medication. Documentation of the reason for selection and its reporting is equally important to formulate guidelines for prescribing antipsychotics in schizophrenia and also in the formulation of policies.

This article writes about the factors to be considered while prescribing antipsychotics in schizophrenia, evidences in support of considering those factors and variation in selection of antipsychotics with respect to those factors across the world.

Antipsychotics: Brief history

Antipsychotics remain the mainstay of treatment in schizophrenia. With the advent of chlorpromazine "the pharmacological era" heralded as an alternative to biological therapies like electroconvulsive therapy, insulin coma, frontal lobotomy etc. Before Chlorpromazine, member of Phenothiazines, other derivatives of phenothiazine were also synthesized by Paul Charpentier and his team.they explored the antihistaminic properties of this group to use as a pre-anesthetic medication.

Henrie -Marie Laborit , the French surgeon tried promethazine combination with Barbiturates to prevent surgical shock and termed it as "Lytic cocktail". Research on phenothiazines led to a Chlorinated derivative of Promethazine, RP-4560, which is Chlorpromazine of today. The enthusiasm of Laborit dampened when despite promising potential scientific community did not show interest in it.

In 1952,Joseph Hammon tried Chlorpromazine in a manic patient. The patient calmed down was maintaining in that state. Elkes and Elke in 1954 conducted a randomized and placebo-controlled study on psychotic patients and showed the effectiveness of chlorpromazine. This study was a milestone as it had strengthened the neurobiological basis of mental illnesses.

After Chlorpromazine, Haloperidol, Trifluoperazine, thioridazine, and fluphenazine came into the market. Although with comparable efficacy, but serious neurological side effects like

neuroleptic malignant syndrome. Efforts were on for drugs with fewer side effects when in 1958, a group of tricyclic compounds was developed, some of which had responses similar to Chlorpromazine. Clozapine was among one of them. Following mixed results in initial studies, later trials confirmed Clozapine to be an effective antipsychotic with the absence of serious neurological side effects. Following large trials by Hippus and Stille, Clozapine was approved in several countries in Europe. In 1975, in Finland 16 out of 1600 patients on Clozapine developed agranulocytosis with 8 deaths of the 13 patients following around 50 deaths around the world clozapine was withdrawn from the market in most European countries. Before withdrawn it was seen that with regular monitoring agranulocytosis was reversible when the drug was stopped. Later Clozapine was again introduced in the market and subsequently other second-generation antipsychotics like Olanzapine, Quetiapine, Risperidone came. But still, till now no antipsychotic has been considered as an "ideal antipsychotic".[1, 5]

Factors

Patient factors to be considered while choosing antipsychotics:

Age: Antipsychotics have been used extensively in all age groups in patients with schizophrenia. In adult population, no specific antipsychotic has been preferred over another just on the basis of age. There is limited research in younger and older age groups. Atypical antipsychotics are preferred in early-onset schizophrenia because of less chance of extrapyramidal symptoms compared to typical antipsychotics. Limited research is there on the selection of antipsychotics in early-onset schizophrenia. In a study done in united states to formulate guidelines for prescribing antipsychotics in older patients with schizophrenia low dose risperidone and similar results were obtained from research done in European countries.[4]

Gender: Gender needs to be taken into account when prescribing. The pharmacokinetics and pharmacodynamics of antipsychotic drugs differ in women and men and are influenced by gender-specific

factors such as body build, diet, smoking, concurrent medication, exercise, substance use, and hormonal transitions. In general, and for some drugs in particular, women require lower doses in order to stay well. The enzyme CYP1A2 appears to be less active in women than in men, leading to relatively higher blood concentrations in women, not only of olanzapine but also of clozapine. Studies have shown a better response to clozapine in females and better quality of life with olanzapine in females. No difference in response has been seen in males and females on risperidone. The results of several trials confirm that women are more susceptible to drug-induced hyperprolactinemia than men. Some side effects, such as sedation and orthostatic hypotension, are equally prevalent in the two sexes and may interfere with optimal functioning. In women with parenting responsibilities, however, these relatively benign side effects can have serious consequences—e.g., loss of child custody. other issues with a female. Most experts suggest minimal use—no use, if possible— of antipsychotics during weeks 6–10 of gestation to prevent teratogenesis and low doses before expected delivery to prevent toxicity and withdrawal in the infant, with immediate resumption of a full dose after delivery because of the high risk of the mother's decompensation. Neurodevelopmental effects of antipsychotic drugs have never been demonstrated in humans but remain a theoretical concern. Not much is yet known about the newer drugs. Clozapine poses special potential risks for the foetus: seizure and agranulocytosis. Thus far, olanzapine appears relatively safe. Yet no agent can be said to be without risk. The risk benefit assessment always remains individual in each case.

The rule of thumb is that, for any drug in breast milk, infants should be exposed to less than 10% of the dose per weight that would be prescribed to them directly. Olanzapine has been found to be a safe option in lactating mother, infants did not develop any adverse effect upon breastfeeding by mothers on olanzapine. Novel agents, the safety for which there are few data, are better avoided, and clozapine is a problem because of the frequent blood monitoring it requires.

There is plenty of evidence that Women need lower doses than men. Depot doses should be given at longer intervals in women than in men. Prolactin levels are higher in women. Obesity is more of a problem in women. Women need mammograms, ECGs, and bone density scans Women need diabetes and cardiovascular workup. Dose needs to be modulated in aging women .Impact of side effects is gender specific. Some evidence's are also in favor for the need of differential dosing over the menstrual cycle and Need for a reassessment of the dose at menopause. Studies have also found that men and women who gain weight on treatment with olanzapine and haloperidol are more likely to benefit from the olanzapine and haloperidol.[6]

Ethnicity and race: There is significant variation in different ethnic groups with respect to genetic polymorphism of cyt p450 enzyme, drug binding proteins and number and affinity of a target, prescribing practices and development of adverse effects. Specifically, CYP2D6 is involved in the metabolism of haloperidol, perphenazine, risperidone, and thioridazine, in addition to a number of other psychotropics. Studies estimate that approximately 6-10% of Caucasians in Europe and North America have mutations at the CYP2D6 isoenzyme, causing them to be unable to effectively metabolize drugs degraded by this enzyme.P: while the estimated frequency rate for poor metabolizers in Chinese, Japanese, and other Asian populations is less than 1 %. The frequency of poor metabolizers in African populations varies considerably, from 0.7-5% for Ghanaians, 3-8% for Nigerians. and as high as 19% for Sans Bushmen.

The a1-Acid glycoprotein is a protein that binds many basic compounds, including haloperidol, chlorpromazine, fluphenazine, loxapine, and thioridazine. "Zhou et al." found that plasma binding of certain drugs to a1-acid glycoprotein is significantly reduced ($p < 0.05$) in Chinese subjects compared with Caucasians. Further research is needed to elucidate whether a decrease in aI-acid glycoprotein concentrations will translate into a change in antipsychotic response.

Enhanced prolactin response in Asians following haloperidol administration may be an example of a pharmacodynamically based difference," a blockade of dopamine receptors in the hypothalamus with typical antipsychotics results in elevated prolactin concentrations." Ethnic variants in the dopamine D4 receptor have recently been discovered, but these have not been associated with schizophrenia or antipsychotic drug response."

In Japan, the recommended daily dose of antipsychotic drugs is lower than in Western countries and Japanese psychiatrists often use a combination of antipsychotics to treat target symptoms.

Studies have found that African-American patients are more likely than Caucasians to be misdiagnosed, to be diagnosed with a more severe diagnosis such as schizophrenia, to be treated with antipsychotic agents irrespective of diagnosis, and to be treated with significantly higher dosages of antipsychotic agents.

Non-biologic factors such as special beliefs of patients', patient expectations, quality of care, placebo response, and economic and compliance issues that are subjected to inter-ethnic variations are important in determining the effectiveness of antipsychotics. For example, several studies have shown that Hispanics tend to underuse mental health services, possibly due to the cultural insensitivity of the healthcare professionals.

A major histocompatibility complex haplotype occurs significantly more frequently in patients who develop agranulocytosis with clozapine treatment." This particular haplotype (human leukocyte antigen B38, DR4, DQw3) occurs more frequently in the Ashkenazi Jewish population, and therefore Jewish patients with schizophrenia may be at greater risk for developing agranulocytosis when treated with clozapine. Individuals of non-Jewish descent have also been found to possess this haplotype but at a lower prevalence rate.[7]

Diet: Diet affects the pharmacokinetics of drugs. Certain foods such as cruciferous vegetables (cabbage, broccoli, Brussels sprouts) are potent inducers of chemical oxidation and increase the expression of CYPIA2.56 A diet regularly containing one serving of such foods per day was found to decrease the systemic availability of phenacetin

by 50%.57 Therefore, consumption of cruciferous vegetables may lower the serum concentrations of antipsychotics, such as haloperidol and clozapine, that are metabolized by CYPIA2.12 Polycyclic aromatic hydrocarbons formed during charcoal broiling also contribute to enhanced drug oxidation rates," whereas as little as 8 ounces of grapefruit juice (but not orange juice) inhibits CYPIA2 and causes clinically meaningful increases in the serum concentrations of certain medications."

The amount of protein and carbohydrate consumed in the diet may affect P450 enzymes and alter rates of metabolism of drugs that are substrates of P450 isoenzymes. Certain compounds isolated from Chinese medicinal herbs are able to induce or inhibit cytochrome P450 enzymes. Muscone, pan ax ginseng, and Glycyrrhiza, which are compounds isolated from animal or plant sources, are used in traditional Chinese medicine." These compounds induce cytochrome P450 enzymes and therefore have the potential for significant drug interactions. Clinicians who treat patients of diverse ethnic backgrounds should be aware that traditional herbal and natural medicines are often used in combination with prescribed drugs.[7]

Substance use: Smoking, alcohol intake, concurrent drug use, and exposure to environmental or occupational toxins are factors associated with a faster drug elimination rate. Tobacco smoking is known to cause enzyme induction in humans, leading to increased clearance and decreased the concentration of a number of medications." Jann et al." found that smokers who consumed more than one pack of cigarettes per day had significantly lower concentrations of haloperidol and reduced haloperidol than did non-smokers, and the clearance of haloperidol was significantly greater in smokers compared with non-smokers. Smoking has also been found to decrease serum concentrations of chlorpromazine and fluphenazine."

Caffeine is highly dependent on cyp1a2 for its metabolism and competitively inhibits the enzyme thereby affecting the concentration of enzymes metabolized by it. Olanzapine and

clozapine are metabolized by this enzyme and their concentration is affected by both smoking and use of caffeine.

Alcohol can affect the clearance rate and disposition of a number of drugs. Acute administration of ethanol inhibits the cytochrome P450 oxidase system and decreases the clearance rate of drugs subject to oxidative metabolism," particularly drugs that are subject to a high first pass effect. Conversely, chronic alcohol use induces the P450 oxidative system and the clearance rate of many drugs subject to oxidative metabolism is increased by chronic alcohol intake." Continued chronic, heavy ethanol consumption results in cirrhosis of the liver for many patients, which then results in a diminished capacity for oxidative metabolism.[7]

Weight and BMI: Body weight has an important influence on plasma drug concentrations. Since people with low body weight may require lower drug doses than do people with high body weight to produce similar plasma concentrations, dosage adjustments in very lean or very obese individuals should be made on the basis of body surface area." In the case of obese patients, apparent volumes of distribution for highly lipophilic drugs like haloperidol are increased, necessitating higher doses. There is a risk of weight gain with many 2nd generation atypical antipsychotics which includes olanzapine, clozapine and quetiapine which should be taken into account while prescribing in people with a high body mass index.[7]

Comorbidity: Medical and psychiatric comorbidity of the person with schizophrenia should also be considered and also the medications being taken for those conditions should be considered. Patient's accessibility to health care facility and ability to afford the medication is also an important issue while selecting antipsychotics.

Other patient-related factors which should be considered are patients insight into illness, their attitude towards illness and medication, adherence to drugs in the past , response to drug in the past, family history of schizophrenia and response to medication in family members, family history of diabetes mellitus, allergies, past history of adverse drug reaction when on antipsychotics, side-effects patient willing to tolerate and preferences and stigma associated

with the disease. Advance directives if available must be considered to avoid any legal ramifications.

Drug and illness-related factors

Choice of antipsychotics in schizophrenia depends upon the clinical presentation, phase of illness, any general medical condition, any concurrent medication use, considering the possible side effects of the antipsychotic agent (extrapyramidal, cardiovascular, metabolic, hormonal and hematological etc), contraindications, cost and cost-effectiveness of the agent chosen.

The CATIE study showed that each of the drugs might be most useful in particular situations. For patients whose symptoms do not improve with first-line treatment, clozapine was most effective. Olanzapine was effective in all phases of the study but so was clozapine but clozapine was found to be associated with most serious side-effects. Cutlass study has also not found the difference in the quality of life following the use of first and second generation antipsychotics.

Clozapine has been found to be superior to other antipsychotic agents in efficacy, effectiveness and has comparable cost-effectiveness. Its use is limited to treatment of resistant cases of schizophrenia due to the risk of side effects which are though rare can be life-threatening. For patients who switched medication because of the side effects then the best alternative depended upon the type of individuality of side effects and severity of patients illness. However, it has been found to be underutilized in the first episode of schizophrenia due to a difference in the definition of treatment-resistant schizophrenia in different countries of the world.[8,9]

Contraindications: contraindications of individual drugs while prescribing antipsychotics should be considered. FDA has issued black box for the use of atypical antipsychotics in the patient with Dementia. Haloperidol is contraindicated in patients with a past history of acute stroke or coma and allergy to Butyrophene class of drugs.

Cost and cost-effectiveness: some studies have found atypical antipsychotics more cost-effective than first-generation agents. however similar results were not replicated in different studies done in different countries including Brazil and Pakistan. However despite lack of sufficient evidence for the cost-effectiveness of atypical antipsychotics they are being used a lot all over the world. [11, 12,13]

Abuse potential: atypical antipsychotics have been abused and misused by inpatients and outpatients. Most published case reports of antipsychotic abuse involve quetiapine, although other agents may also be involved including olanzapine. Serotonin, histamine and a-adrenergic neurotransmitters have a role in abuse potential of 2nd generation antipsychotics.[25]

Investigations: Need for therapeutic drug monitoring, monitoring of other lab parameters that needs to be done when an antipsychotic agent is being should also be considered while selecting an antipsychotic.

Others: Knowledge of pharmacogenetics and biomarkers with respect to antipsychotics and schizophrenia should also be considered to personalize the medicine in patients with schizophrenia. The new field of Personalised Medicine is pertinent in this regard.

Negative symptoms: Atypical antipsychotics are found to be better than typical antipsychotics for negative symptoms. Clozapine has shown its superior efficacy in both negative and positive symptoms. Among other atypical agents, amisulpride was better than all the other agents for negative symptoms. Other agents effective in negative symptoms are cariprazine and risperidone. [10]

Treatment-resistant schizophrenia: Clozapine is the gold standard for resistant cases. Zotepine is another molecule put forward for control of negative symptoms but the molecule is yet to get momentum and is unavailable in market for undisclosed reason.

Clinician-related factors

The pharmacological treatment of choice for schizophrenia is antipsychotics of different generations. Along with differences in pharmacological and clinical profiles there exist differences in terms of the cost of these two classes of drugs. Therefore, choosing the appropriate molecule from the available armamentarium requires a holistic approach on the part of the clinician. There are many studies examining the efficacy of antipsychotic drugs and a large number of prescribing guidelines that broadly recommend atypical antipsychotics as first-line agents for people with schizophrenia (National Institute for Clinical Excellence, 2002; Lehman et al,2004).

As we all know, health care is a costly and complex endeavor. In clinical situations, the choice may be influenced by local guidelines or restrictions and other considerations such as cost and formulations. Factors related to the clinician in choosing an antipsychotic may be first, his knowledge and concept regarding evidence-based medicine, second, his level of training in psychiatry, third his willingness to adapt to new medicines. Most clinicians make their decisions on the basis of best available evidence. The advent and proliferation of randomized controlled trials have led to a rapid increase in the quantity and quality of clinically valid evidence concerning clinical history taking and physical examination, issues of diagnosis, prognosis, therapy, and other important healthcare issues.

A psychiatrist considers each drug as a separate molecule based on its individual properties. Some readily accept the advent of new drugs, while others cannot. Agne Lobloy explored the factors affecting new drug acceptance in the clinical settings. In this study, it was found that at the prescribed level, the most significant influencers included interest in particular clinical or therapeutic areas, clinical trial participation, prescribing habits, targeted marketing efforts of pharmaceutical companies, and peer pressure through interpersonal communication. Interest in particular clinical or therapeutic areas exerted influence on new drug uptake in the majority of cases.[14, 15, 16]

Capitalism might affect treatment ethics more than you think

Global Schizophrenia market was valued at 6.8 billion US dollar's in 2016 and expected to have a CAGR of 2.5%. (17) And global market for antipsychotics as a whole was estimated to be 11.7 billion in 2015 and estimated to have a CAGR of 2.1% (21) although some other agencies found a decreasing CAGR for antipsychotic among the psychotropic. The Average price of the same antipsychotic has a wide variation in the Indian market, considering the chronic nature of the disease and requirement of a long-term requirement of treatment, improved adherence can be achieved by lowering the cost of the drug. The largest number of formulations in India is seen for Olanzapine followed by Quetiapine. (18).

Pharmaceutical companies use aggressive methods for marketing to keep up with the competition and invest over 60 billion per year on marketing, the largest share of it goes for the interaction with doctors through medical representatives. The euphemism used for marketing to doctors would be "detailing". An interaction of medical representative with a trainee/resident has shown to result in more knowledge of brands names products compared to evidence-based generic prescriptions of lower cost. These results have given way to policies enforced in many medical schools in USA which restricts MR and trainee interaction. (19)

Since FDA approved indications for a drug is limited, pharma companies have pushed the off-label uses of a medication often at the risk of patient safety.

"The nation's physicians are concerned that a growing proliferation of commercially-driven promotions is fueling demand for new and more expensive treatments regardless of the clinical effectiveness of less costly alternatives."

- The American Medical Association (20)

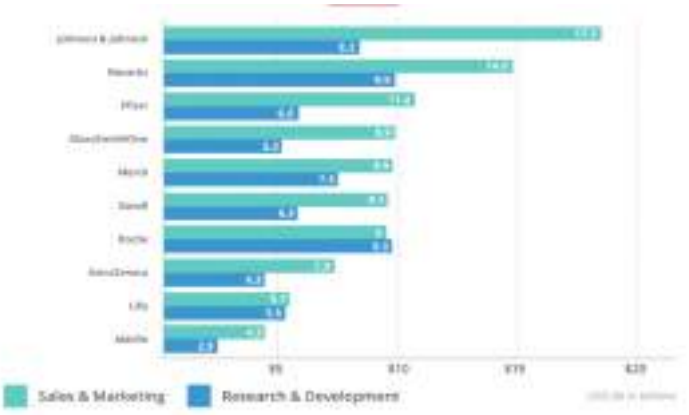
While prescribing generic or preferred medications within a therapeutic group for treatment of chronic diseases have shown to increase Medication adherence. (22)

To increase transparency the government has to take measures to document the influence of interaction of pharmaceutical companies with doctors, A worthy of a mention here would be Open payments program created by The Affordable care act in The USA, which documents all the payments and benefits a doctor has received from a pharmaceutical company, it will be part of public records for anyone to see (23)

Prescription samples given to doctors have found to influence prescribing behaviour and diversion of the stock was seen, i.e personal use by doctors, their families, practice staff.

The free trip for the conferences provided by the drug companies seen to increase the chances of prescribing a particular drug by 80 to 190%

Direct to Consumer (DTC) Marketing is made legal in the USA and New Zealand, under the false pretext of educating the public about the medication which has directly translated to increased pricing of medications in those countries and 81% of the doctors surveyed have stated DTC marketing results in overuse of medications. It is important to notice drug companies are spending more money on marketing than on R & D. (20)



DTC has also cloaked the serious risk associated with prescription drug and made people view it as a consumer product -

soap or snack foods.

Distracting images has shown to make people overlook the risk information in the text, (23)

Prescription drugs advertised directly to consumers are now the largest and fastest selling medicines

CONCLUSION

Different countries of the world vary tremendously with respect to population variables like age gender, race, ethnicity, culture, customs and tradition, beliefs, economy, health care policies, accessibility and affordability of the health care services and medical practices. All these factors influence the choice on antipsychotic medication needed. It is therefore important to know the variation in prescription practices across the world and to understand the reasons for existing differences and their effect on the outcome of diseases. For this, it is very important to have a reporting system for the prescriptions of antipsychotics prescribed by the psychiatrists in different parts of the country so that patterns and reasons for differences in prescription writing can be identified. In United states, Medicaid and in China, Chinese Psychopharmacology Algorithm Project contributes for the same and serves the purpose. More such systems are needed in different parts of the world for a comprehensive understanding of the factors influencing the choice of antipsychotic agents in schizophrenia.[16]

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Cognitive Enhancers in Schizophrenia

Hemanta Dutta

ABSTRACT: *The role of cognitive enhancers in schizophrenia has been studied widely, but a definite neurobiological link could not be established. Although these factors are examined to be improving the overall cognitive functions of the patients with schizophrenia and helping them to lead a self-sufficient and productive life*

Keywords*: cognitive enhancer, schizophrenia, remediation*

INTRODUCTION

Schizophrenia is often considered to be linked with disability and poor prognosis. Cognitive dysfunction is an inevitable component of schizophrenia apart from its regular positive and negative symptoms. Cognitive dysfunction plays a major role in inability to do optimum performance. Cognitive dysfunction also plays a determinant factor in prognosis. Surveys have indicated that the Atypical Antipsychotics has considerable benefits over the conventional one. [1]

Research shows that various neurotransmitters like dopamine, serotonin, glutamate, and GABA have a part in neural modulation and neural plasticity, so pharmacological agents facilitating them have demonstrated efficacy in improving cognition. [1]

Cognitive Enhancers

Among the different cognitive domain's verbal memory, processing speed, executive dysfunctions, encoding failures are primary areas of involvement. [2] Various studied cognitive enhancers and their role in schizophrenia are discussed beneath

Modafinil is a wakefulness-promoting agent showing the manipulation of monoaminergic mechanism and partially supports cognitive enhancing properties. Morein-Zamir et al. suggested that areas like executive function and attention process show a remarkable improvement with it. In a study presented by Danielle et al. among 20 schizophrenic patients shows considerable improvement in verbal memory, visual memory and spatial orientation with 200mg of Modafinil. [3, 4]

Benzodiazepine antagonist flumazenil has demonstrated an increased processing load in people with schizophrenia while performing the NBack test. Gabanergic drugs like Lorazepam shows deteriorating effect and worsening of the results of NBack test. [4]

Davunitide is a Neuroactive peptide and has been demonstrated promoting neuronal outgrowth in animal models. Intranasal administration of one to two dosages of Davunitide leads to significant growth in comparison to the placebos. [5]

NIMH-funded "Measurement and Treatment Research to Improve Cognition in Schizophrenia" (MATRICS) had projected to develop guidelines for clinical trials of cognitive-enhancing drugs for schizophrenia (Buchanan et al., 2005). Moreover, in the third meeting of the Cognitive Neuroscience, Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) project, it was agreed that six areas or cognitive domains suffered impairment in schizophrenia: perception, working memory, attention, executive functions, long-term memory, and social cognition. [6] They considered various cognitive domains like episodic memory, processing speed, working memory and executive functioning by utilizing MATRICS consensus cognitive battery (MCCB). [6]

Dopamine hypothesis is playing a major role in explaining the neurobiological basis of Schizophrenia. Egan et al. stated that cognitive deficits in schizophrenia are mainly predicted by COMT genotype, which is related to dopamine metabolism in the forebrain. Currently approved Antipsychotics are seen to be improving the cognitive function, but it may be due remission of psychotic

disorganization. Atypical antipsychotic drugs as a group appear to be superior to typical neuroleptics regarding cognitive function. Herbert et al. stated that patients with Clozapine and Olanzapine showed improvement in their verbal fluency, working memory and attention span, etc. [1, 2, 3]

Tolcapone, a COMT inhibitor has been established to be improving the cognitive functions such as working memory and executive functioning. [5]

fMRI studies have shown increased blood flow to the prefrontal cortex in the subjects using Amphetamines leading to improvement in various cognitive parameters. But due to the concern of exaggeration of the psychosis these agents may not be preferable as an add-on with Antipsychotic agents. [6, 7]

Surveys were done by Mu et al., 2007 showed increased cortical perfusion in prefrontal and none prefrontal areas with short-acting selective D1 agonist Dihydrexidine. [6]

A single administration of D-Cycloserine improves consolidation of memory in animal models. [8]

Mood stabilizers like Lamotrigine acting on the reduction of excessive glutamate neurotransmission and acting on NMDA dysfunction which leads to improvement of cognitive disabilities (Anand et al., 2000). Two large clinical trials with Lamotrigine 400 mg and metabotropic mGlu2/3 agonist, LY354754 has shown influence on cognitive function by reduction of glutamate release. [1, 4]

Serotonergic receptors have been distinguished as promising targets for cognition but to date, none has shown compelling evidence for efficacy in schizophrenia. [9]

Muscarinic and nicotinic acetylcholine receptors play a role in cognitive impairment in schizophrenia. Alterations in the central cholinergic system of patients with schizophrenia such as reduced numbers of muscarinic and nicotinic receptors in the cortex and hippocampus may contribute to the cognitive impairment of schizophrenia. Data from blinded placebo-controlled studies have failed to show significant results with administration of Donepezil,

but Galantamine has shown some promising results which may be due to its unique properties like combined acetylcholinesterase inhibition and allosteric potentiation of the nicotinic receptor, a newly studied agent, modulates these receptors and has a prominent role in the improvement of cognitive deficits. Emre et al. in their case series reported a significant improvement in patients who received Galantamine as an adjunct to the Antipsychotics. [5, 6]

Pregnenolone, an endogenous neurosteroid modulates GABA, NMDA, and hippocampal dopamine and has neurodevelopmental and neuroprotective effects. They come with promising results in patients with cognitive dysfunctions. [1, 2, 6]

Role of Omega 3 fatty acids is still not convincing, and benefits among patients are yet to be studied. [7,8,10]

What are the possibilities of not getting significant results with cognitive enhancers?

There may be multiple mechanisms that may be implicated for apparent inadequacy of the cognitive enhancers in treatment of cognitive symptoms of schizophrenia.

- Progressive cortical volume loss in patients with schizophrenia may interfere with the effects of pharmacological treatments.
- Antipsychotic medications may interfere with the effects of adding pharmacological cognitive enhancers. Effect of antipsychotics on various neurotransmitters may be the possible causes of interference with the cognitive enhancers
- Delivery and Pharmacokinetics may lead to problems in administration.
- Neurotransmitters may not be the viable target for cognitive enhancement. [9, 10]

BEYOND PHARMACOTHERAPY

Cognitive remediation therapy in schizophrenia

Cognitive remediation for schizophrenia is a behavioral training-based intervention that trains to improve cognitive processes with the goal of durability and generalization. Models of remediation

therapy are mainly compensatory and restorative. Compensatory approach tries to bypass the specific cognitive deficit while restorative one aims at the neural plasticity to correct the specific deficiency. Cognitive adaptation training, integrated neurocognitive therapy, Neuropsychological educational approach to remediation is widely practiced among the various intervention techniques. [1, 9]

CONCLUSION

Although Studies have failed to demonstrate the use of cognitive enhancing agents as an absolute indication in patients with schizophrenia with cognitive deficits, their role cannot be completely ignored. Cognitive rehabilitation measures along with optimum pharmacotherapy may help the person to lead a self-sufficient and productive life.

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Personalised Medicine in Schizophrenia

Sujata Borkakoty, Pallabi Konwar

ABSTRACT: *Schizophrenia has always been a baffling mystery to the researchers and the physicians. The fact that not all people have the same response to drugs is a known phenomenon encountered everyday. In the era of molecular sciences it has become imperative to seek more targeted treatment approaches and do away with the trial and error prescribing. The concept of personalised medicine has revolutionised medical sciences, but the rate of success is greater for some disciplines than others. Psychiatry in general and schizophrenia in particular is still in its nascent stage when it comes to adopting personalised medicine in clinical settings. The knowledge in the fields of genetics, neuroimaging, epigenetics, biomarkers and endophenotypes of schizophrenia is an ever expanding one, enabling us to explore newer drugs and therapies that can optimise treatment of patients at an individual level. This can lead to a shift in schizophrenia management from reaction to prevention using safer and more effective drugs, including using preventive measures in susceptible individuals, leading to an overall improvement in the quality of life. Newer ethical and legal challenges will arise, but the ultimate goal should be to optimise diagnostics, minimise side effects, maximise efficacy while maintaining cost effectiveness and acceptable treatment for each individual, keeping in mind their distinct genomic framework.*

Keywords*: personalised medicine, schizophrenia, pharmacogenomics, epigenetics, endophenotypes*

INTRODUCTION

Physicians have observed for ages that different people respond differently to drugs. The response to drugs is not homogenous across the population. While a drug in general has similar effects on most people, but some individual variations in response side effect

profile and effective dosage has been seen- the "one size fits all" method of prescribing medicine has its own pitfalls. But while these observations have been there for ages, the reason behind this has evaded physicians for a long time. Only in recent times has there been some progress into finding the answers to this puzzle.

The completion of the Human Genome Project on April 14th, 2003- a project that took 13 years to complete after it was formally launched in 1990 has been a landmark in revolutionising medical sciences leading it towards a new era, where understanding of diseases and the response to drugs and other therapies can now be understood at a molecular level. Thus, the generalised approach to treatment can in future perhaps be replaced by a model where individual susceptibility testing, diagnosis and individualised treatment become the norm rather than the exception. This approach holds true not only for physical illnesses but also for psychiatric conditions although many challenges are to be overcome before this approach gains momentum in the field of psychiatry.

PHARMACOGENOMICS- AN EVOLVING CONCEPT

That a substantial variability in drug response is genetically determined, with age, nutrition, health status, environmental exposure, epigenetic factors and concurrent therapy, ethnicity and geographical distribution having contributory roles has become clear in the last six decades[1]. This concept that had begun in the 1950s led to the birth of an emerging discipline that is a merger of genetics, biochemistry and pharmacology which came to be known as 'Pharmacogenetics'. Pharmacogenetics in turn led to advances in molecular medicine, and ultimately a newer field dedicated to understanding all the molecular underpinnings of drug response arose – 'Pharmacogenomics'. The clinical application of pharmacogenomics for the diagnosis and treatment of individuals is what we today know as 'personalised medicine'.

Since 2003, following the mapping of the human genome, the development and clinical application of personalised medicine has accelerated markedly. It may be considered as an extension of the traditional approaches to understanding and treating diseases but

with greater precision. Here, a patient's genetic profile and their gene variations can guide us towards the selection of drugs or treatment protocols that minimise harmful side effects and give us a more successful outcome. An individual's susceptibility to a disease before it manifests clinically so that a physician along with the patient can design a plan for its monitoring and prevention can become possible with personalised medicine. More effective treatment for individual patients can be planned wherein, a structured model for efficient health care that is preventive, co-ordinated and participatory is provided.

Key advantages of personalised medicine in all fields is a shift in medicine from reaction to prevention, selection of optimal therapy and reducing trial and error prescribing, using safer drugs that avoid serious drug reactions, reducing the time and cost of clinical trials leading to overall attenuation in healthcare expenses, morbidity and mortality.

PERSONALISED MEDICINE- ROLE IN MEDICAL SCIENCES

Personalised medicine has been in practise in various fields of medicine for many decades allowing for development of targeted therapeutics, serving as an important predictor in deciding who would benefit from the treatment and who would suffer ill-effects. It also allows for informed drug prescription and more efficient treatment planning.

For example, the presence or absence of rheumatoid factor is applied to guide the choice of treatment in arthritis. The molecular diagnosis of cancers is routinely exploited to select tailored treatment that affects survival rates. Say for instance, treatment targeting BRAF-positive melanoma and ALK- positive non-small cell lung cancer have better improvement rates than the conventional trial and error medications. Patients with breast cancer having overexpression of HER-2/ NEU receptor show phenomenal response to monoclonal antibody treatment, trastuzumab. Imatinib targets the BCR-ABL fusion gene in patients developing chronic myeloid leukaemia (CML). The field of oncogenomics is growing and personalised medicine has established its foothold, with many notable successes,

in the world of oncology. Besides directing selection of optimal therapy, it has also provided opportunity to focus on prevention. For example, BRCA- 1 and BRCA-2 genetic testing not only identify inherited susceptibility to breast cancer but also ovarian cancer, which develops in 60 per cent of the patients testing positive for the genes. Likewise, certain DNA mutations increases an individual's risk of developing type-2 diabetes, therefore, lifestyle changes and other disease monitoring options can lessen the overall likelihood of the disease in later life.

PERSONALISED MEDICINE IN PSYCHIATRY

While personalised medicine application in fields like oncology have been so successful as to completely change the outlook and approach, management of the subject, the same is yet to be achieved in Psychiatry [2]. Important applications in Psychiatry are in the fields related to the study of contributing factors to psychiatric heritability and study of the predictability of treatment response and non-response (therapeutic and side effect profile). Among the contributing factors of heritability are the study of genetic determinants of susceptibility or protective factors imparted through genetic change like the polymorphisims and variable tandem number repeat regions(VNTR) in the 5HT transporter(5HTT) gene associated with the development of major depressive disorder [3]. Epigenetic modifications too are important contributory factors implicated in neural processes ranging from learning and memory to neurogenesis and seizures and disorders like depression, chronic stress and addictions [4, 5]. As psychiatric disorders still rely heavily on symptoms for diagnosis and a biological marker reflects function, response to treatment or indicates the natural progression of the disorder, endophenotypes and biological markers become some other areas of interest [6, 7]. Example is the presence of anhedonia as a endophenotype for MDD [8] and CSF concentrations of MHPG as a biomarker for suicide [9, 10].

Environmental factors like stress may also play contributory role with precipitation or exacerbation of various disorders in response to stress. HPA axis dysregulation is thought to be the underlying

mechanism of such symptoms and a gene coding for CRHreceptor 1(CRHR1) is now identified to be associated with mood disorders [11] and also response to various antidepressants seems to be related to CRHR1 haplotypes [11]. In utero exposure has been widely studied in relation to schizophrenia and to a lesser extent in bipolar disorder.

On the other hand genetic alterations in drug metabolising enzymes are useful predictors of response and extensive studies of the cytochrome P450 family has shown that differential expression in the genes coding for these enzymes leads to differential metabolism of psychotropic medications[12], that can render the drug useless or potentially life threatening like CYP2D6 polymorphism may cause an individual to be highly susceptible to serious side effects of TCAs, SSRIs and antipsychotics due to increased bioavailability and prolonged elimination half-lives[13].

Thus we see that an individual's unique psychiatric phenotype can make him susceptible or resistant to develop the disorder and also make him suitable or unsuitable for a drug.

PERSONALISED MEDICINE IN SCHIZOPHRENIA

Understanding schizophrenia has always been a baffling mystery to the researchers, let alone the psychiatrists.with the discovery of chlorpromazine which was a revolutionary landmark to the atypical antipsychotics dominating the markets today, managing the mentally ill has come a long way and it is an ongoing process with new advancements unfolding every other day. But the million dollar question that remains is "how far have we been able to effectively tackle the burden of psychiatric illness" and "how effective are the antipsychotic medications in this regard". Undoubtedly, these medications remain an immediate measure to resort to when it comes to calming down a patient and bringing the acutely symptomatic back to their senses within a few days of treatment, but when the question arises as to if the psychoactive medicines lead on to an overall psychosocial wellbeing, there is very little to answer. With many patients being continued on powerful tranquilisers at high doses for long periods and studies providing

evidences that antipsychotic drugs are responsible for shrinkage in brain matter found in chronic schizophrenics [14], it can be said that pharmaceuticals may sabotage meaningful recovery in some patients. So, while antipsychotics remain a necessary evil in psychiatric practice, there is a growing concern to explore other treatment options which would prove more beneficial to the nature of the illness.

The phenotypal presentation of schizophrenia is heterogenous and so is the clinical response to antipsychotics, with about a third of patients declared treatment resistant, the annual cost for who is 3to 11 fold higher than the responders, with irregular clinical course and poor recovery rates standing as major hindrances to effective treatment. All of it calls for a more holistic take in understanding the underlying psychopathology and adopting treatment practices considering the biological individuality, identifying a more homogenous subsets of patients through the personalised approach

Genetics- importance and scope

To identify a definite "schizophrenia gene" might seem improbable but undoubtedly it stands as the most heritable among all psychiatric conditions with hereitibility estimates of 50- 80 per cent [15, 16], 8- 10 fold increased risk in family studies compared to the rest of the population and twin studies showing higher concordance in monozygotic twins with heritability estimates between 53-90 per cent. But the GWAS studies conducted has concluded that schizophrenia stays a genetically complex condition with a polygenic inheritance pattern [17]. The relation between MHC genes and schizophrenia is also explored and the studies done have implicated the genomic region (b/w 26- 33 million bp) containing the MHC. Schizophrenia associated genes and genetic regions outside of MHC region including the zinc finger 804A (ZNF-804A) is also studied. Another gene associated with schizophrenia is transcription factor 4(TCF-4), a gene necessary for neurodevelopment[18,19], with mutations leading to a condition called Pitt- Hopkins syndrome which is characterised by mental

retardation, epilepsy, hyperventilation episodes and distinct facial features [19,20]. Neuregulin 1 (NRG1), gene regulating neuronal migration, expression and activation of glutamate receptors, and oligodendrocyte development is also identified to be associated with schizophrenia.[21-25].NRG1 gene 8p22-21 has been identified as a possible " schizophrenia susceptibility locus" in the linkage studies conducted[26-29]. NRG1 haplotype hapICE is also found more significantly associated with schizophrenic samples than control groups. GWA studies have also found association for certain genes with atleast nominally significant effects namely DRD2; GRM3, GR1N2A, SRR, GRIA1 (glutaminergic transmission and synaptic plasticity); CACNAIC, CACNB2, CACNA11(calcium signalling genes). It has been found that majority of the variants associated with schizophrenia exert their influence by altering gene expression rather than the protein structure. Special attention here is given to the COMT gene, encoding a protein responsible for metabolic degradation of catecholamines, and whose location in the genome is also interesting. This gene is located on chromosome 22 within a region that when deleted it causes velocardiofacial syndrome (VCFS). It has been seen that around a quarter of patients with deletion of 22q1121 go on to develop schizophrenia. Therefore, it stands as an important risk factor predicting schizophrenia. The high risk of developing schizophrenia associated with the CNV's (copy number variations) throws need on estimating their penetrance and using the information for genetic counselling. The DISC (disrupted in schizophrenia) locus encoding balanced translocation between chromosome 1 and chromosome 11 is also said to be associated with schizophrenia with positive correlation studies for DISC1 and schizophrenic individuals available [30,31]. Other schizophrenia associated CNV's include NRXN1, coding for cell adhesion molecule neurexin 1, specific to synapses in the brain.

Hoffer's theory of abnormal adrenaline metabolism says that anxious states in genetically susceptible individuals produces adrenolutin, a toxic form of adrenaline, which results

in the hallucinations and sensory dysperceptions encountered in schizophrenic individuals. Therefore, genetic differences while considering catecholamines and adrenaline can induce schizophrenia- like syndrome.

Imaging Genetics

Neuroimaging is a rapidly advancing area and imaging genetics seeks to relate genetic variations with imaging phenotypes so as to have a better comprehension of the psychopathologies of psychiatric illnesses, also aiding in our understanding of changes in vivo and over the course of the disease. Some significantly replicated findings are reduced prefrontal and temporal lobe volumes with reductions in neuronal spine density in layer 3 of prefrontal cortex, consistent reductions in amygdala- hippocampal volumes, ventricular dilatations especially, the third and lateral ventricles,Thalamus volume shrinkage and volumetric increase of the caudate putamen complex in basal ganglia.

Magnetic resonance spectroscopy (MRS) studies have demonstrated elevated anterior cingulate glutamate levels in poor responders of first episode psychosis and this associated with persistence of negative symptoms and poor level of functioning (Egerton 2012).

SPECT studies have provided evidence that higher level of perfusion in the striatum, thalamus and prefrontal cortex is noticed following symptomatic improvement with clozapine treatment and this can be used as a predictor of clozapine response (Rodriguez, 1997). Therefore, neuroimaging studies can be used to suggest the treatment outcomes in patients.

Epigenetic modifications- what we know so far

The role of epigenetics in personalised medicine is another important aspect to look into.

Methylation patterns in schizophrenia has been a focus since many years as methylating agents like methionine can result in exacerbation of psychosis in schizophrenic individuals [32, 33] and it induces schizophrenia-like behvavioural abnormalities in

animal studies [34]. Differences also lie between schizophrenic individuals and controls when it comes to methylation pattern in the regulatory regions of COMT and reelin (RELN), encoding a glycoprotein important for cell to cell interaction during migration and neuronal position [35]. Dysregualtion at both these genes can result in psychopathologies. Schizophrenic individuals, compared to the controls show significant hypomethyaltion and consequently overexpression of membrane bound MB-COMT promoter [36], resulting in a hypodopaminergic state due to excess dopamine depletion. On the contrary, RELN mRNA expression was found less in schizophrenics compared to controls. However, these findings are not replicated [36, 37] in other studies.

A significant association of HTR2A SNP (5HT2A receptor gene) with schizophrenia has been found in the European population [38-40] and decrease in HTR2A mRNA expression is found exaggerated in schizophrenic individuals.

Another important epigenetic mechanism found associated with schizophrenic psychopathology is histone modification. Post mortem samples of schizophrenic brain show increase levels of HDAC1 (histone deacetylase type 1) in prefrontal cortices. This enzyme is responsible for silencing gene expression [41-43]. Drugs like valproate exert their mood stabilising effects by targeting this epigenetic property [44], and inhibiting HDAC1, resulting in attenuation of behavioural abnormality.

Studies on micro RNAs have produced inconsistent results. So while micro RNA dysregulation and altered mi RNA expression is frequently observed in schizophrenics compared to controls (Beveridge and colleagues, 2008- 2010), the studies have produced differing results in the context of upregulation (Beveridge study) or downregulation (Perkins study) of the identified mi RNAs.

Biomarkers and Endophenotypes

While there is a subtle difference between these two terms, considering that endophenotypes are trait markers while biomarkers can be both state and trait markers, there is a significant overlap between the two. Certain criteria has been laid down for

defining endophenotypes (Gottesman and Gould, 2003), some of which include- it should be heritable with more prevelance in the affected than unaffected families, specific to illness, should be reliably measured and these are markers irrespective of phenotypic presence or absence of illness Studies show that higher genetic risk for schizophrenia is associated with worse treatment outcomes (Frank et al, 2015). Although many researchers suggest that anti-psychotic induced side effects and efficacy are associated with a modest effect with candidate gene polymorphism, the findings are inconsistent as it has not been replicated across studies. However, some biomarkers have been found promising in this regard. For example, ABCD1 gene polymorphism is considered predictive of serum clozapine levels (Krivoy, 2015). More studies are needed to substantiate the results as no single polymorphism can be used for prediction of clozapine levels. Others biomarkers include drugs targeting dopamine and serotonin receptor, drug metabolising enzyme especially CYP450 enzymes and COMT, and HLA alleles.

Drug metabolising enzyme like CYP2D6, genes for which are highly polymorphic [45], which is an important member of the CYP enzyme family and which metabolises around half of the psychoactive medications including tricyclic antidepressants (TCA), specific serotonin reuptake inhibitors (SSRI) and anti-psychotics is also important in this regard. Poor metabolisers of this enzyme are at a risk of side effects while the ultra- metabolisers show poor therapeutic response [13]. Therefore, genetic alterations in CYP enzymes could predict efficacy but how far its genotyping is applicable in clinical settings prior to drug prescription remains a big question.

It has also been found that lower dopaminergic metabolite levels are associated with a poor response to anti- psychotic treatment while higher plasma levels of homovanellic acid, a metabolite of dopamine, is associated with a good response. Treatment resistant patients do not how a time dependant decrease in homovanellic acid with anti- psychotic treatment (Pickar, 1986, Davila, 1988)
Proper understanding of the biomarkers would help improve clinical diagnosis as it enhances the ability to predict in advance

whether or not a patient would respond to a medication, it helps in identifying hypersensitive individuals, especially to medications like carbamazepine. Screening for HLA B 1502 allele in people of South East Asian ethnicity would reduce the possibility of carbamazepine toxicity as positivity for this allele is associated with development of Steven Johnson syndrome or toxic epidermal necrolysis (Ferrell, 2008). Likewise, positivity for HLA B5701 allele is associated with hypersensitivity to abacavir treatment in HIV (Mallal, 2008).

A genome wide association study, drawing data from CATIE trial, analysed 738patients with schizophrenia and identified one single locus at rs17390445 associated with improved schizophrenic positive symptoms to ziprasidone treatment.

Antipsychotic treatment response with KCNH2 (gene for voltage gated K+ channel, subtype H) gene is also studied and it was found that individuals with TT genotype exhibit greater symptomatic improvement than those with TC or CC genotype. This trial shows that genotyping may help guide therapeutic decisions in schizophrenia.

Biomarkers also help in checking adverse drug effects and efficacy of the medications. 759T/C polymorphisms in the HTR2C gene and polymorphisms in the gene for leptin, which is important for satiety and adipose regulation, is associated with significant risk of weight gain (Arranz ,2011) and is seen with drugs like olanzapine and clozapine as both of them have strong affinity for 5HT2C receptors. The HLA system so far has promising genetic association with clozapine induced agranulocytosis (CIA). HLA DQ B1 locus is implicated in development of clozapine induced agranulocytosis but being dominated by small sample studies and owing to its low sensitivity, its use is limited in clinical settings (Choudhury 2011, Verbelen 2015). In relation to adverse effects, polymorphisms near the DA receptor D3 gene is found to increase susceptibility to tardive dyskinesia while polymorphisms near the DA receptor D2 gene is associated with protection against tardive dyskinesia.

Cognitive deficits are also considered as important endophenotypes[46] considering their strong genetic influence and

heritability. Cognitive domains are found to be frequently affected in schizophrenics compared to controls with maximum deficiency in verbal memory recall and executive functioning(Sitzkoorn and collegues). Cognitive deficits are also identified in the genetically susceptible relatives compared to controls with greatest effect size seen for semantic and phonological verbal fluency (Szoke et al)

CHALLENGES TO PERSONALISED MEDICINE IN SCHIZOPHRENIA

The complexity and heterogeneity of schizophrenia phenotype stands as the major challenge as schizophrenia is not only complex genetically but the social and environmental factors are also not clearly defined. Also there is a poor understanding in the mechanism of antipsychotics which is more of a clinical observation, limiting our ability to decide which biomarkers might be relevant towards generating a therapeutic response. Also lacking are guidelines for the clinical use of pharmacogentic markers. Talking about this approach, it will require a profound change in prescribing practise, with treatment decisions based on genetic tests and other biomarkers. So clinician attitude towards this issue might also influence advances in this field as many important treatment decisions might no longer be in control of the physicians. Also for widespread utilization of personalised medicine there is a heavy dependence on the use of highly integrated patient records, to ensure that the information is available for all clinicians during any future clinical encounter. If we look at health economics, evaluation of the costs and outcomes of the use of pharmacogenetic tests in schizophrenia is still a poorly researched area. The cost effectiveness will also depend on the prevalence of test positive individuals and a big ethical question remains that patients with less profitable genotypes might stand at a risk of becoming therapeutic orphans with a reduced change of having treatments developed for them.

CONCLUSION and FUTURE DIRECTIONS

Even though personalised medicine is an exciting and powerful field, the right test for the right person with the right

interpretation stands critical towards making appropriate management decisions. New ethical and legal issues will arise from molecular and genetic testing so it depends heavily on the degree to which the provider is educated in the field and is prepared to face the outcomes that follow. One can only hope that diagnostic and drug research targeting cells, tissues and organs at the genomic and molecular level pushes us towards optimizing and revolutionizing management of schizophrenia. Currently approved drugs that have limited market share due to its toxicity or limited efficacy may get an enhanced value if physicians are able to identify those individuals in whom they are both safe and effective. Drug related diagnostics can provide better utilization parameters for new products as well as improve safety profile and efficacy of the older ones. Overall a wider variety of effective medical care options may be provided to the patients based on their unique genotypic, phenotypic and environmental profile.

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Current Approach in Management of Substance Induced Psychosis

Shijo John Joseph, Sanjiba Dutta

ABSTRACT: *Rates of substance use amongst psychiatric patients are considerably greater than in the general population with occurrences up to 50% having been reported in adults. There is unquestionably a dearth of literature regarding substance-induced psychosis, both in India or around the globe; especially regarding the outcomes and trajectories of such psychotic disorders. And, the same applies to the treatment of substance-induced psychosis probably because of the challenges in terms of management and the future routes these disorders may take at times.*

Keywords: *Induced psychosis, cannabis, stimulant, alcohol.*

INTRODUCTION

Substance-induced psychosis is defined as a disorder in which psychotic symptoms are produced by a psychoactive substance and resolve within a period of time. The fact that substances cause transient psychotic symptoms was first cited in studies from the sixties. [1, 2] Numerous experimental studies revealed that substances can cause effects which appear similar to positive, negative and cognitive-related symptoms of schizophrenia. [1, 3, 4]

Key pharmacological theories of schizophrenia have their basis in the effects of substance abuse. Worthy examples include lysergic acid diethylamide (LSD) and serotonergic model, the amphetamines and the dopamine hypothesis, phencyclidine (PCP), ketamine and the glutamatergic model, and, lately, the effects of cannabis and the role of endocannabinoids. [5]

Nosological Status

Following are the criteria as laid down in ICD-10 and DSM-5 classificatory systems:

ICD-10

- A psychotic disorder occurring during or immediately after drug use (usually within 48 hours) provided that it is not a manifestation of drug withdrawal state with delirium or of late onset. Late-onset psychotic disorders that are with onset more than 2 weeks after substance use may occur.
- The disorder typically resolves at least partially within 1 month and fully within 6 months. [6]

DSM-5

- The disorder represents a clinically significant symptomatic presentation of a relevant mental disorder; psychosis in this case.
- There is evidence from the history, physical examination, or laboratory findings of both of the following:
- The disorder developed during or within 1 month of a substance intoxication or withdrawal or taking a medication; and
- The involved substance/medication is capable of producing the mental disorder; psychosis in this case.
- The disorder is not better explained by an independent mental disorder (i.e., one that is not substance or medication-induced). Such evidence of an independent mental disorder could include the following:
    a) The disorder preceded the onset of severe intoxication or withdrawal or exposure to the medication; or
    b) The full mental disorder persisted for a substantial period of time (e.g., at least 1 month) after the cessation of acute withdrawal or severe intoxication

or taking the medication. This criterion does not apply to substance-induced neurocognitive disorders or hallucinogen persisting perception disorder, which persist beyond the cessation of acute intoxication or withdrawal.

- The disorder does not occur exclusively during the course of a delirium.
- The disorder causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. [7]

The Challenge Before Treatment

Unsteady and variable diagnoses may occur in cases where there is a coexistence of psychosis with substance misuse, and when the substance-free duration is inadequate. In such instances, usually, a default or temporary diagnosis of psychosis not otherwise specified (NOS) is what we tend to make. This lessens the possibility of over-diagnosing primary psychotic syndromes which are in actuality the effects of intoxication or withdrawal, but at the same time upsurges, the possibility of underdiagnosing substance-induced psychosis.

In case of both the DSM-5 and ICD-10 diagnostic structures, determining whether symptoms resolve within the set timeframe necessitates observing the patient for that time period, unaffected by psychotogenic substances. Nevertheless, keeping patients hospitalized or away from substance use for adequate lengths of time presents challenges. Substance users frequently present when they are floridly psychotic and incapable to care of themselves, but are then discharged rapidly when their symptoms settle down, either due to pressure for bed availability, or the patients' own choice.

Moreover, neither the ICD-10 nor the DSM-V permits for coding of "persistent states" of substance-induced psychosis, even though there is evidence in literature signifying that in certain chronic users, psychotic symptoms can last markedly longer than the specified timeframes. [8, 9] In those cases, according to diagnostic criteria, the diagnosis should be altered from substance-induced

psychosis to primary psychosis. But even then, the question of whether chronic use of psychotogenic substances in these cases induces a long-lasting psychotic syndrome or whether it triggers a primary psychotic disorder rests unanswered.

A diagnosis changing over time is common in cases of psychotic disorders and percentage of change from substance-induced psychosis to primary psychosis ranges from 25% to 50%. [10, 11]

Treatment

Determining the precise diagnosis can be puzzling in early-phase psychosis where there is substance misuse. The extensive range of distinctive test instruments, diagnostic standards, and cut-off criteria make it challenging to draw any definite conclusions with regards to the cause, effect, and risk. However, differentiating between substance-induced psychosis and primary psychosis is fundamental in understanding illness and delivering ideal treatment. Primary psychosis follows a curve at the opposite end of the spectrum to substance-induced psychosis, often involving chronicity as opposed to transiency.

The primary goal in substance-induced psychosis is stopping substance use. In substance-induced psychosis, patients may be admitted and observed while eliminating access to substances, under vigilant medical observation in order to safely control any withdrawal symptoms.

Agitation and aggression are frequently what necessitates medication, but more often than not, symptoms are self-limiting, receding in hours to days. Pharmacotherapy is needed at times, usually in the form of benzodiazepines or antipsychotics.

CANNABIS INDUCED PSYCHOSIS

DSM-5 labels cannabis-induced psychotic disorder (CIP) as a substance-induced psychotic disorder. There are certain characteristics of CIP that differentiate it from other psychotic disorders like schizophrenia. Marked features of CIP include mood lability of abrupt onset and paranoid like symptoms, occurring

in 1 week of use or even as early as 24 hours after use. CIP is generally triggered by a rapid increase in potency such as THC content percentage or quantity of cannabis intake. Like in case of all substance-induced psychotic states, abstinence from cannabis may be the absolute measure to prevent recurrence. As a result of inadequate research pertaining to CIP, attaining symptomatic treatment in acute phases of CIP has proven to be difficult.

Pharmacotherapeutic interventions include the second-generation antipsychotic drug olanzapine and haloperidol. While both are equally effective, their different adverse effect profiles should be taken into consideration when treating a patient; olanzapine is associated with significantly fewer extrapyramidal adverse effects.

Report by Perera T, Webler R in 2017 showed that antipsychotics deteriorated the condition in some patients.[12] Conventional antipsychotics failed to decrease the symptoms of CIP in a 20-year old man. Trials of olanzapine, lithium, and haloperidol had minute to no effect on his psychosis. Risperidone was tried but provoked temporal lobe epilepsy with auditory, somatic, and olfactory hallucinations. Conversely, the use of valproate sodium significantly improved his symptoms and cognition.

Carbamazepine also seems to have rapid effects when used as an add-on to antipsychotics.[13]Use of anticonvulsant medications in CIP treatment has been hypothesized to diminish neuroleptic adverse effects, subsequently bettering the tolerance of antipsychotics.[12,13]These results suggest the use of adjunctive anticonvulsant can be considered in treatment strategies.

Abstaining from cannabis is the most advantageous and effective measure for preventing future CIP events; however, it is likely to be the most challenging to implement. Psychosocial intervention has a noteworthy impact on early-phase psychosis, and it plays an important role in disease outcomes. A delay in delivering intensive psychosocial treatment has been linked to more negative symptoms compared with a delay in administrating antipsychotic medication. [14] When compared to standard of care, motivational interviewing notably increases the number of abstinent days from

cannabis and aids in lessening short-term consumption.

STIMULANT INDUCED PSYCHOSIS

A number of case studies provide guidance for clinical practice, which reports the use of antipsychotics including risperidone and olanzapine in the management of acute methamphetamine (stimulant) induced psychotic symptoms.[15-18] An apt clinical trial relating to stimulant-induced psychosis is found in the 2009 Cochrane review of treatments for amphetamine psychosis.[19] This small randomized trial (N=58) found both olanzapine and haloperidol to be efficacious in treating psychotic symptoms, with significantly better tolerability and fewer extrapyramidal symptoms associated with the use of olanzapine .[20]

Bramness and colleagues pointed out in 2012 [21] that the increased anhedonia putatively produced by the antipsychotic action of blocking the DRD2 receptor may heighten vulnerability to methamphetamine relapse, a proposition with some reassuring clinical evidence.[22,23] Also, one preclinical study recognized a potential methamphetamine-haloperidol interaction producing GABAergic cell death, which in turn, could heighten the risk of seizures and hyperkinetic movement disorders.[24] At the same time, there may be some protective effects of neuroleptics against stimulant related toxicity.[25]

There are no FDA-approved agents for treating methamphetamine abuse. [26] Numerous drugs have been attempted with varying degrees of success, including bupropion, modafinil, and naltrexone. Naltrexone may be a reasonable medication to consider because of the high prevalence of comorbid alcohol abuse among methamphetamine users. Other treatments for methamphetamine addiction include behavioural interventions such as cognitive-behavioural therapy. First-generation antipsychotics, such as haloperidol or fluphenazine, need to be used sparingly in patients with methamphetamine-induced psychosis because of the risk of developing extrapyramidal symptoms (EPS) and because these patients are vulnerable to develop motor complications as a result of

methamphetamine abuse. Second-generation antipsychotics, such as risperidone and olanzapine, may be more appropriate because of the reduced risks of EPS.[27] The occurrence of high norepinephrine levels in some patients with recurrent methamphetamine psychosis suggests that drugs that block norepinephrine receptors, such as *prazosin or propranolol*, might be of therapeutic benefit if they are shown to be effective in controlled clinical trials.

ALCOHOL-INDUCED PSYCHOSIS

When the patient requires sedation due to alcohol-induced psychosis, neuroleptics, such as haloperidol, have been considered the first-line medications for treatment. Benzodiazepines, such as lorazepam, are used, especially if there is an apprehension for withdrawal since these are used to treat alcohol withdrawal seizures. It is important to avoid any medication that may lower the seizure threshold.

Certain atypical antipsychotics, such *as ziprasidone*, have also been used to help sedate patients with acute psychosis. At times patients may require the use of physical restraints to protect the patient themselves as well as the staff. Patients with alcohol-induced psychosis must also be assessed for suicidality as it is linked to high rates of suicidal behaviours. [28-30]

CONCLUSION

Thus in substance induced psychosis the clinical symptoms and nature of treatment may be different depending on the primary substance used. Transient nature is the main issue that differentiates with other primary psychotic disorders. Chronicity of symptoms in absence of intake of the substance may necessitate review of diagnosis.

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Current Update on Neurobiology of Inhalant Use Disorders and Future Direction

Satya K Dutta

ABSTRACT: *Inhalants are used in many household products as solvents, propellants, thinners, and fuels. Multiple factors contribute to the etiology of inhalant-related disorders-availability,rewarding effects, quick high and risk-taking propensity particularly in an adolescent. Different methods of use are sniffing vapour through the nose, or huffing through the mouth, breathing through a solvent-soaked cloth, huffing vapour sprayed into a plastic bag, or breathing vapour from a gasoline. Absorption is increased by moderate exercise, alcohol. Inhalants have a reinforcing effect due to their ability to modulate mesolimbic dopaminergic activity. Toluene induces c-fos activation in both the ventral tegmental area (VTA) and nucleus accumbens. Toluene produces a rapid, non-competitive, almost complete and reversible inhibition of the cationic currents through NMDA receptors. Gliosis and activation of astrocytes in white matter, is the main mechanism of toluene encephalopathy. Gasoline containing tetraethyl lead, can lead to the neurocognitive impairment.*

Key words:*mesolimbic dopaminergic pathway, inhalants,gliosis, astrocytes*

INTRODUCTION

Inhalants are used in many household products as solvents, propellants, thinners, and fuels. It includes a wide range of volatile hydrocarbons, such as toluene, xylene, hexane, trichloroethylene and trichloroethane etc. At room temperature, these compounds volatilize to gaseous fumes that can be inhaled through the nose or mouth, entering the bloodstream by the transpulmonary route. Due to certain pharmacologic properties shared by them, they are grouped under the term inhalants.

Definition: Diagnostic and Statistical Manual of Mental Disorders(DSM-5) includes "Inhalants Related Disorder." The first category is the inhalant use disorders. The second category is inhalant intoxication result from the toxic effects of inhaled substances. Other two categories are other inhalant-induced disorders and unspecified inhalant- related disorder.

The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) refers to inhalants as "volatile substances." ICD-10 does not use the term abuse, instead of the term "harmful use."

Epidemiology- prevalence, comorbidity:

The most informative surveys of inhalant use are the Monitoring the Future (MTF) survey, the Youth Risk Behavior Survey (YRBS), and the National Survey on Drug Use and Health (NSDUH). An estimated 9 per cent of the U.S. population age 12 and older has used an inhalant at least once (NSDUH). 58 per cent of users reporting first use by the end of ninth grade (MTF). 13 per cent of students in grades 9 through 12 reported having ever used an inhalant on the 2007 YRBS. Most inhalant users initiate the behaviour young, and discontinue it. Those who drop out of school continue using inhalants at higher rates than those who stay.

In an Indian study done in the north-eastern area, it was found that out of 312 persons interviewed only 0.64% of persons used inhalants.[1]

Comorbidity

Inhalant use is a risk for injected drugs use which further increases human immunodeficiency virus and hepatitis C. Other disorders commonly seen with inhalant use are other substance use disorders, delinquent behaviours and conduct disorder, antisocial personality disorder, depression and anxiety disorder.

Commonly Abused Inhalants and their Constituents

1. Volatile solvents
   Correction fluids (1, 1, 1-trichloroethane)

Dry-cleaning fluids (trichloroethylene, 1, 1, 1-trichloroethane)
Glues (n-hexane, toluene, xylene)
Nail polish remover (acetone, esters)
Paint removers (dichloromethane, toluene and xylene)
Petrol (benzene, n-hexane, toluene, xylene)

2. Aerosols
   Deodorants and hairsprays
   Fabric protector sprays
   Spray paints (toluene, methyl isobutyl ketone)
   Vegetable oil sprays
3. Gases
   Bottled gas (propane)
   Cigarette lighter fluid (butane)
   Medical anaesthetics (ether, chloroform, nitrous oxide)
   Whipped cream (nitrous oxide)

Aetiology

Inhalant users can be grouped into three different types. First, some users use a high number of different inhalants, had high levels of psychopathology (i.e., depression, anxiety), serious family problems, high levels of affective instability, and utilized inhalants to help cope with those problems. Second, they appear to have lower levels of these problems, and most of them have only utilized one type of inhalant. A third group appeared to use inhalants because they were easy to obtain.

Multiple factors contribute to the aetiology of inhalant-related disorders.

Extrinsic factors

1. Availability is important in determining factor. Inhalants are cheap, easily available, easily concealed, legal to possess, and simple to take.
2. Inhalant use is rewarding, both through direct pharmacological action and through the drugs social effects.

3. Inhalants quickly produce a high that passes within a few hours, thus often evade detection or punishment by parents or school authorities,
4. It is one of the few exciting and novel experiences available to youths in impoverished communities.

Intrinsic factors

Risk-taking propensity particularly in persons with adolescent conduct disorder or adult antisocial personality disorder is important.

Pharmacology and Toxicology

The most commonly used inhalants by adolescents of the United States, in descending order are glue/shoe polish (contains toluene), gasoline, spray paint, correction fluid. Different methods of use are sniffing vapour through the nose, or huffing (deep breaths) through the mouth, breathing through a solvent-soaked cloth, huffing vapour sprayed into a plastic bag, or breathing vapour from a gasoline. We lack such data from India. Inhalants get transpulmonary absorption with rapid access to the brain. Absorption is increased by moderate exercise through increased respiration and alcohol through competition for hepatic metabolizing enzymes. Brain and fat achieve higher concentrations than blood because of lipophilic nature of inhalants.

About 15 to 20 breaths of 1 per cent gasoline vapour produce several hours of intoxication. Toluene concentrations in blood of intoxicated persons range from .8 to 8 µ/g. Industrial exposure of 100 ppm produces blood levels around .5 µ/g. 20 per cent of toluene is excreted unchanged in the breath but most are metabolized in the liver to hippuric acid before urinary excretion. After the end of the prolonged exposure, breathe concentrations of toluene fall by half within a few minutes. Blood concentrations fall slowly, becoming undetectable 4 to 10 hours after exposure.

Gasoline containing tetraethyl lead, can lead to the neurocognitive impairment. Tetraethyl lead is also responsible for

lead-gasoline encephalopathy. Replacing leaded with unleaded gasoline eliminate psychotic emergencies, severe headaches and abdominal cramps.

Neurobiology

Inhalants have a reinforcing effect due to their ability to modulate mesolimbic dopaminergic activity. Toluene induces c-fos activation in both the ventral tegmental area (VTA) and nucleus accumbens.[2] Perfusion of toluene directly into the VTA increases dopamine concentrations within both the VTA and the nucleus accumbens. Microdialysis reveals that toluene is more effective in increasing dopamine concentrations within the nucleus accumbens when infused into the posterior compared with the anterior VTA. Long-term exposure to toluene induces persistent dopaminergic dysfunction within the basal ganglia, which is associated with behavioural and cognitive deficits.[3-5]

Similar to other CNS depressants, inhalant exposure results in biphasic changes in motor activity and behaviour. At low concentrations that is, 500– 4000 ppm inhaled toluene produces motor excitation and at higher concentrations that is at 6000–15 000 ppm toluene produces sedation, motor impairment and anaesthesia. Prolonged exposure to high concentrations can result in coma and subsequent death due to respiratory depression.[6,7]

At receptor level

Relatively little work has been done exploring the neurobiology of inhalant use. Acute solvent exposure produces NMDA receptor inhibition.[7] Toluene produces a rapid, non-competitive, almost complete and reversible inhibition of the cationic currents through NMDA receptors.[8] Semi-chronic (4days) exposure to toluene increases in NMDA evoked responses with a decrease in GABA-evoked responses. In parallel, NMDA receptor subunits (NR2A and NR2B) are upregulated.[9]

Acute toluene exposure increases m-opioid receptor protein in brainstem nuclei, including the dorsal raphe and periaqueductal

grey.[10]while chronic exposure has a myriad of effects. 80 ppm of toluene for 6 h a day, 5 days a week over 3 months resulted in reduced [3H]neurotensin binding in the orbital cortex, but increased accumbal binding of [3H]etorphine to opioid receptors[11]

In another experiment Williams et al. (2005) exposed rats to toluene (8000 ppm) for 10 days (30 min day_1) and found that increased NR1 and NR2B receptor subunits in the medial prefrontal cortex and NR2B subunits in the nucleus accumbens, suggesting an increase in neuronal excitability with prolonged exposure. Chronic exposure was also found to increase GABAA a1 subunit levels in the medial prefrontal cortex, but decrease expression in the ventral mesencephalon.[12] Such findings highlight the potential for excitotoxic neuronal damage with chronic inhalant exposure.

Animal studies suggest that gliosis and activation of astrocytes in white matter, rather than neuronal death is the main mechanism responsible toluene encephalopathy.[13,14]Using magnetic resonance spectroscopy in a sample of chronic users, Aydin et al. (2003) demonstrated decreased levels of N-acetyl aspartate (a metabolite within neuronal mitochondria which reflects neuronal functional viability) and increased myoinositol-containing compounds. [15] These findings suggest that inhalant abuse does not cause demyelination or breakdown in the neuronal membrane, rather may lead to diffuse axonal injury due to impaired functional viability.

Radiological findings

Computed tomography (CT) and magnetic resonance imaging (MRI) reveal diffuse cerebral, cerebellar, and brainstem atrophy with white matter disease, a leukoencephalopathy.

House painters and factory workers who have been exposed to solvents for long periods are found to have brain atrophy on CT scans, with decreased cerebral blood flow.

Although neuroimaging and postmortem studies suggest that inhalant-related brain injury may be irreversible, few longitudinal studies are available. Younger individuals having a shorter duration of gasoline inhaling, and less severe baseline neurological

impairments, completely recover after total abstinence.

Acute effects

Users are at risk of suffocation or burns from exploding solvents. The most serious adverse effect is death, which can result from respiratory depression, cardiac arrhythmias, asphyxiation, aspiration of vomitus, or accident or injury (e.g., driving while intoxicated with inhalants). There is no apparent safe level of use, with even first-time users at risk of sudden sniffing death as a result of cardiac arrhythmias. Inhalants appear to sensitize the myocardium to endogenous catecholamines, which may result in fatal ventricular arrhythmias if the user is startled or agitated. Spraying inhalants directly into the mouth is also potentially fatal, as the cooling agents within aerosols can produce death by laryngeal spasm or pulmonary oedema.

Chronic effects

Neurological: Neurological and behavioural signs and symptoms may include hearing loss, peripheral neuropathy, headache, paraesthesias, cerebellar signs, persisting motor impairment, parkinsonism, apathy, poor concentration, deficits in executive function, working memory, and information processing (with relative sparing of language), visual-spatial dysfunction, and lead encephalopathy.

Even a single experience of inhalant intoxication can produce long-term memory problems and processing speed impairments. The combination of organic solvents with copper, zinc, and heavy metals has been associated with brain atrophy, temporal lobe epilepsy, decreased IQ, and a variety of EEG changes

Other adverse effects: Adverse effects include gastrointestinal (GI) symptoms (e.g., pain, nausea, vomiting, and hematemesis), cardiovascular and pulmonary symptoms (e.g., chest pain and bronchospasm, asthma). Serious adverse effects are irreversible hepatic damage, renal tubular acidosis and rhabdomyolysis.

Psychosocial Effects

Little is known about the natural history of inhalant use. Youths who had used inhalants are more likely than non using peers to have used another psychoactive drug. Inhalant users have higher rates of major depression, suicidal ideation and attempts, anxiety disorders, and other substance use disorders than nonusers of inhalants.

Effects on the Fetus

Maternal inhalant use during pregnancy may produce effects similar to that fetal alcohol syndrome.[16,17] One study, reported high rates of head and facial deformities, smaller head and brain development, low birth weight, developmental delays, and other pregnancy and birth complications in infants born to women who inhaled solvents recreationally.[18]

CONCLUSION

Although there is substantial research on the neurobiology of inhalants, most of them are done on acute exposure to toluene, with little emphasis on neuropharmacological differences across volatile substances. Future studies are needed to determine the similarities and differences of specific abused inhalants. Future studies are also needed on the neuromaturational changes that occur on the brain during childhood and adolescence, and to investigate the neuropharmacological and toxicological profile of inhalant exposure during this developmental period. Studies are also needed to determine neurobiological abnormalities present premorbidly in chronic abusers.

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Neurobiology of Opioid Addiction and Emerging Treatment Options

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ABSTRACT: *The opioid users are vulnerable to addiction. The cellular changes develop from the first use of the opioid itself. The use of opioids causes the release of dopamine in the mesolimbic area which gives pleasurable sensation to the person. This reinforces the future use of the drug. The effect is mediated mainly by μ-opioid receptors. But apart from dopamine, there are various other neurotransmitters and neuropeptides are involved in the process of addiction to opioids. Relapse to opioid is another aspect. Studies related to it are mostly animal-based and have focused on a variety of receptors like dopamine, opioid, NMDA, GABA, cannabinoid, corticotrophin, vasopressin and orexin. The corresponding neural substrates with respect to the different types of opioid relapses are also varied. An understanding of the step by step development of opioid dependence and later on relapse will help in identifying novel approaches in the management of opioid addiction.*

Keywords: *Opioid addiction, opioid tolerance, opioid withdrawal, opioid relapse.*

INTRODUCTION

Opioid addiction is a chronic relapsing disorder which is associated with the compulsive use of the opioids, inability to limit its use and episodes of craving for the drug because of circumstances previously associated with its use.[1] The motivation of a person with an addiction to drugs occurs from a desire to experience the pleasurable or rewarding effects of the drug and also to avoid the anhedonia and aversive consequences due to drug withdrawal.

Chronic drug use causes long-lasting adaptations in neurons that mediate drug reward or incentive salience. Hypersensitivity of these neuronal systems result in enhanced incentive value to future drug use causing compulsive drug-seeking behaviour and makes the person vulnerable to relapse long after cessation of drug use. [1, 2]

A commonly held view is that addiction or dependence to opioids is characterized by physical symptoms of withdrawal like lacrimation, rhinorrhoea, body aches, tremors, loose motions and cold/hot sweats. Physical or somatic symptoms are just one facet of dependence. Rather anxiety and negative affective state following opioid cessation are more likely to be driving force behind the future use of the drug. [3, 4]

Dependence to opioids is seen following repeated use of the drug so to alleviate the negative drug-induced affective state which further reinforces the drug-taking behaviour. This pattern of chronic use of the drug that contributes to dependence, however, overlooks the early adaptive changes which happen even with single-use or in drug naive cases. This phenomenon of initial neuronal changes induced by drug exposure is termed as Acute Dependence may provide us with insights on early mechanisms of opioid dependence and knowing about the withdrawal severity that increases with repeated exposures. [5]

The neural basis for opioid dependence has focused mostly on the mesolimbic dopaminergic projections involving the ventral tegmental area (VTA) to nucleus accumbens (NAc) along with the involvement of areas of the medial prefrontal cortex, amygdala, ventral pallidum and locus ceruleus.[1,6] But recent evidence have suggested that within the VTA itself, opioids are capable of producing dopamine independent positive reinforcement.[7] The role of GABA, glutamate and other factors like, corticotropin releasing factor, vasopressin and cannabinoid receptor agonist has been implicated. The role of μ-opioid receptors is very significant along with other opioid receptors and endogenous opioids. [1, 8, 9]

The relapse to use of opioids following abstinence is a major problem and study of it provides targets that can be utilized for

pharmacological interventions. Animal models have been mostly used to study relapse for which reinstatement of drug seeking model is the most popular. [9, 10]

Pharmacology

The use of term opiates refers to drugs like morphine and codeine that are extracted from opium. Opioid refers to any drug or endogenous substrates that act on the opioid receptor. The endogenous substrates or the endogenous opioids are endorphin, endomorphin, dynorphin and enkephalin. Orphanin-FQ or nociceptin is the new addition to the list of endogenous opioids. The endogenous opioids coded by genes and are the product of proteolytic cleavage of the respective polypeptide precursor protein. The opioids act via three types of receptor: μ-opioid receptor, κ-opioid receptor and δ-opioid receptor. Opioid receptor-like (ORL1) is the new addition to the types of opioid receptor. [9, 11]

Acute Dependence vs. Chronic Dependence

Acute Dependence to opioids consists of an appearance of withdrawal signs with the first dose of opioids and was first reported in 1953 by Wikler and Carter. It was not accepted initially as studies related to this phenomenon were limited to opioid agonist-antagonist administration paradigms in rats. But similar findings were later seen across different species of animals and humans and also with a range of opioid agonists both naturally occurring and synthetic. [5] The symptomatology of acute dependence is similar but not identical with chronic dependence. Withdrawal signs are subtle in acute dependence and physical withdrawal or somatic signs are less prominently seen than that in chronic opioid dependence. The receptor profile involved is however similar. The receptors are central and stereoselective. In both cases, the μ-opioid receptors along with δ and κ- receptors are involved. There is a differential effect of glutamatergic antagonists on the expression of acute and chronic dependence. In animal studies, NMDA receptor antagonist blocked the appearance of withdrawal signs in acute dependence

but not so in chronic dependence. Also, the role of noradrenaline is similar in both acute and chronic withdrawal cases as evidenced by preclinical studies with use of clonidine, a α_2-adrenergic agonist. Other neurotransmitters like serotonin, GABA, Ach, adenosine also has similar parallels in both cases. In spite of mostly being similar in most aspects, the severity of acute withdrawal though initially mild may, however, increase in intensity across repeated exposures. [4,5] Study of this acute dependence thereby gives an insight into the early adaptive changes in the brain following initial exposure to opioids and also the successive adaptive changes that occur with repeated exposure to opioids.

Opioid Tolerance

Opioid tolerance is characterized by a reduced effect with similar doses of the drug and the need to take a higher quantity to achieve the desired effect. Tolerance is the result of adaptive changes at receptor level as well as cellular and synaptic levels so to maintain the homeostatic balance in spite to regular disturbances caused by opioid agonists. Acute and chronic tolerance is demonstrated in animal models and it due to rapid μ-receptor desensitization and internalization. [9, 12] The μ-opioid receptor is coupled to G-protein receptor in the cell surface. Upon activation by an opioid agonist, phosphorylation of μ-opioid receptor occurs with help of G-protein coupled receptor kinase-2 (GRK-2) which increased affinity for Arrestin (Arr3). Binding of a μ-opioid receptor with Arr3 causes uncoupling from the G-protein resulting in desensitization of the μ-opioid receptor. Desensitization is followed by internalization and sequestration of the μ-opioid receptor. Chronic opioid use do not cause a decrease in the number of receptors but rather downregulation as a small number of receptors are subjected to lysosomal sequestration following internalization thereby making receptor desensitization more important in case of tolerance with chronic use.[3,13] Chronic opioid use induces the emergence of ş opioid receptors in the cell surface which form heterodimers with μ-opioid receptors and this influences the process of internalization

of the later leading to the development of tolerance. This is supported by animal studies where δ-opioid receptor knockout was associated with blunting of tolerance to opioids. [9, 14]

Opioid Withdrawal

The withdrawal due to opioids is divided into somatic and affective. The somatic withdrawal symptoms are the physical manifestations like tremors, sweating, tachycardia, goose bumps, diarrhoea etc. while affective symptoms are because of negative emotional state like anxiety, dysphoria is due to withdrawal. [15] With repeated use of opioids, there occur functional changes in the mesolimbic DA neurons. There is decreased DA release during opioid abstinence phase which causes anhedonia and negative affective state.

The prefrontal cortex sends glutamatergic projections to the VTA which excites the DA neurons causing the release of DA in NAc. There are also glutamatergic autoreceptors which restrict the further release of DA when it is released in excessive amount. With an increase in the intensity of excitation following regular or frequent use of opioids, the release of DA is increased. Consequently, the action of glutamatergic autoreceptors on the DA neurons in VTA is also increased to regulate this raised level of DA. In the process, this feedback process is set to a higher point. Due to it, the opioid user needs to take a higher amount to get the similar release of DA. When the opioid user stops the use of the drug, DA deprivation results causing dysphoria and other symptoms causing drug-seeking behaviour in the person. [6]

The locus ceruleus which is the seat of noradrenergic neurons is also important in the genesis of withdrawal symptoms. The opioid agonist act on the μ-opioid receptors located on the LC neurons causing suppression of NA activity and thereby causing symptoms like sedation, slowed psychomotor activity and decreased respiration. With continued use of opioid, this balance is offset so that an adequate amount of NA can be released to maintain alertness, breathing and blood pressure. When opioids are not

available, more amount of NA is released into the circulation causing anxiety, insomnia, jitteriness, raised blood pressure, tremors and diarrhoea. [6, 16]

The GABA receptors are present as interneurons in VTA dopaminergic neurons. The μ-opioid receptors are present on theses GABA interneurons. On activation by an opioid agonist, they cause suppression of GABA causing disinhibition of VTA DA neurons which was till now under tonic inhibition of GABA. This causes release of DA in the mesolimbic area, thereby reinforcing the effect of the drug. With chronic use of opioid, cellular adaption in the VTA and GABA network results which lead to compensatory upregulation of GABA release following drug withdrawal. This finally results in a decrease in dopaminergic tone in the mesolimbic area causing craving and features of opioid withdrawal. [17, 18]

In animal studies, use of a D2 receptor agonist seems to attenuate opioid withdrawal whereas D2 blockers precipitated affective signs of withdrawal. The use of naloxone, an opioid antagonist in morphine-dependent animals precipitates somatic and affective withdrawal signs. This effect is the result of antagonism of a μ-opioid receptor in NAc and other areas of the brain like the VTA, locus ceruleus (LC) and amygdala. [1]

There is involvement of Şopioid receptors in the expression of affective withdrawal symptoms as evidenced by the use of Şopioid receptors antagonist in opioid-dependent animals which cause jumping and vocalization suggestive of aversive states.[19] This is in support of previously mentioned finding regarding the expression of Şopioid receptors in cell surface with chronic opioid use.[9,14]

Dynorphin which is produced by medium spiny neurons of NAc acts as an agonist on the Şopioid receptor. The Şopioid receptor agonist causes dysphoria and negative affective state and also decreases DA release by inhibition of DA neurons in NAc. Though the acute administration of opioid do not cause any change in levels but with repeated use of opioid there occurs an increased expression of dynorphin. The upregulation of dynorphin with chronic opioid use is a very significant event. The elevated

dynorphin levels cause diminished pleasure (decrease DA release in NAc) and in absence of opioid results in dysphoria, anhedonia and negative affective state. [1]

Opioid Seeking Behavior/ Opioid Relapse

Relapse is very common in opioid use no matter how much time a person remains abstinent. The relapse rate seen in persons who were on opioid use treatment program was nearly 60% after 3months and 75-85% after 12 months of abstinence. [20] The relapse to opioid use can be divided into three factors: drug priming, drug-associated cues and stress-induced. [21]

The reinstatement model of drug seeking is mostly used to study relapse. There are a few paradigms of this model. Operant responding and conditioned place preference (CPP) are the two most used paradigms. In operant responding, the animal in order to get the drug need to perform a certain task like pressing the lever. Following this, extinction of response is done by withdrawing the drug despite performing the desired behaviour. In conditioned place preference, which is based on Pavlovian conditioning, the animals are conditioned to associate a particular environment (unconditioned stimuli) with drug experience (conditioned stimuli). Extinction of this association is done in a similar way like operant responding. Following the extinction of response as in both cases, reinstatement of drug-seeking behaviour is then seen by the response of the animals with respect to different drug-paired manipulations like drug priming, drug cue associated or stress induced. [8]

Opioid Primed Opioid Seeking Behavior

Initial studies have shown that morphine infusion in VTA reinstates heroin seeking while the use of opioid antagonist blocks reinstatement of heroin seeking behaviour following morphine priming in operant response paradigm. Lesions in VTA and NAc shell were associated with attenuated response in morphine primed CPP. [22] Thus mesolimbic DA play an important role in

opioid reinstatement behaviour. The role of noradrenaline (NA) in opioid relapse behaviour was studied. The use of morphine is found to cause a release of NA in the prefrontal cortex which further mediates elevation in DA levels in NAc. [23] Neuropeptides like corticotrophin, vasopressin and orexin are also implicated. Corticotrophin-releasing hormone receptor 1 (CRF1) antagonist injected in the central amygdala caused attenuation of morphine-induced reinstatement of morphine CPP in rats. The use of the orexin 1 receptor antagonist was also associated with similar findings. Vasopressin V1b receptor antagonist injected systemically in rats was found to block heroin-seeking behaviour in rats. [24-26] Other non-dopaminergic agents like glutamate, GABA and cannabinoids were also involved in opioid-seeking behaviour. Glutamate acts via the NMDA receptor and causes a rise in DA in mesolimbic area. The antagonist acting on NR2B subunit of NMDA receptor when injected in CA1 region of hippocampus and NAc shell caused a decrease in morphine primed reinstatement of morphine CPP in rats. Glutamate is associated with both opioid primed and cue-induced opioid-seeking behaviour. [27]

In striatal neurons, the cannabinoid receptor1 (CB1) acts along with the μ-opioid receptor on the second messenger systems causing a release of DA. This synergy of μ-opioid receptors and CB1 is dependent on adenosine A_{2A} receptor (A_{2A}) activation. The adenosine also interacts with glutamate and regulates its effect on NAc. Rimonabant, a CB1 antagonist caused attenuated opioid primed and cue-induced opioid-seeking behaviour while the use of A_{2A} receptor antagonist decreased heroin primed heroin-seeking behaviour in animal studies. [28-30] The GABAergic system is associated with mesolimbic DA with the help of $GABA_B$ receptors. Baclofen, a $GABA_B$ agonist was found to cause dose-dependent decrease in heroin-primed heroin-seeking behaviour in rats. [18-31]

The various neural substrates involved in opioid primed opioid-seeking behaviour are VTA, NAc (both core and shell), central amygdala, prefrontal cortex and hippocampus. The role of the basolateral amygdala (BLA) is significant. BLA is associated

with learning behaviour that occurs with drug use which causes the pairing of particular stimuli with drug use. This results in precipitating opioid use with both drug primed and cue-induced reinstatement of opioid seeking. [8]

Stress-Induced Opioid Seeking Behavior

Stress is a major reason for relapse of drug-seeking behaviour following abstinence. In animal models, stress is replicated by designs like footshock, acute food deprivation and injection of stress hormone like corticotrophin-releasing factor (CRF). [8] Injection of CRF1 antagonist in rats was found to attenuate footshock induced morphine use. In fact, use of CRF1 antagonist in the bed nucleus of stria terminalis (BNST) especially was more responsible for this behaviour. Similar findings were seen with an injection of clonidine ($\S_2$-adrenoceptor agonist) in BNST and not with locus ceruleus. Noradrenaline is implicated with anterolateral BNST where lesion in the ventral noradrenergic bundle is associated with attenuated footshock induced morphine use.[24,32] The footshock stressor in animals increased the VTA levels of DA, glutamate and CRF.[33] As previously with a drug primed response, dopamine is indirectly related to stress-induced drug use. This was so as the use of dopamine antagonist or opioid antagonist was not associated with a decrease in stress-induced opioid use. The lowered levels of dopamine in dorsal BNST cause activation of endogenous CRF which in turn enhance the NMDA receptor activity. [8, 34] So CRF activity seems to be more significant in stress-induced relapse. Also as in drug-primed drug use behaviour, vasopressin has a role in stress-induced drug use. Vasopressin 1b antagonist when injected systemically in rats blocked footshock induced heroin-seeking behaviour. Vasopressin interacts with noradrenaline in the extended amygdala to regulate this behaviour. [25]

Cue-Induced Opioid Seeking Behavior

Cue-induced drug use is a learned association that develops between the drug user and the place where they consume the drug.

Such association occurs because of classical Pavlovian conditioning process and they remain dormant only to become active in response to cue in the environment. Drug-induced cues may be: discrete cues and contextual cues. Discrete cues include the drug paraphernalia which is associated with the pleasurable effects of the drug while contextual cues are the particular environment that predicts the availability of the drug. [8]

The basolateral amygdala (BLA) is implicated in the animal studies with respect to cue- induced reinstatement of opioid use. Apart from it, other regions involved were dorsal and ventral prefrontal cortex, NAc core, central amygdala, ventral BNST, caudate putamen and substantia nigra. [35] Imaging studies in humans have implicated that aberrant functioning of the prefrontal cortex is responsible for such relapse. The increased activity of glutamatergic pathway from the prefrontal cortex to NAc core is associated with cue-induced opioid-seeking behaviour. [36, 37] There are also non-dopaminergic mechanisms which are responsible for cue-induced opioid seeking. These are cannabinoids, acetylcholine and N-acetylcysteine. The former two are associated with regulation of dopamine in NAc. N-acetylcysteine through the glutamate-cysteine exchange restores the presynaptic glutamate concentration thereby decreasing raised glutamate level associated with drug-seeking behaviour.[38] A differential effect of dopamine D1 activity in cue-induced opioid-seeking behaviour is observed. The D1 receptor in the NAc core is associated with cue-induced opioid seeking while receptors in the NAc shell are associated with context-induced reinstatement. [39]

CONCLUSION

Opioid addiction is associated with high relapse. The adaptive changes associated with opioid use start from the first use of the drug. With subsequent opioid use the intensity of dependence increase. For the development of tolerance, the desensitization and internalization of the μ-opioid receptor are critical. This process depends on arrestin 3 binding, Şopioid receptor and other second messenger systems. Withdrawal is the result of functional changes in

the mesolimbic DA neurons caused by repeated use of opioid. The functional changes in DA neurons are associated with changes in glutamate, GABA and noradrenergic pathways resulting in opioid withdrawal symptoms. The δ-opioid receptor and κ-opioid receptor along with dynorphin are associated with affective symptoms of opioid withdrawal.

The study of opioid relapse is mostly related to animal studies. The reinstatement model of drug-seeking behaviour in animals finds that dopamine, glutamate, GABA, cannabinoid, corticotrophin, vasopressin, orexin, adenosine and N-acetylcysteine are associated with opioid primed and cue-induced opioid-seeking behaviour. Apart from VTA, NAc, prefrontal cortex, central amygdala and hippocampus, the basolateral amygdala is implicated in both cue-induced and opioid primed opioid-seeking behaviour. In case of stress-induced opioid relapse, corticotrophin, noradrenaline and vasopressin are directly involved while BNST serves a neural substrate for it.

The study of these neurobiological substrates, in future, will help in developing potentially novel targets for pharmacological treatment of opioid addiction from the existing opioid agonist and antagonist management strategy.

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Upcoming Molecules as Anti-Craving Agents for Substance Use Disorders

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ABSTRACT: *Craving, defined as an intense desire or urge for a drug, has been understood as one of the important constructs of the preoccupation/ anticipation stage in the three stage cycle of addiction. It has long been a part of the criteria for diagnosis of Dependence in ICD 10 and also has found place in the DSM 5 criteria for substance use disorders. Persistent craving can lead to frequent relapses and thus reversal of craving can possibly reduce the risk of relapses. Various agents have been long studied as well as FDA approved as anti-craving agents for substance use disorders (e.g. Acamprosate and Naltrexone for alcohol use disorders, Methadone and Buprenorphine for opioid use disorders, Varenicline for tobacco cessation) along with many off-label drugs. In this article we try to briefly review the molecules currently being used as anti-craving agents for substance use disorders along with some of the upcoming molecules that are being investigated as anti-craving agents.*

Keywords: *Anti-craving agents, Baclofen, Oxytocin*

INTRODUCTION

Substance use disorders are serious health problems with a high global burden of disease. They have effect on personal, social, occupational, mental domains as well as significant impact on the healthcare systems as well as the economy of a nation being risk factors for many of the non-communicable diseases. According to National Mental health Survey of India, 2015-16, substance use disorder was prevalent in 22.4% of the population above 18 years in all the surveyed states with the prevalence of tobacco use disorder being 20.9% and that of alcohol use disorder 4.6% which

is a serious cause for concern. A rough estimate gives a number of 60,913,200 for Alcohol Use disorder as defined by ICD 10 which is likely to be underreporting.

The treatment interventions for substance use disorders have seen significant improvement with the growing knowledge of the neurobiology of addiction. Addiction has been conceptualized as a three-stage cycle– binge-intoxication, withdrawal/ negative affect, and preoccupation/ anticipation[1] that involvea disruption in incentive salience, reward and stress and executive function, respectively, involving various neuro-circuits and neurotransmitters. Newer treatment strategies are being developed to target each of these stages. Craving is one of the important constructs of the preoccupation/ anticipation stage and one of the key factors that lead to frequent relapses.

Craving is an intense desire or urge for the drug that may occur at any time but is more likely when in an environment where the drug previously was obtained or used[2]. Craving has been described as reward craving (paired with self-administration of the drug with positive reinforcement), relief craving (characterized by anxiety and dysphoria) and obsessive craving (characterized by loss of control). Dysregulation of various neurotransmitter systems has been implicated for craving[3], e.g., dopaminergic/ opioidergic dysregulation in reward craving, GABAergic/ glutamatergic dysregulation in relief craving and serotonergic dysregulation in obsessive craving. Pharmacotherapeutic agents targeting these deficits have been used as anti-craving agents for the treatment of substance use disorders. In this article, we try to have a brief review of current anti-craving agents and the upcoming molecules as anti-craving agents.

CURRENT KNOWLEDGE

Many molecules, both FDA approved as well as those which are not approved by the FDA are used as anti-craving agents. A summary of these molecules is given in Table 1.

Table 1: Commonly used anti-craving agents in Clinical Practice. (This also includes off-label drugs)

Drug	Mechanism of action	Dose	Adverse Effects	Remarks
Alcohol Use Disorders				
Acamprosate (FDA Approved)	Uncertain; restoring the equilibrium of GABA-ergic and glutamatergic systems; affecting calcium metabolism	1332mg/day(<60kg), 1998mg/day (>60kg)	Diarrhoea, headache, dizziness, pruritus, paraesthesia, decreased libido, confusion	Not metabolized by the liver, can be used in patients with mild to moderate liver dysfunction
Naltrexone (FDA Approved)	Opioid receptor antagonist	25mg/day increased to 50mg/day; Also available as extended- release injectable formulation as well as subdermal implant	Nausea, headache, anxiety, sedation	Contraindicated in patients with hepatitis or liver failure, avoided in patients on long-term opioids for chronic pain
Baclofen	GABA-B receptor agonist	30-60mg/day	Sedation, CNS depression,	Well tolerated, can be given in patients with liver cirrhosis

Nalmefene	Opioid receptor antagonist	18mg on as required basis	Nausea, vomiting, tachycardia, hypertension	Longer duration of action, lack of dose-dependent liver toxicity, and higher affinity for opioid receptors compared to Naltrexone
Topiramate	Antagonism of glutamate activity and facilitation of GABA	25-300mg/day	Dizziness, somnolence, ataxia, confusion, fatigue, paraesthesia, cognitive impairment	Primarily excreted in the urine, useful in comorbid seizure disorder; requires 4-wk dose titration
SSRIs	Selective serotonin reuptake inhibition	E.g. Fluoxetine 20-60mg/day	GI side effects, rash, sweating, agitation, anxiety, headache insomnia, tremors, sexual dysfunction	Useful in patients with comorbid depressive or anxiety disorders
Ondansetron	5HT3 receptor antagonist	4mcg/kg twice a day	constipation or diarrhoea, headache, and light-headedness	QTc changes
Pregabalin	Blocks voltage-gated Ca2+ channels	150-450mg/ day	Somnolence, dizziness, ataxia, fatigue	Useful in patients with comorbid anxiety symptoms

Gabapentin	Blocks voltage-gated Ca2+ channels	Up to 1800mg/day	Somnolence, dizziness, ataxia, fatigue	Excreted unchanged in urine
Opioid Use Disorders				
Methadone (FDA Approved)	Mu receptor agonist	80 to 120 mg/day	Constipation, respiratory depression, and QTc interval prolongation	Given as a daily observed treatment
Buprenorphine (FDA Approved)	Mu receptor partial agonist, Kappa receptor antagonist	Up to 16 to 24 mg daily for maintenance	Sedation, constipation, and nausea	Can precipitate withdrawal in patients currently taking opioids
Nicotine Use Disorder				
Varenicline (FDA Approved)	Partial agonist at α4β2 nicotinic acetylcholine receptor	1 mg twice a day	nausea, vivid dreams, mood and behavioural changes, increased cardiovascular risk	Excreted unchanged in urine

STUDIES, MOLECULES AND FUTURE DIRECTIONS

Craving is understood to be involving three pathways[3], viz., (i) reward craving arising from dopaminergic/ opioidergic pathway (ii) relief craving from GABAergic/ glutamatergic pathway and (iii) obsessive craving from serotonin pathway. Pharmacologic interventions are being studied with molecules targeting these pathways as well as newer targets for intervention.

Dopaminergic/ Opioidergic Pathways:

Antipsychotic agents (both the first and the second generation antipsychotics) have been used and found to be useful in decreasing craving, especially in alcohol use disorders. Haloperidol has shown to decrease craving for alcohol, amount of alcohol and impulsivity with pre-treatment in alcohol dependence.[4] However, the adverse effect profile limits its usage. Aripiprazole has been shown to reduce craving in[5] a double-blind comparison trial[5] but these results could not be replicated in a multicentre randomized controlled trial[6]. Quetiapine has been shown to decrease craving and improve abstinence especially in the context of a comorbid mood disorder[7] as well as comorbid schizophrenia or personality disorder[8]. In an RCT including Olanzapine, a single dose of olanzapine was found to reduce craving[9]. These agents, however, have not shown consistent results and may be beneficial in patients with a comorbid psychiatric illness.

GABAergic/ Glutamatergic Pathways:

Apart from Topiramate and Baclofen, other agents like Lamotrigine, levetiracetam, zonisamide, Gamma-hydroxybutyric acid (GHB) and Memantine have been tried in alcohol use disorder. Lamotrigine was found to decrease craving in trials[10]. Levetiracetam was shown to decrease craving in few studies[11] but such results could not be replicated in an RCT[12]. Zonisamide was noted to reduce the amount of alcohol as well as craving in open-label studies[13] and in an RCT[14]. Although GHB (approved in some European countries for the treatment of alcohol use disorders), it

has a short half-life necessitating multiple doses to be given daily. It also has addictive potential. The effect of memantine to decrease the craving[15]was not replicated in a placebo-controlled trial.

Other Pathways:

Varenicline, a partial agonist at α4β2 nicotinic acetylcholine receptor, which has been approved by FDA for smoking cessation, has been studied for alcohol use disorders and has been found to decrease craving[16].

Oxytocin, a neuropeptide produced by the hypothalamus and released by the posterior pituitary, has been studied for substance use disorders. Intranasal oxytocin has been shown to reduce cue-induced craving for nicotine[17], stress-induced craving for marijuana[18] as well as withdrawal and anxiety symptoms. Preclinical studies have also shown decreased self-administration of heroin[19], cocaine[20] and methamphetamine with oxytocin.

N-acetyl cysteine, which activates the cysteine-glutamate exchange and thereby stimulating extra synaptic metabotropic glutamate receptors decreases cocaine seeking in animal models. It has also shown to reduce cocaine-related withdrawal symptoms and craving[21]. It has been considered for treatment of cannabis use disorder at doses of 1200-2400mg/day.

Cannabinoids like dronabinol[22] and nabilone[23] have shown to reduce withdrawal symptoms related to cannabis use disorder and increase retention in treatment.

Other novel treatment strategies include corticotropin-releasing factor (CRF) receptor antagonists, dynorphin antagonists, vasopressin antagonists, Neuropeptide Y and Nociceptin which act on brain stress systems as targets. Majority of the studies with these agents involve animal studies with rats and they seem to reduce the stress response or aversive response during withdrawal[24].

Newer emerging agents for the treatment of Addictive disorders:

Restore Executive Control Over Drug Use	Restore Response to Natural Rewards and Inhibit Drug Reward	Manage Withdrawal and Restore Balance to Stress Response
NK1 antagonist, *N*-acetyl cysteine, Modafinil TMS, tDCS	NK1 antagonist, Lorcaserin, Oxytocin, Pregnenolone, Gabapentin, Topiramate, Vaccines	KOR antagonists, Lofexidine, Gabapentin, *N*-acetyl cysteine, Peripheral nerve stimulation

CONCLUSION

The increased understanding about the mechanism of addiction has helped in developing many promising molecules. The newer molecules are mostly targeted to the three pathways a. restore response to natural reward and inhibit drug reward b. manage withdrawal and restore balance to stress response c. restore executive control over drug use[25].

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Clinical Utility of Pharmacotherapy of Addiction Behaviour

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ABSTRACT: *Alcohol and other substance addictions contribute to a significant health-related burden throughout the world. In a country like India where sufficient human resources are lacking to provide comprehensive psychosocial management, pharmacotherapy is the mainstay of treatment. In this article, we discussed the efficacy of available psychopharmacotherapy of all prevalent addictions. We also briefly discuss the approach of management of the individual with addictive behaviour. Pharmacotherapy of two commonly associated co-morbidity or vulnerability has also been discussed.*

Keywords: *Addiction, anticraving, efficacy*

INTRODUCTION

Drug addiction is a chronically relapsing disorder that is characterized[1] by:

1) Compulsive drug seeking and taking,
2) Loss of control in limiting drug intake, and
3) The emergence of a negative emotional state (like dysphoria, anxiety, irritability) when the drug isunavailable.

In the light of the recent understanding of addiction[2], DSM-5 also minimized its emphasis on physical dependence (withdrawal symptoms, tolerance) and added craving as a cardinal feature of addiction/ substance use disorder. They have also included gambling under the addiction-related chapter. So, all 'addiction behaviours' have been given importance. In this article, we will briefly discuss available pharmacological agents to curve addiction behaviors. We will discuss alcohol, cannabis, tobacco, opioid and gambling

addiction. But at the same time, we need to remember that only managing addiction behaviour is not enough. We also need to take care of vulnerabilities as well as consequence of addiction. That's why we will touch upon the pharmacological management of 2 vulnerability/co-morbidities commonly associated with addiction as examples.

Agents used in Alcohol addiction

Currently, there are 3 drugs and 4 of their preparations have got FDA approval as anti-craving in alcohol addiction. They are Disulfiram, Naltrexone (Both oral tablet and long-acting injection preparations), Acamprosate.

First approved drug (in 1951) in alcohol addiction is Disulfiram[3]. It is a deterrent. As we know that its mechanism of action for maintaining alcohol abstinence is primarily psychological[4, 5, 6] and based on a highly disagreeable pharmacological effect if alcohol is consumed. Disulfiram blocks the enzyme aldehyde dehydrogenase (ALDH). If alcohol is present, then acetaldehyde accumulates[7], usually resulting in an unpleasant reaction, the disulfiram-ethanol reaction (DER), consisting primarily of tachycardia, flushing, nausea, and vomiting. Disulfiram is most effective when given after full discloser and under supervision. Patients who might do better with unsupervised disulfiram are older ones, more socially stable patients, those with higher in motivation[8]. But clinician needs to consider several contraindications before prescribing disulfiram like any kind of cardiac ailment (coronary heart disease, severe heart arrhythmia), oesophageal varicosis, hypothyroidism, bronchial asthma, liver cirrhosis[3].

A meta-analysis of 22 studies showed a higher success rate of disulfiram compared to controls. When comparing blind and open-label RCTs, only open-label trials showed a significant superiority overcontrols. As expected,RCTs with blind designs showed no efficacy of disulfiram compared to controls, probably because the threat of DER would be evenly spread across all groups.

While discussing the effectiveness of naltrexone and acamprosate, two robust addiction pharmacotherapy studies need mentioning. The COMBINE study[9] has been done in the USA (n=1383) comparing the efficacy of Naltrexone, Acamprosate and behaviour intervention. Patients receiving naltrexone, behaviour intervention, or both fared better on drinking outcomes. But acamprosate showed no significant effect on drinking vs placebo. Another large study[10] in Europe (PREDICT study) (n=426) neither acamprosate nor naltrexone to render any additional benefit compared to placebo.

In respect to the clinical utility of naltrexone and acamprosate,one meta-analysis[11] is very insightful. Most discussion over the use of oral naltrexone and acamprosate to treat alcohol dependence often focus on whether they work better than a placebo or one works better than the other. But in reality, clinicians may be most interested in the circumstancesunder which each medication is most effective. For example, which of the two would be preferable if a patient is focused on maintaining abstinence? Whichever is selected, should treatment start only after thepatient has detoxified? This meta-analysis[11] of 64 randomized, placebo-controlled, English languageclinical trials, provide some of the answers to these questions. First of all, for abstinence outcomes, the overall effect size for acamprosate studies (0.36) was significantly larger than the overall effect size fornaltrexone studies (0.16). Whereas naltrexone studies had significantly larger heavy drinking and craving aggregate effect size (0.18) compared to acamprosate studies (0.04). Though the effects of naltrexone and acamprosate are somewhat smaller compared to other psychiatric medications,still they have clinical relevance as one line of treatment. Based on effect sizes, 8 people would need to be treated with acamprosate to have an additional case of complete abstinence [Number Needed to Treat (NNT) = 7.5). Whereas 9 people wouldneed to be treated with naltrexone to prevent an extra case of relapse to heavy drinking(NNT = 8.6).

Based on the findings, the authors suggested that naltrexone should be considered for patients who want to restrict heavy drinking, whereas acamprosate is a better option for those who prefer complete abstinence. Meta-analyses also indicated that both medications are more efficacious when detoxification before the trial and a few days of required abstinence were in place.

Common side-effects of naltrexone are nausea, dizziness, headache, and insomnia. In the USA, it carries a black box warning for its potential to cause liver dysfunction. But in low doses that was not substantiated till date[3]. Acamprosate has almost no drug-drug interaction and does not influence alcohol toxicity. Its main side effects are gastrointestinal symptoms like diarrhoea as well as headache and pruritus[3].

Baclofen is another drug that has gained popularity throughout the world as off-label anti-craving. (It is approved in France)[1]. There are only a handful of RCTs on Baclofen to date. Recently a meta-analysis[12] has been done based on those RCTs. It showed treatment with baclofen was 2.67 times more likely to lead to abstinence following treatment than placebo using intention to treat analysis. The NNT demonstrated that 8 (95% CI = 5, 16) patients would need to be treated with baclofen for one to maintain abstinent due to the treatment.

Among the other anti-cravings, Topiramate, Gabapentin, and Nalmefene are the important mentions. Topiramate has proven efficacy as per at least 6 randomized studies. But side-effect profile and slow dose titration made its use limited[3]. Gabapentin is the newest drug to get FDA approvalbased on the results of the four randomized, double-blind studies. The daily dose of Gabapentine ranged from 600 to 1,500 mgin these studies. Gabapentin hadthe positive effect on multiple drinking-related outcomes and often had a posttreatment effectthat lasted weeks[13]or months[14]. But its efficacy needs to be established by further well-controlled RCTs. Nalmefene may be a good alternative to naltrexone but it is not available in India.

Agents used in Tobacco addiction

Tobacco is considered one of the most addictive substances. Fortunately, we have effective arsenals against the menace. There are three FDA-approved classes of smoking cessation pharmacotherapies – nicotine replacement therapies (NRTs) (please see table 2 for relative efficacy), sustained-release bupropion, and varenicline. All of them are having level 1 evidence of efficacy[3]. Other off-label and novel medications are Nortriptyline and Cystine.

Table 1: Effectiveness of Tobacco Use and Tobacco-Related Disorder Treatment Interventions[15]
No professional or formal intervention 5% Physicians' advice 10% Nicotine lozenge (2 mg/4 mg) 24.2% Nicotine patch 21 mg (6–14 weeks) 23.4% Nicotine gum (long-term >14 weeks) 26.1% Nicotine inhaler 24.8% Nicotine nasal spray 26.7% Bupropion (7–12 weeks) 25% Varenicline (2 mg/day) 33.2% Medication and behavioural therapy 40%

Table 2: Cochrane review of NRT[16]

Medication	**Route and Dose Range**	**Odds of Abstinence with NRT Over Placebo***
Nicotine patch	Transdermal (7–21 mg/day)	OR 1.81 (95% CI = 1.63–2.02)
Nicotine gum	Buccal (20–40 mg/day; 2–4mg pieces up to 10×/day)	OR 1.66 (95% CI = 1.52–1.81)
Nicotine lozenges	As for the gum	OR 2.05 (95% CI = 1.62–2.59)
Nicotine nasal spray	Intranasal (1–2 mg spray in each nostril, up to 16×/day)	OR 2.35 (95% CI = 1.63–3.38)
Nicotine vapour inhaler	Inhalation and buccal (6–16 mg/day, puffing up to 120×/day	OR 2.14 (95% CI = 1.44–3.18)

The EAGLE study[17], the biggest randomized, double-blind, triple-dummy, placebo-controlled and active-controlled (nicotinepatch; 21 mg per day with taper) trial of varenicline (1 mg twice a day) and bupropion (150 mg twice a day) showed that Varenicline-treated participants achieved higher abstinence rates than those on placebo (odds ratio [OR] 3·61, 95% CI 3·07 to 4·24), nicotine patch (1·68, 1·46 to 1·93), and bupropion (1·75, 1·52 to 2·01). Those on bupropion and nicotine patch achieved higher abstinence rates than those on placebo (OR 2·07 [1·75 to 2·45] and 2·15 [1·82 to 2·54], respectively).

Another importance of the EAGLE study is that it clearly demonstrated the efficacy and safety of all the medications in individuals with the psychiatric disorder.

Agents used in Cannabis addiction

Cannabis was not traditionally believed to be a substance resulting in true addiction. Recent consensus has changed. Cannabis activates the mesocorticolimbic system, a property common among all addiction[18]. In addition, there is a well-described withdrawal syndrome associated with cessation of cannabis use[2].

Despite its recognition as a truly addictive substance, there are currently no FDA-approved medications for the treatment of cannabis addiction. Table 3has described the efficacy of some medications that have been tried.

Table 3: Cannabis pharmacotherapy-related clinical trials

Reference	Medications	Designs/Duration	Subjects	Dose	Outcome
Levin et al[19]., 2004	divalproex sodium	randomized controlled double-blind/ 6 weeks	25 subjects		no differences between the Divalproex sodium and placebo groups, with few individuals achieving abstinence.
McDowell et al.[20] 2006	bupropion & nefazodone	randomized controlled double-blind placebo control//	130 treatment-seeking cannabis-dependent individuals	bupropion 300 mg/day, or Nefazodone600 mg/day.	neither medication was significantly more effective than placebo in either initiating abstinence from cannabis or alleviating the symptoms of cannabis withdrawal
Gray [21], et al.2010	*N*-acetylcysteine (NAC) *(along with Contingency-management)*	open-label trial/ 4 weeks	25 subjects	2400mg/day	well tolerated and associated with significant decreases in self-report measures of marijuana use and craving

Gray et al.,[22] 2012	*N*-acetylcysteine (NAC)	randomized controlled double-blind placebo control/8 weeks	116 adolescents	2400mg/day	Compared with placebo, the NAC grouphad significantly greater odds of providing cannabis-negativeurine drug screens (odds ratio = 2.4, 95% confidence interval= 1.1–5.2)
Mason[23], et al.2012	gabapentin	randomized controlled double-blind placebo control//12 weeks	50 adults	1200 mg/day	Gabapentingroup showed significantly less cannabis use by self-reportand urine toxicology screens, and also significantly fewercannabis withdrawal symptoms andsignificantly betterperformance in neuropsychological tests.
McRae-Clark[24] et al.2010	Atomoxetine	randomized controlled double-blind placebo control	36 subjects	25–80 mg/day	not statistically significant from placebo
McRae-Clark[25] et al.2010	Buspirone	Double-blind, Placebo-controlled	50 subjects	Up to 60 mg	Reduced cannabis use
Levin[26] et al., 2011	Dronabinol (in addition to a manualized CBT therapy)	randomized controlled double-blind placebo control/12 weeks	156 adults	40mg/day	The dronabinol the group did show better retention in treatment than the placebo group (77% vs. 61%, p = 0.02) and experienced significantly fewer cannabis withdrawal symptoms

Agents used in Opioid Addiction

Although the prevalence of opioid addiction is much less compared to other substance of uses in a country like India, opioid-related complications are very troublesome. There is a clear surge of opioid in the recent past, especially prescription opioids[27]. Punjab opioid dependence survey[28] showed that picture clearly. Opioid uses are very commonly associated with fatal complications like the overdose, injection-related complications.

There are two very distinct approaches to treat opioid addiction. The first approach is agonist maintenance therapy (AMT). Methadone is the 1st medication that was used as substitution therapy of opioids since the 1970s. Later on, Buprenorphine got its popularity in late 1980s[18]. In the context of India, there are few treatment centres that are using Methadone. So, Buprenorphine is the mainstay of AMT.

2013 Cochrane review[29] compared Buprenorphine with placebo as well as Methadone (N=5430). Authors concluded that Buprenorphine is an effective medication in the maintenance treatment of heroin dependence. Buprenorphine appears to be less effective than methadone in retaining people in treatment if prescribed in a flexible dose regimen or at a fixed and low dose (2-6 mg per day). Fixed-dose Buprenorphine (>7 mg per day) was as good as fixed dose methadone (≥40 mg per day) in retaining people in treatment or in the suppression of illicit opioid use.

Another very important review/meta-analysis[30] looked intothe risk for all-cause and overdose mortality in individuals with opioid dependence during and after replacement treatment with methadone or buprenorphine. They found that retention in both replacementtreatments is associated with significant reductions in the risk forall-cause as well as overdose mortality. It was observed that the first four weeks after treatment induction (11.4 deaths/1000-person-years) and cessation (32.1/1000-person-years) of methadone treatment are the highest risk periods (during which focus efforts for prevention of drug-related deaths needs to be taken).In the case of Buprenorphine, induction period (i.e. first four weeks) was not

associated with increased risk of morbidity. Similar to Methadone a significantly increased mortality was seen in the first four weeks after treatment cessation compared with the remaining time out of Buprenorphine treatment (32.0 versus 10.9/1000-person-years).

The second approach is antagonist maintenance therapy. Different preparations of Naltrexone are used for that purpose. According to Cochrane review[31] of 2011, (including 13 RCTs, N=1158), oral naltrexone, with or withoutpsychotherapy, was no better than placebo in terms of retention in treatment, use of the primary substance of abuse. Only 28% of people retained in treatment were included studies. But (based on 2 studies) one outcome that was clearly in favour of oral naltrexone, was reduction of re-incarceration by about 50%. So, oral Naltrexone may be an efficacious adjuvant in therapy, especially for participants who fear severe consequences if they do not stop taking opioids (like professionals, who might lose their job or parolees who risk re-incarceration). None of the studies was of high qualities. According to authors from these studies, an adequate evaluation of oral naltrexone treatment in opioid addiction is not possible.

The above review showed that compliance with oral Naltrexone is a major issue in its utility in opioid addiction. To enhance the compliance others preparations (like injectables/implants) had been tried with variable success. The RCTs[32, 33] that have been published in the last few years have largely confirmed the positive results. 2 recent RCTs done in Russia (where substitution therapy is forbidden by law, and naltrexone is the only availablepharmacotherapy for heroin dependence) worth mentioning.

First of them was a multicenter study of Vivitrol[34], a long-acting depot Naltrexone injection (that led to FDA approval of Vivitrol for opiate dependence in 2010). This 24-weeks long double-blind RCT compared monthly intramuscular Vivitrol 380 mg (n=126) or an identical-looking placebo (n= 124) with 12 biweekly counselling sessions. It confirmed abstinence, based on opioid-negative urine drug tests were significant ($p = 0.0002$) with Vivitrol yielding a median of 90% confirmed abstinent weeks versus

35% for placebo. Vivitrol-treated patients self-reported a median of 99.2% opioid-free days versus 60.4% for placebo (p = 0.0004). The anti-craving effect was also significant of Vivitrolcompared to placebo(p < 0.0001). Median retention was >168 days with Vivitrolversus 96 days with placebo (p = 0.0042).

Another study[35] (n=306) compared Prodetoxon, a long-acting, sustained-release NTX implant (1000mg, 3 times – every other month), Oral Naltrexone and placebo. Medications were administered under double-dummy/ double-blind conditions. It showed a clear advantage of the NTX implant group over the two others.

In the recent past, there were also comparative efficacy studies of Depot Naltrexone and Buprenorphine. In a multicenter, outpatient, open-label randomized clinical trial (n=159), Tanum L. et al.[36] reported that retention in the extended-release naltrexone group was comparable to the buprenorphine-naloxone group with mean (SD) time of 69.3 (25.9) and 63.7 (29.9) days, correspondingly (*P* = .33, log-rank test). Treatment with extended-release naltrexone was not inferior to buprenorphine-naloxone on group proportion of the total number of opioid-negative urine drug tests. Another 24 weeks, open-label, randomized controlled, comparative effectiveness trial[37] showed that extended-release naltrexone (XR-NTX) had a substantial induction hurdle: fewer participants successfully initiated XR-NTX (204 [72%] of 283) than Buprenorphine (270 [94%] of 287; p<0·0001). Among all participants who were randomly assigned (intention-to-treat population, n=570) 24-week relapse events were greater for XR-NTX (185 [65%] of 283) than for Buprenorphine (163 [57%] of 287; hazard ratio [HR] 1·36, 95% CI 1·10–1·68), most or all of this difference accounted for by early relapse in nearly all (70 [89%] of 79) XR-NTX induction failures. Interestingly, among participants successfully inducted (per-protocol population, n=474), 24-week relapse events were similar across study groups (p=0·44). So, it is more difficult to start some patients to extended-release naltrexone than Buprenorphine but after successful initiation, both medications were equally safe and effective.

But unfortunately, implantsare not readily available in the Indian market and yet to get FDA approval.

Agents used in Gambling Disorder

Despite the significant personal costs associated with Gambling Disorder, research indicates that less than 6% of the gamblers seek formal treatment. A desire to take care of the problem on their own, lack of information/knowledge about treatment facilities, and stigma have been identified as contributing to this low rate of help seeking[15]. Till now there is no approved drug for the treatment of Gambling Disorder. At least 18 double bind placebo control studies have been conducted. The following table mentioned some important studies which showed empirical evidence of modest efficacy of at least 2 drugs.

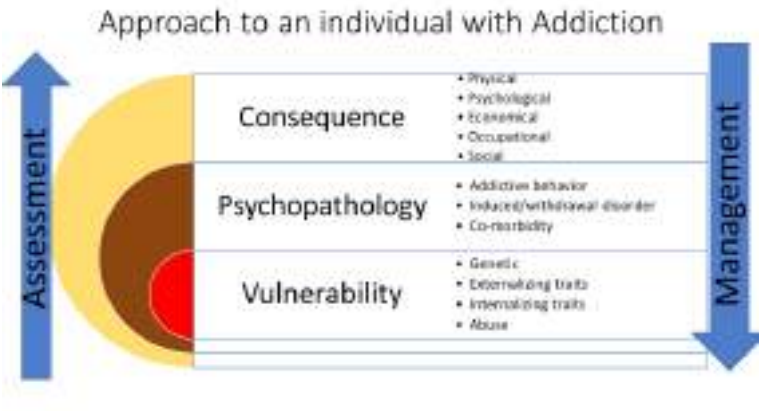

Diagram 1

Table 4:

Reference	Medications	Designs/Duration	Subjects	Dose	Outcome
Kim[38] *et al.* 2001	Naltrexone	Parallel design 12 weeks with 1 week placebo lead-in	89 enrolled; 45 completers	188 _ 96 mg	First systematic investigation of naltrexone; atypical gender distribution of PG Naltrexone group improved significantly compared with placebo
Grant[39] *et al.* 2008	Naltrexone	Parallel design 18 weeks	77 enrolled; 49 completers	Fixed dose (50 mg, 100 mg, 150 mg)	Longest PG trial investigating naltrexone; excluded bipolar disorder and substance use disorders. Naltrexone group improved significantly compared with placebo

Grant[40] *et al.* 2006	Nalmefene	Parallel design 16 weeks	207 enrolled; 73 completers	Fixed-dose study (25 mg, 50 mg, 100 mg)	Large sample size; excluded bipolar disorder and substance use disorders Nalmefene 25 mg and 50 mg significantly improved compared with placebo
Grant[41] *et al.* 2010.	Nalmefene	Parallel design 16 weeks with 1 week placebo lead-in	233 enrolled; 126 completers	Fixed-dose study (20 mg, 40 mg)	Large sample size; current Axis I disorders and individuals seeking psychotherapy were excluded intention-to-treat nalmefene no different from placebo. *Post hoc* analyses: 40 mg nalmefene significant improvement on the primary measure

Kim[42] *et al.* 2002	Paroxetine	Parallel design 8 weeks with 1 week placebo lead-in	53 enrolled; 41 completers	51.7 _ 13.1 mg	Only one subject dropped out due to an adverse event; excluded Axis I disorders and atypical gender distribution of PG. Paroxetine group significantly improved compared
Grant[43] *et al.* 2003	Paroxetine	Parallel design 16 weeks	76 enrolled; 45 completers	50 _ 8.3 mg	Multisite study; significant baseline differences between treatment groups and exclusion of Axis I disorders Paroxetine and placebo groups with comparable
Blanco[44] *et al.* 2002	Fluvoxamine	Parallel design 6 months	32 enrolled; 13 completers	200 mg	6-month study duration; small sample size Fluvoxamine not statistically significant from placebo

Sáiz-Ruiz[45] *et al.* 2005	Sertraline	Parallel design 6 months	60 enrolled; 44 completers	95 mg	6-month study duration; high placebo response rate Similar improvement in both groups
Hollander[46] *et al.* 2005	Lithium carbonate	Parallel design 10 weeks	40 bipolar-spectrum patients enrolled; 29 completers	1,170 _ 221 mg	Included bipolar spectrum disorders; sample may not generalize to all individuals with PG Lithium group significantly improved compared with
Grant[47] *et al.* 2007	N-acetyl cysteine	8 - w e e k open-label followed by 6 weeks double-blind discontinuation	27 enrolled in open-label; 13 randomized to double-blind; 13 completed	1476.9 _ 311.3 mg	Only trial to investigate NAC; small sample size 83.3% of those assigned to N-acetyl cysteine were still responders at end of the double-blind phase, compared with 28.6% assigned to placebo.

Some observations from these studies are worth mentioning. First, Opioid antagonists and N acetyl cysteine are effective for short duration of treatment of Gambling Disorder. Secondly, there was a large proportion of drop out. Thirdly, there is a high placebo effect in almost all studies. Finally, Naltrexone effective dose used was significantly high (around 200mg) compared to the dose used in alcohol.

Apart from above RCTs, there were RCTs of Olanzapine, Topiramate and on Bupropion. Results were largely comparable with placebo[48].

Approach to management of addiction

Many a time, while managing a case of addiction, we only focus on addictive behaviour and try to treat that as a singular entity. But in reality, addiction is a dynamic process. It has its roots in somevulnerability. That may be individual (like genetic, externalizing or internalizing traits etc.) or environmental (familial, abnormal parenting, childhood abuse, substance availability etc.). Moreover, these individuals' vulnerabilities are not mutually exclusive. Externalizing traits like ADHD can lead to multiple skill deficits in adult life. Hence, they may fail in different social/ economic context. That, in turn, predisposes them to depression which is an internalizing disorder. These vulnerabilities in one hand can predispose individuals to addiction; on the other hand can maintain the addictive behaviour. While approaching for proper assessment of a case of addiction, it is utmost important to start from vulnerabilities and gradually move towards psychopathology and its consequences (please see the diagram 1). During management consequence should be taken care of first. Then gradually we should address addiction-related psychopathology. Till now mainly we have discussed how psychopharmacology can help us to manage the addictive behaviours. Now we will briefly discuss the role of psychopharmacology in managing two psychopathologies or vulnerability very commonly associated with addictive behaviour.

ADHD as vulnerability/co-morbidity and its pharmacological management

Externalizing disorders are disruptive toward others and include attention-deficit/hyperactivitydisorder, oppositional defiant disorder, conduct disorder and anti-social personality disorder.The Drug Abuse Treatment Outcome Study – Adolescent (DATOS-A) studies[49] found that nearly two-thirds oftheir adolescent substance-abusing sample had a comorbid externalizing diagnosis. A 10-year follow-up study[50] of monitoring children into young adulthood byshowed that ADHD subjects were 1.47 times more likely to develop addiction compared to controls.The National Comorbidity Survey Replication Study (NCS-R) [51] has also found that adults with ADHD have higher rates of having an addiction than those without ADHD (15.2 % vs. 5.6 %). Similarly, individuals with addiction are more likely to have ADHD than those without an addiction (10.8 % vs. 3.8 %).

Several issues that are problematic when assessing individuals for ADHD[3] include (1) the developmental appropriateness of the symptoms, (2) the age criterion, (3) determining what defines other specified or unspecified ADHD, (4) additional Psychopathology. But these are beyond the scope of our discussion.

Recognizing the link between ADHD and substance abuse is relevant to clinicians in that substance abusers with ADHD who enter addiction treatment has been shown to have a worse outcome than those without ADHD, despite more treatment exposure[52,53,54]. Further, substance abusers with ADHD entering treatment have higher rates of other psychiatric comorbidities (e.g., depression) that may worsen treatment success unless these additional comorbidities are simultaneous addressed[54, 55]

In 2003, Wilens et al.[56] performed a meta-analyticreview of 6 major studies conducted to determine an important question in regards to pharmacotherapy- whether or not stimulant treatment affectthe development of addiction. After 4 years of follow up [n= (674 medicated ADHD + 360 unmedicated)], they found that the pooled estimate of the OR indicated a nearly two-fold reduction in

the risk for addictions in youths who were treated with stimulants compared with youths who did not receive stimulants.

In table 5, notable studies of the efficacy of pharmacotherapy in ADHD with comorbid addiction has been mentioned.

Table 5:

Reference	Comorbid addiction	Medication used for ADHD	ADHD outcome	Addiction outcome
Levin[57] et al. 2006b	Cocaine	Bupropion	No benefit	No benefit
McRae-Clark[58] et al. 2010	Cannabis	atomoxetine	Better than Placebo	No benefit
Michelson[59] et al. 2003	Alcohol	atomoxetine	Better than Placebo	Better than Placebo
Schubiner[60] et al. 2002	Cocaine	methylphenidate	Better than Placebo	No benefit
Levin[61] et al. 2006a	Cocaine	methylphenidate	No benefit	Mild improvement
Winhusen[62] et al. 2010	Tobacco	OROS-methylphenidate +Nicotine patch	Better than placebo plus a nicotine patch	No benefit
Riggs[63] et al. 2011	Substance use disorder	OROS-methylphenidate	Better than Placebo	No benefit

OROS=Osmotic Release Oral System

Importantly, none of these trials observed misuse or abuse of the prescribed medications. Despite concerns that prescription stimulant use may lead to the increased craving for cocaine or amphetamine use, this effect has not been reported in the controlled clinical trials conducted to date[3].

In summary, the clinical trials using methylphenidate have been mixed in reducing ADHD symptoms, with perhaps a mild to moderate effect on cocaine use reduction. Atomoxetine outperformed placebo in ADHD symptoms reduction and alcohol use in alcohol addict but has not shown superiority over placebo in cannabis addiction.

Anxiety as vulnerability/co-morbidity and its pharmacological management

Comorbid anxiety and addiction represent a serious clinical challenge, affecting both management and prognosis[64]. The comorbidity between anxiety and addiction appears to be a worldwide phenomenon, with similar prevalence rates andhigh and significant risk of co-occurrence as compared with the general population.Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) on 43,093 adults shows that people suffering from an anxiety disorder had an odds ratio of 1.9 for any substance use disorder and of 1.7 for any alcohol use disorder.Panic disorder with agoraphobia seems to show the strongest association with a co-occurring substance use disorder[65].

Three main etiological hypotheses of co-occurrence are-

1. The "self-medication" hypothesis[66].
2. Substance use and/or related withdrawal syndromes causing anxiety[67].
3. Shared genetic and environmentalfactors (like a disruptive family environment and parental abuse or neglect) [67].

Whatever is the reason for common co-occurrence, comorbidity between anxiety and addictions makes treatment and management of both disorders difficult. Individuals with an alcohol addiction and co-occurring anxiety disorders are significantly more disabled, worse health-related quality of life and use health services more than addicts without this comorbidity[68, 69, 70], supporting the need to define specific treatment options for this population.

So, early identification and treatment of both the disorder are of immense importance. In their meta-analysis Hobbs et al.[71]suggests that, due to the potentially serious consequences of unsuccessful treatment for alcohol addiction, an integration with interventions addressing co-occurring anxiety disorders could be important, even if the amount of absolute benefit is small to moderate.

There is a scarcity of evidence-based effective pharmacological interventions for both anxiety and addiction, whereas onlysporadic intervention studies are available, e.g., foralcohol use disorders. Selective serotonin reuptake inhibitors (SSRIs) seem effectivein reducing and preventing anxiety symptoms, but there is a lack of clinicaltrials assessing their efficacy in comorbid patients[18].

In a small placebo-controlledtrial[72] on alcohol addiction and co-morbid socialphobia, the paroxetine-treated group showed significantly lower symptoms on Clinical Global Index.

Studies on Buspirone, a partial 5-hydroxytryptamine 1Aagonist, have shown mixed results on comorbid generalized anxiety and alcoholaddiction[73]. Although benzodiazepines are effective inthe treatment of anxiety disorders, their use in current or lifetimeaddicts may be complicated by their addiction-forming potential. Whether there is theneed for full detoxification before startingpsychopharmacological treatment for comorbid anxiety/ depressive disorder? The evidence is scanty and inconclusive. Best is to take a judgment on severity and treatment setting[74].

In one RCT conducted at threeoutpatient clinics on 254 patients with an axis I psychiatric disorder andalcohol dependence, the efficacy of disulfiram and naltrexone, or their combination,was investigated. Individuals treated with any of the true medication showed more successiveweeks of total abstinence and less craving than those prescribed withplacebo, but there were no significant differences in other measures of alcoholconsumption. Furthermore, subjects treated with disulfiram experienced significantlylesser obsessive-compulsive and phobic symptoms over time. Noclear advantage of combining medications was observed[75].

A secondary analysis of a study evaluating the efficacy of naltrexone inveterans suffering from alcohol addictionreported that naltrexone withantidepressant medications for mood and anxiety symptoms, had significantly smaller percent drinking days than those receivingplacebo plus antidepressant medication. So, antidepressant boosted the effect of naltrexone.[76]

CONCLUSION

As our understandings of the neurobiology of addiction are becoming clearer, many avenues are opening up in the field of addiction pharmacology. There are 26 medications (some for multiple drug addiction, 7 for each of cocaine, opiate, and nicotine addiction, 5 for alcohol addiction and 3 for methamphetamine dependence treatment) in development for addictive disorders by the pharmaceutical industry[77].

Another novel approach for the treatment of addiction/ substance use disorders is the use of biologics which include immunotherapies, such as vaccines or antibodies, as well as enzymes. These are usually large and complex molecules that do not cross the blood-brain barrier and do not have effects on the central nervous system. Biologics are investigated for the treatment of SUDs because they prevent the access of the drug of abuse to the brain and, thus, prevent their effect on brain reward systems. It is expected that over a period of treatment with biologics, an extinction of the brain mechanisms of addiction may take place. Addictions being complex conditions require multiple therapeutic approaches and biologics may offer a new way to treat these disorders without directly affecting the brain[78].

Moreover, to make Pharmacological treatment more effective, we should follow some principle along with it (as proposed by American Society of Addiction Medicine) [79]

i. No single treatment is effective for everyone- treatment should be patient-tailored.
ii. Medically assisted detoxification is only the first stage of de-addiction. It has very little to do with long-term

maintenance of abstinence.

iii. Treatment should be readily available- otherwise, there is a chance of losing the patients. Like any other chronic disease, earlier the treatment initiation, better is the outcome.

iv. To take care of the multiple needs of the patient- along with drug addiction problems, we need to take care of a person's medical, psychological, social and vocational problems.

v. Medications, when combined with counseling and behavior therapy/ motivational enhancement therapy, are more effective.

vi. Treatment does not always need to be voluntary to be effective. Many a times sanctions or enticements from employment settings, justice system or family members can increase treatment entry/success

vii. Monitoring drug use during treatment can be a powerful incentive for patients and can motivate to withstand the craving to use drugs as well as can indicate early relapse to intervene early.

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Management of Delirium in Elderly-An Overview

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ABSTRACT: *Delirium in the elderly population is a common clinical entity which poses a significant challenge to the health professionals due to difficulties associated with its diagnosis and more importantly its adequate management. In this review,various current guidelines pertaining to the pharmacological management of delirium in elderly assessed including Medline (PUBMED), Cochrane Central, EMBASE & SCOPUS. A multi-disciplinary approach is the key to manage delirium in elderly. Combined non-pharmacological and pharmacological management is the best way to go forward in such patients.*

Key-Words: *Delirium; elderly; pharmacological; non-pharmacological*

INTRODUCTION

Delirium or acute confusional state is a known clinical entity in the elderly population, not only in the hospitalized subgroup of a population but also in the community. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) defines delirium as: "a disturbance of consciousness that is accompanied by a change in cognition that cannot be better accounted for by a pre-existing or evolving dementia"[1].Thus, a patient presents with a cluster of acute onset, rapidly progressive cognitive, emotional, behavioural and psychotic symptoms that varies over the course of the day and are accompanied by lowering of consciousness & disorientation to time, place and person. It is often the presentation with the backdrop of an underlying medical, and or surgical cause.

Clinical Presentation

Theoretically, delirium is known to mental health professionals, however, in spite of that, delirium is often missed in clinical practice. The reasons are multiple, one because delirium has a variable course and the symptoms fluctuate over the course of the day showing a sun-downing effect. Secondly, delirium in elderly does not always present in a hyperactive type, which is the well known clinical entity, but, in contrast, presents as a hypoactive type where the patient often appears to be withdrawn with little movement or response, and thus, is often misdiagnosed or overlooked.

Delirium which is often known to be multi-factorial in origin can be a fatal condition in the elderly. Prevalence of delirium in elderly increase significantly in a hospital setting in comparison to its prevalence in the community; also the rates of delirium in elderly rise noticeably in ICU setting[2].The incidence of delirium in elderly, during a hospital stay, rises to over 50% and rises to 70% in the intensive care units (ICU). Postoperative delirium is again very common in the elderly with an incidence rate of 15% and 60% [3, 4].

Identifying delirium in a hospital setting

Identification and appropriate management of delirium in elderly is a challenge for mental health professionals who are dealing with geriatric mental health services. Sensitization of the caregivers, hospital staff, and all health professionals engaged in the care of the elderly is one of the important ways in early identification of delirium in elderly, which otherwise is often diagnosed at a delayed interval due to unawareness. Early diagnosis results in better management of a patient and reduces the risk of morbidity and mortality. There are many bedside standardized approved screening tools for delirium, most well known of which is Mini-Mental Status Examination (MMSE), which though is not designed for the purpose of delirium per se, but is definitely useful in a clinical setting[5].Confusion-Assessment Method (CAM) is a well researched screening tool with a reported sensitivity of >94%, specificity of >90% and is easy to use in a clinical setting and is

recommended by The Australian Society for Geriatric Medicine, The American Psychiatric Association and The British Geriatrics Society[6]. Delirium Rating Scale (DRS) is a useful instrument for the purpose of diagnosis and also, for measuring the severity of delirium, however, it requires specialist trained in applying it which limits its utility in acute clinical setting[7].

Another important dimension in managing delirium in the elderly is to differentiate between delirium, dementia and depression, which can be done with thorough clinical history, physical examination and mental status examination.

Risk factors relating to delirium

Multiple risk factors have been found to be associated with delirium in the elderly. According to the National Institute for Health and Clinical Excellence (NICE) guidelines, the most important risk factors that one needs to be cautious of in elderly include- prior cognitive impairment or dementia, older age, multiple co-morbidities, previous history of delirium, stroke, neurological disease, falls or gait disorder, psychoactive drug use, polypharmacy[8,9,10,11,12]. Additionally, other studies have reported that elderly who had been admitted due to water and electrolyte disturbances were at higher risk of developing delirium. Also, other independent risk factors for having a delirium after acute admission were an elevated urea nitrogen level, and the number of leucocytes[13]. Another, important risk factors that have been isolated for delirium in elderly include illness severity, evidence of visual impairment, urinary catheterization, low albumin level and length of hospital stay[14]. Depression is also an identified risk factor for elderly developing delirium[15].

Identification of risks factors in elderly can help to identify high-risk patient group and thus, facilitate early recognition and immediate management of the elderly patients. There is enough evidence to suggest that certain risk factors for delirium in the elderly are fairly consistent and thus their monitoring should be part of the routine screening of elderly patients being hospitalized.

Non-pharmacological management of delirium

There is ample evidence to suggest and promote non-pharmacological management of delirium in elderly. Correct identification of the underlying medical condition, its correction, and close supervision and monitoring of the patient can bring about improvement in cognition, emotional and behavioural problems encountered in delirious patients. A well-trained staffthat is consistent and provide repeated orientation cues in a non-threatening environment can facilitate much improvement in managing these patients, especially in ICU set up. It is suggested that both over and under-stimulation of the patient in acute confusion needs to be avoided diligently, as both results in worsening the clinical presentation.

NICE Guidelines (2006)**,** CCSMH National Guidelines for Seniors' Mental Health (2010) and Indian Psychiatric Society guidelines (2018)suggest the following basic points in dealing with such patients apart from pharmacological agents- Improving mobility and function, provide safe consistent environment for care, improving communication, behavioral management, ambient environment, assess the need of care providers/ caregivers, increasing fluid intake to prevent dehydration (use subcutaneous fluids if necessary), ensuring good diet, fluid intake and mobility to prevent constipation, encouraging good sleep pattern (use milky drinks at bedtime, exercise during the day), avoiding wandering, managing rambling speech[16,17,18].

Adequate pain assessment and management, monitoring of regular bladder and bowel movements in elderly, timely identification and management of an infective foci in body, early identification of changes in mood, changes in normal daily routines, and changes in the regular scheduled activities is important as preventive measures concerning elderly and lower their risk of developing delirium. Recognition of sensory deficits like visual and or hearing impairment and their adequate correction is also an important step to minimize the risk of delirium or its worsening. American Psychiatric Association Practice Guidelines (2010) also

recommend cognitive, emotional & supportive measures that help in providing reorientation, reassurance and information concerning delirium to patients that helps reducing fear or demoralisation [19].

Pharmacological management of delirium

Treatment of delirium should mainly focus on identifying and managing the risk factors, providing supportive care, and preventing and treating complications. There is fairly consistent literature pertaining to the use of pharmacological measures to manage delirium in elderly. Antipsychotic medications- haloperidol, risperidone, quetiapine and olanzapine have been used in elderly patients with delirium with fairly similar efficacies, however, different risk profiles. The gold standard drug till date remains haloperidol. Haloperidol is most frequently used because it has few anticholinergic side effects, few active metabolites, and a relatively small likelihood of causing sedation and hypotension. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adults(2002)and evidence and consensus-based German guidelines for the management of analgesia, sedation and delirium in intensive care (2010) recommend that low dose neuroleptic like haloperidol[19].

These guidelines recommend the lowest possible dose of haloperidol which can be increased in increments if necessary after an interval of 2 hours (i.e. 0.25 mg to 0.5 mg in divided doses). This helps in correcting the behavioural changes associated with delirium. It may be administered orally, intramuscularly or intravenously[20].

Some research evidence suggests that atypical antipsychotics like olanzapine, risperidone and quetiapine are as efficacious as haloperidol in reducing the severity of delirium and also improve the cognitive functions and are associated with lower incidence of side effects as compared to haloperidol. Regarding the duration of treatment, some authors suggest that antipsychotics should be discontinued immediately after the resolution of delirium, whereas others recommend tapering off of antipsychotics after a week of a symptom-free period.

Benzodiazepines (BZD) as monotherapy are not advocated in patients of delirium in elderly as they pose a risk of masking the underlying clinical condition, however, delirium which is secondary to alcohol withdrawal, necessitates the use of BZD, mostly lorazepam in elderly[21].

CONCLUSION

Delirium is a common medical emergency in elderly patients and requires the judicious use of integrated non-pharmacological and pharmacological techniques. Treatment modalities concerning delirium management in the elderly have been fairly consistent with little variation over the last decade.

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Current Updates in Pharmacological Treatment of Dementia- a narrative review

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ABSTRACT: *Dementia is a tremendous global health concern in both developed and developing countries. There are significant gaps in managing dementia, which include a delay in diagnosis and initiating medications approved for enhancing cognition. Hence, there is an urgent need to improve the quality of life of patient's struggling to deal with this life-changing diagnosis which impacts the carers too because of caregiving burden and burnout. We aim to provide a brief background about the extent of the burden of dementia especially Alzheimer's dementia and then focus on the pharmacological agents currently approved to treat Alzheimer's dementia which is the most common form of dementia. We then reviewed currently available three Cholinesterase Inhibitors (ChEIs) which include Donepezil, Rivastigmine & Galantamine, and one NMDA receptor antagonist Memantine. Subsequently an overview of BPSD, current treatment recommendations in other types of dementia, treatment gap in India and finally about future treatments in Alzheimer's dementia.*

Keywords: *Dementia, Neurocognitive Disorder, Cholinesterase Inhibitors, Memantine*

INTRODUCTION

Dementia is a progressive neurodegenerative condition, which can affect multiple cognitive domains. It is also associated with symptoms like aggression, psychosis, agitation, depression or anxiety which are classed under behavioural and psychological symptoms of dementia (BPSD). There are various subtypes of Dementia with Alzheimer's disease accounting for 60%-70% of dementias. Due to the heterogeneity in presentation and symptoms,

there is an inconsistent approach to diagnosis and treatment. There are ongoing attempts to standardise this and a major revision was recently done in DSM-5, where the term Dementia was replaced by Neurocognitive disorder.[1] ICD-10 criteria for diagnosing Alzheimer's dementia are shown below in table 1.[2]

It is estimated that 35.6 million people lived with dementia worldwide in 2010, with numbers expected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050. In 2010, 58% of all people with dementia lived in countries with low or middle incomes, with this proportion anticipated to rise to 63% in 2030 and 71% in 2050.[3] It is estimated that India has 4 million people suffering from some form of Dementia as per Alzheimer's Association India.

Table 1. F00 Dementia in Alzheimer's disease (ICD-10)

Diagnostic guidelines

The following features are essential for a definite diagnosis:

a) Presence of dementia with a primary requirement for diagnosis is evidence of a decline in both memory and thinking which is sufficient to impair personal activities of daily living

b) Insidious onset with slow deterioration. While the onset usually seems difficult to pinpoint in time, the realisation by others that the defects exist may come suddenly. An apparent plateau may occur in the progression.

c) An absence of clinical evidence, or findings from special investigations, to suggest that the mental state may be due to other systemic or brain disease which can Induce dementia (e.g. hypothyroidism, hypercalcaemia, vitamin B12 deficiency, niacin deficiency, neurosyphilis, normal pressure hydrocephalus, or subdural haematoma).

d) An absence of a sudden, apoplectic onset, or of neurological signs of focal damage such as hemiparesis, sensory loss, visual field defects, and incoordination occurring early in the illness (although these phenomena may be superimposed later).

Includes: primary degenerative dementia of the Alzheimer's type

Treatment paradigms in Alzheimer's Dementia (AD)

There are various treatment approaches in AD. The common ones in clinical practice are addressing cognitive decline and reducing the rate of progression with neurotransmitter modulators, and using various non-pharmacological and pharmacological approaches to manage BPSD. Another approach involves primary prevention, which aims at delaying the time to the onset of illness. The identification of at-risk and preclinical AD populations is becoming important for targeting primary and secondary prevention clinical trials in AD.[4]

Neurotransmitter-related therapies

In Alzheimer's dementia (AD), there is reduction in the activity of cerebral cortical choline acetyltransferase (ChAT), the key enzyme in acetylcholine synthesis,[5-7] along with the loss of cholinergic cell bodies in the nucleus basalis.[8,9] We now know that many other neurotransmitters are also affected in AD. Since there is a reduction in central cholinergic functioning, potentiation of central cholinergic function helps to improve the cognitive impairment associated with AD.

There are currently two classes of drugs approved for the treatment of AD, the ChEIs (Choline-esterase Inhibitors) such as tacrine, donepezil, rivastigmine and galantamine and the N-methyl-D-aspartate receptor (NMDA) receptor antagonist, memantine.

Cholinesterase Inhibitors (ChEIs)

Physostigmine was used in the early trials in the treatment of AD and then there were trials of other ChEIs tacrine, velnacrine, and sustained-release physostigmine.[10-12] Tacrine was the first ChEI to be approved for the treatment of AD and is no longer used due to hepatotoxicity. The three ChEIs donepezil, rivastigmine, and galantamine are now used in clinical practice. There are slight variations in the mode of action of the three clinically available ChEIs for treatment of AD, but there is no evidence of meaningful difference among them with respect to efficacy.[13]

Donepezil

Donepezil is a long-acting highly selective and reversible ChEI. It was initially approved for treatment of early to moderate stages of AD by FDA in 1996. In 2006, FDA approved its use in severe AD after clinical trials demonstrated its efficacy in severe AD.[14,15] It is observed in most studies, that donepezil treatment leads to greater improvement in daily functioning than placebo.[16]

Dosing: Donepezil is initiated at 5mg/day and then increased to 10mg/day after 4–6 weeks. Doses of 10 mg tend to be more effective and have a propensity for higher adverse side effects than 5mg. It is also available as an orally disintegrating tablet, which is particularly useful for patients with swallowing difficulty.

In 2010, the FDA approved a higher daily dose of donepezil (23 mg/day) for the treatment of AD in the moderate-to-severe stages based on positive results from a large, global, Phase 3 clinical trial that compared switching to donepezil 23mg/day with continuing treatment on donepezil 10mg/day. In that trial, no benefit was seen in the co-primary endpoint of global functioning; however, donepezil 23mg/day provided a small but significant improvement in the cognitive endpoint compared with donepezil 10mg/day.[17] A 1-year extension study with donepezil 23mg/day did not reveal any increase in adverse events beyond the initial weeks of the study.[18]

Common side-effects: Gastrointestinal side effects are commonly seen and include nausea, vomiting, diarrhoea, and anorexia. Some patients may develop muscle cramps, headache, dizziness, syncope, flushing, insomnia, weakness, drowsiness, fatigue, and agitation. Weight loss of >7% of baseline occurred at twice the rate of placebo in a nursing home study, but not in outpatient trials. Adverse effects occurred at higher rates when the titration from 5 to 10 mg was made in 1 week compared with 6 weeks.

Rivastigmine

Rivastigmine is a selective pseudo-irreversible AChE subtype inhibitor, which also inhibits Butyryl Cholinesterase. After binding to AChE, the carbamate portion of rivastigmine is slowly

hydrolysed, cleaved, conjugated to a sulphate, and excreted. Thus, its metabolism is essentially extrahepatic and is unlikely to have significant pharmacokinetic interactions.

Rivastigmine also comes in a transdermal patch form, which has been found to have similar benefits to oral rivastigmine at lower doses but with fewer side effects, and with similar side-effect burden at higher doses.[19] The patch appears to have better tolerability than rivastigmine capsules, with fewer gastrointestinal adverse events and discontinuations because of these adverse events.[20] There is evidence that daily rotation of patch location appears to reduce the frequency of skin reactions.

Dosing: The recommended starting dose of oral rivastigmine is 1.5mg BD, taken with meals, which can be increased to 3 mg BD after a minimum of 2 weeks of treatment if well tolerated. Subsequently, it can be increased to 4.5 and then 6mg BD after a minimum 2-week treatment interval. There is some evidence that higher daily doses, averaging about 9–10 mg, were associated with better efficacy than lower doses. Rivastigmine is available as an oral solution too. Transdermal rivastigmine is started with an initial 4.6 mg patch daily for at least 4 weeks and can be increased to a 9.5 mg patch daily based on tolerability.

Side-effects: Gastrointestinal side-effects are commonly seen particularly in the high-dose (6–12 mg/day) group. These occurred mainly during dose escalation and led to withdrawal in one study in 23% of the high-dose group, 7% of the low-dose group, and 7% of the placebo group.

Other side-effects in the higher dose group include sweating, fatigue, asthenia, weight loss, malaise, dizziness and somnolence. In the maintenance phase, dizziness, nausea, vomiting, dyspepsia, and sinusitis occurred more in the 6–12 mg/day group than in the placebo group.

Galantamine

Galantamine is a reversible, competitive inhibitor of AChE with relatively little Butyryl Cholinesterase activity.[21] Competitive

Table 2. Key Published Placebo-Controlled RCTs in ChEIs[23-25,28-36]

Study	No	Duration (weeks)	Age (years)	Dose (mg/day)	Completers (%)
Tacrine Knapp et al. (1994)	663	30	73	120 160 P	52 28 68
Donepezil Rogers et al. (1998)	473	24	73	5 10 P	69 68 60
Burns et al. (1999)	818	24	72	5 10 P	78 74 60
Tariot et al. (2001)	350	24	68	10 P	74 62
Feldman et al. (2001)	290	24	74	10	67
Whitehead et al. (2001)	286	52	73	P	67
Rivastigmine Corey-Bloom et al. (1998)	699	26	73	1-4 6-12 P	69 65 64
Rosler et al. (1999)	725	26	72	1-4 6-12 P	68 67 67
Galantamine Tariot et al. (2000)	978	30	77	8 16 24 P	74 78 78 64
Raskind et al. (2000)	636	24	73	24 32 P	68 66 81
Wilcock et al. (2002)	653	24	72		

inhibitors compete with ACh at AChE binding sites, so their inhibition is, theoretically, dependent on intrasynaptic ACh. It also causes allosteric modulation of nicotinic receptor sites, thus possibly enhancing cholinergic transmission by presynaptic nicotinic stimulation.[22] Several multicentre trials involving over 2400 subjects[23-26] have been published regarding treatment with Galantamine. One trial found that daily doses of 16 or 24 mg were effective and 8 mg was not. There is evidence of continuing Galantamine treatment after an initial response. In one study. patients with mild-to-moderate AD who demonstrated cognitive benefits with up to 5 months of galantamine treatment, maintained their achieved benefit if they continued as compared to patients who had more disease progression after galantamine was discontinued.[27]

Dosing: The starting dose of galantamine is 4mg BD, which is increased to 8mg BD after 2–4 weeks. If tolerated, it can be increased to 12mg BD after 4 weeks. It is also available in an extended release

formulation which is started at 8mg/day. It can be increased to 16mg/day after 4 weeks and further increased to 24 mg/day in 4 weeks. This depends on clinical improvement and tolerability, which requires regular monitoring of response and side-effects.

Side-effects: Common side effects include nausea, vomiting, diarrhoea, anorexia, weight loss, abdominal pain, dizziness, and tremor. These are more frequent during the early phase of treatment and during dosage titration from 16 to 24 mg/day and higher. Doses of 16 mg/day when titrated over a 4-week period were best tolerated.

Cardiac monitoring and ChEIs

ChEI's are mainly (although not exclusively) prescribed for older people, who have a higher prevalence of cardiac co-morbidity. ChEI's can cause bradycardia and dizziness and increase the risk of falls which can lead to fractures and hospital admissions. Due to this, as a precaution, there are clinicians who do a routine baseline ECG prior to prescribing ChEI's. The rationale for undertaking an ECG is made on the basis of precaution i.e. the possibility of identifying cardiac conduction abnormalities and therefore potentially reducing the risk of bradycardia or syncope. However, one review found that abnormal ECGs are not predictive of cardiovascular adverse events and that these events also occur in those with a normal pre-treatment ECG. The evidence is therefore unclear. Whilst a routine baseline ECG is not recommended, a baseline pulse check is clinically useful and a patient with a pulse rate of less than 50 bpm should not be prescribed/continued on ChEIs.[37]

Glutamatergic therapies

There is evidence that the N-methyl-D-aspartate (NMDA) receptor, a glutamate receptor subtype, has important effects on learning and memory. After stimulation by glutamate, which is an excitatory amino acid, there is a long-term potentiation (LTP) of neuronal activity basic to memory formation.[38] There seems to be a decrease in cerebral cortical and hippocampal NMDA receptors in AD.

Memantine

Memantine is a non-competitive NMDA receptor antagonist, which binds to the NMDA receptor-operated cation channels and modulates excitotoxicity. Memantine also acts as a non-competitive antagonist at the 5-HT3 receptor but the clinical significance of this is unknown.[39] FDA approved memantine for a moderate-to-severe AD in 2003, but not for mild AD. There are randomised, placebo-controlled trials that have demonstrated benefits over placebo in several measures including cognition and behaviour.[40-42] According to the Cochrane Database of Systemic Reviews, pooled data on memantine in the mild-to-moderate AD show a marginally beneficial effect at 6 months that was clinically insignificant with no effect on behaviour or ADLs.[43]

Dosing: Memantine is available in tablet and oral solution form. Treatment is initiated with 5mg/daily for 1 week and increased by 5 mg/daily in divided doses to a maintenance dose of 10 mg twice per day. An extended-release version with once-daily dosing (7, 14, 21, 28 mg) is also available.

Side-Effects: Common side effects can include dizziness, constipation, headache, and confusion. Generally, memantine is well tolerated, and is thought to have a low potential for drug interactions.

Combined Cholinesterase Inhibitor and Memantine

There seems to be a lack of consistency in the clinical use of combining ChEI with memantine. Although commonly combined clinically, there is a lack of clear and consistent evidence. A review suggests using the combination in patients with moderate to severe AD[44] however there is a concern of increased adverse events.[45] The UK Donepezil and Memantine in Moderate to Severe AD (DOMINO) study,[46] which randomised those on stable donepezil with moderate to severe dementia (Standardised Mini-Mental State Examination (SMMSE) score 5–13) to continuation donepezil, discontinuation, a change to memantine or adding memantine, showed that continued donepezil treatment (or a switch to

memantine or combination therapy) was associated with cognitive and functional benefits over the following 12 months, compared to placebo.

Behavioural and Psychological Symptoms of Dementia

Behavioural and Psychological Symptoms of Dementia (BPSD) is an umbrella term for a heterogeneous group of non-cognitive symptoms that are very common in dementia. Suffice to say that the majority of people with dementia will experience BPSD at some time during their illness, particularly in the middle and later stages. Behavioural symptoms include physical aggression, loud vocalisation, restlessness, agitation and wandering. Psychological symptoms include anxiety, depressive mood, hallucinations and delusions. Rates of BPSD vary according to how symptoms are ascertained, thresholds of severity, and setting. For example, rates of BPSD have been estimated at 61%–88% among people with dementia in a community setting[47] and 95% among hospitalised patients in long-term acute care.[48]

Due to its diverse symptomatology, it is important to do a comprehensive assessment and identify target symptoms in case of BPSD. Non-pharmacological methods should be utilised as the first line if possible. At times, when the patient is at a serious risk of harm to self or others, or when non-pharmacological methods have not been successful, medications may be needed. The choice of medications depends on the presenting symptom(s). In case of aggression, a behavioural analysis should be conducted and other possible contributors like pain or an underlying infection should be considered. Medications including antidepressants, benzodiazepines, antipsychotics[49] and ChEI inhibitors are used in managing BPSD.

Current treatment recommendations in other types of Dementia

ChEIs have been used in other types of dementia apart from AD. ChEIs have been recommended for use in Dementia with Lewy Bodies (DLB), Vascular Dementia and Parkinson's disease Dementia

(PDD), but the role in other types of dementia is limited. ChEIs offer modest benefit in the treatment of AD, DLB and PDD. There is some disagreement as to the efficacy of memantine in Parkinson's disease Dementia.

ChEIs and Memantine are not recommended for the treatment of Frontotemporal Dementia.[50] Although, existing evidence does not support the use of ChEIs in FTD, the rates of off-label use remain high, despite increased agitation having been reported with their use in FTD. Selective Serotonin Selective Inhibitors (SSRIs) are the first line of treatment for behavioural problems related to FTD. SSRIs do not improve cognition in FTD.[51]

For vascular dementia, it's important to achieve an effective control of vascular risk factors such as- cessation of smoking, control of hypertension and lowering of cholesterol levels if they are high. Aspirin and Clopidogrel are an important component of the treatment of Vascular Dementia.

For HIV-associated Neurocognitive Disorders (HAND) only effective treatment is the use of anti-retroviral medications. The prevalence of most severe manifestation of HAND- HIV associated dementia has declined with the use of HAART (Highly Active Anti-Retroviral Therapy), but minor neurocognitive disorder has persisted due to poor penetration of blood-brain barrier by antiretrovirals.

Treatment Gap in India

Whilst there are no accurate estimates for the treatment gap for dementia in India, it is estimated to sit around 90% in most parts of the country, with the exception of urban areas and the two southern states of Kerala and Tamil Nadu.[52] In a study on patients with dementia 51% were seen by a doctor in the previous three months but only 5%had received the diagnosis and treatment specific for dementia. This reflects a treatment gap of over 90%. Some other factors mentioned were cost, worries about side effect and lack of understanding of family doctors who advised against it.[53] The barriers to reducing this

treatment gap include lack of awareness about dementia in the general public as well as medical professionals. Often, it is considered a normal part of ageing and specialist help is not sought. Where patients are seen by medical professionals, the treatment is often biological in nature with medications. Whilst medications have a role, there is a bigger role for psychological and social interventions, which are generally missed. Treatment models need to involve training dementia management skills to carers (often family members).

The prescription pattern of antidementia drugs and antipsychotics in dementia patients has not been studied in developing countries where cost may be the most important factor in determining their choice. Hence, the authors of one study from India, performed a retrospective chart review of patients attending their psycho-geriatric clinic, found donepezil and quetiapine to be the most commonly prescribed antidementia drug and antipsychotic, respectively.[28]

Potential Future Treatments

As we enhanced our understanding of the pathogenesis of AD over the last few decades, this has led to other potential targets being investigated in various pre-clinical and clinical trials. These include amyloid-based immunotherapy,[54,55] secretase inhibitors[56,57] and anti-aggregation agents.[58,59] Significant efforts have been made toward developing disease-modifying anti-amyloid therapies, but all have failed to date in short- to intermediate-term clinical trials in AD.

After modest success with ChEIs and memantine, there was great optimism that treatments that target specific pathogenic pathways, particularly the amyloid pathway based on the amyloid cascade hypothesis and amyloid brain pathology, would result in major advances in the treatment of AD. Unfortunately, the results of clinical trials with these agents have been negative. These findings have led some to question the validity of the amyloid hypothesis[60] and others to suggest that the clinical failure of β-amyloid-lowering

agents does not mean that the hypothesis itself is incorrect but rather that manipulating β-amyloid directly is an unrealistic strategy for therapeutic intervention, given the complex role of β-amyloid in neuronal physiology.[61]

CONCLUSION

It is imperative for the clinicians who are involved in the care of people who are at high risk of dementia, to keep a high index of suspicion for dementia. This would ensure early detection and timely utilization of approved medications in the treatment of dementia especially Alzheimer's dementia. One should avoid therapeutic nihilism which sometimes is associated with an illness like dementia and ensure optimum use of ChEIs in the early phase of AD to prolong the quality of life of patients with dementia and delay the eventual institutionalisation or placement in a nursing home. There is a need for supporting ongoing research for finding more effective alternative pharmacological agents to treat dementias, so as to build on a range of options apart from the existing approved pharmacotherapies for dementia. As average life expectancy is increasing in low and medium income countries like India probably time has come to deal with dementia and its related issues with a public health approach.

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Frontiers related to Neurobiology and Management of Dementia- Alzheimer's type

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ABSTRACT: *Dementia is one of the major neuro-cognitive disorders. In recent times there have been significant leaps in both the understandings of its aetiopathology and its treatment and management. The most common neuropathologic presentation associated with dementia reveal mixtures of Alzheimer's disease, vascular, and Lewy body pathologies. Pure syndromes are relatively less common. The commonest singular Dementia is Alzheimer's type. There are various hypotheses for its aetiopathology; amyloid hypothesis, neurotransmitter hypothesis, oxidative stress and mitochondrial hypothesis, inflammatory hypothesis and the epigenetic hypothesis. Researchers have made substantial progress in finding new therapeutics for the treatment of AD. However, clinically, there exist only two classes of compounds in the market for the treatment of AD: AChEIs and NMDA receptor blockers. However, during the last decade, the focus has been shifted to developing new therapeutic strategies for the treatment of AD. Among the newer treatment strategies, the common ones are; antioxidants, some plant-based extracts like ginseng etc., various anti-inflammatory agents etc. Other agents traditionally used and have recent supportive evidenceis; atypical antipsychotics, antidepressants, HMG-COA reductase inhibitors, hormone replacement therapy and Methoxytacrine derivatives.*

Keywords: *Dementia, Alzheimer's type, atypical antipsychotics*

INTRODUCTION

Dementia is probably one of the few neuropsychiatric disorders, which has ever- evolving new frontiers both in its understanding as what causes it as well as its management. In

DSM5 [1], the terminology changes too. Neurocognitive Disorder, as the name suggest, is a set of cognitive disorders, which has clear-cut neurological origin.

Advances in molecular biology diagnostic techniques and medication management havesignificantly improved the ability to recognize and treat cognitive disorders. Cognitionincludes memory, language, orientation, judgment, conducting interpersonalrelationships, performing actions (praxis), and problem-solving. Cognitive disordersreflect a disruption in one or more of these domains and are frequently complicated bybehavioural symptoms. Cognitive disorders exemplify the complex interface amongneurology, medicine, and psychiatry in that medical or neurological conditions oftenlead to cognitive disorders that, in turn, are associated with behavioural symptoms.

Dementia is considered a major neurocognitive disorder. It often challenges clinicians and Nosologists with multiplicity, co-morbidity and unclear boundaries. The boundaries between types of dementia and between dementia and normal ageingcan be quite diffuse. Neuropathologic studies of both clinical and population sampleshave revealed a surprising truth. The most common neuropathologic presentationassociated with dementia reveal mixtures of Alzheimer's disease, vascular, and Lewybody pathologies. Pure syndromes are relatively less common, although often thedementia is ascribed to one of the coexisting pathologies. Strategies regarding how to understand or reconcile multiple pathologies in the clinic are needed, although they lagbehind. *This is one of the most recent advancements in the understanding of Dementias*.

***Dementia,* also referred to as major neurocognitive disorder in the fifth edition of DSM**

(DSM-5) is marked by severe impairment in memory, judgment, orientation, andcognition. The subcategories are (1) dementia of the Alzheimer's type, which usuallyoccurs in persons older than 65 years of age and is manifested by progressiveintellectual

disorientation and dementia, delusions, or depression; (2) vasculardementia, caused by vessel thrombosis or haemorrhage; (3) human immunodeficiencyvirus (HIV) disease; (4) head trauma; (5) Pick's disease or frontotemporal lobardegeneration; (6) Prion disease such as Creutzfeldt-Jakob disease, which is caused by aslow-growing transmittable virus); (7) substance-induced, caused by toxin or medication(e.g., gasoline fumes, atropine); (8) multiple etiologies; and (9) not specified (if a cause isunknown).

Taking a cue from recent studies and what we all knew for long, In DSM-5, a less severe form of dementia called mild neurocognitive disorder is listed.

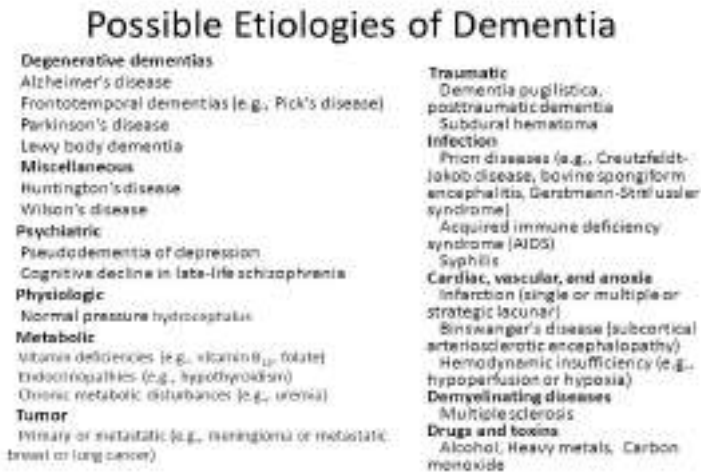
Neuropsychiatric Mental Status Examination

The most common causes of dementia in individuals older than 65 years of age are (1)

Alzheimer's disease, (2) vascular dementia[3], and (3) mixed vascular and Alzheimer'sdementia. Other illnesses that account for approximately 10 percent include Lewy bodydementia; Pick's disease; frontotemporal dementias; normal-pressure hydrocephalus(NPH);

alcoholic dementia; infectious dementia, such as HIV or syphilis; and Parkinson'sdisease. Many types of dementias evaluated in clinical settings can be attributable toreversible causes, such as metabolic abnormalities (e.g., hypothyroidism), nutritionaldeficiencies (e.g., vitamin B12 or folate deficiencies), or dementia syndrome caused bydepression.

The possible etiologies of Dementias can be summarised as follow:



Source: Synopsis of Psychiatry: Kaplan & Saddock's 11th edition.

Dementia of the Alzheimer's type[6]

Clinically, only acetylcholinesterase inhibitors (AChEIs) (donepezil, rivastigmine, galantamine and huperzine) along with N-methyl-D-aspartate (NMDA) receptor antagonists such as -memantine have been used to provide symptomatic relief during AD. However, these agents were not able to prevent or slow the progression in neurodegenerative processes. During the last decade, various new therapeutic strategies showed beneficial effects and are underclinical development for the treatment of AD. One of the major revolutionary approaches in the drug design strategy based

on the multi-target directed (MTD) ligand has been reported as the new hope in the treatment of multi-factorial disease like AD. This is due to classic drug design based around the "one molecule one target" directed ligandstrategy, which was found to be ineffective in the treatment of multifactorial diseases like AD.

Amyloid hypothesis: Amyloid plaques, formed due to abnormal proteolytic cleavage ofAPP, have been reported to play a dominant role in the pathogenesis ofAD. The most predominately formed fragmentsare AŞ1-40 and AŞ1-42. Amyloid peptide deposits have also been reported to interact with theneuronal membrane, resulting in pore formation and an excessive influxof ions that further lead to neuronal loss and progression of ADGenetic Factors: In several well-documentedcases, the disorder has been transmitted in families through an autosomal dominantgene, although such transmission is rare. Alzheimer's type of dementia has shown linkageto chromosomes 1, 14, and 21The gene for amyloid precursor protein is on the long armof chromosome 21.The classic and pathognomonic microscopic findings aresenile plaques, neurofibrillary tangles, neuronal loss (particularly in the cortex and thehippocampus), synaptic loss (perhaps as much as 50 percent in the cortex), andgranulovascular degeneration of the neurons. Neurofibrillary tangles arecomposed of cytoskeletal elements, primarily phosphorylated tau protein, althoughother cytoskeletal proteins are also present. Neurofibrillary tangles are not unique toAlzheimer's disease; they also occur in Down syndrome, dementia pugilistica (punch-drunksyndrome), Parkinson-dementia complex of Guam, Hallervorden-Spatz disease,and the brains of normal people as they age. Neurofibrillary tangles are commonlyfound in the cortex, the hippocampus, the substantia nigra, and the locus ceruleus.

Neurotransmitters: The neurotransmitters that are most often implicated in thepathophysiological condition of Alzheimer's disease are*acetylcholine andnorepinephrine,* both of which are hypothesized to be hypoactive in Alzheimer's disease.

Several studies have reported data consistent with the

hypothesis that specificdegeneration of cholinergic neurons is present in the nucleus basalis of Meynert inpersons with Alzheimer's disease[4]. Other data supporting a cholinergic deficit inAlzheimer's disease demonstrate decreased acetylcholine and choline acetyltransferaseconcentrations in the brain. Choline acetyltransferase is the key enzyme for thesynthesis of acetylcholine, and a reduction in choline acetyltransferase concentrationsuggests a decrease in the number of cholinergic neurons present. Additional support forthe cholinergic deficit hypothesis comes from the observation that cholinergicantagonists, such as scopolamine and atropine, impair cognitive abilities, whereascholinergic agonists, such as physostigmine and arecoline, enhance cognitive abilities.

Decreased norepinephrine activity in Alzheimer's disease is suggested by the decrease innorepinephrine-containing neurons in the locus ceruleus found in some pathologicalexaminations of brains from persons with Alzheimer's disease.

Serotonin (5-hydroxytryptamine, 5-HT), a monoamine neurotransmitter,has been reported to play a key role in regulating cognitivebehavior, sensory and emotional processes, autonomic responses andmotor activity in the CNSGlutamate, a major excitatory neurotransmitter in the CNS, underphysiological conditions, has been reported to play a pivotal role invarious neuronal functions, including, synaptic transmission, neuronalgrowth and differentiation, synaptic plasticity and learning andmemory. Mounting evidence suggests that excessive glutamate-mediatedover-activation of NMDA receptors results in the production of amyloidplaques, leading to neuronal loss [107]. In AD, after Aşdeposition andNFT formation, NMDA receptors are over-activated and resulting inoverflow of Ca2+ into the cytoplasm. The Ca2+ influx further leading tomitochondrial dysfunction and activation of key enzyme CREB (cyclic

AMP response element binding protein) which eliminates the signal,resulting in a decline in levels of phospho-CREB.

Documented evidence supporting the role of dopaminergic neuronaldegeneration in AD, specifically neurons forming the

nigrostriatalpathway showed several pathologic changes like NFT, Aş plaques,neuropil threads, neuronal loss, and a decrease in dopamine content. Many AD patients showed the symptoms of Parkinson's disease,sometimes referred to as the extrapyramidal symptoms of AD, suggestingthe down-regulation of post-synaptic D2 receptors in nigrostriatalpathways. However, these types of symptoms are absent inthe patients lacking Parkinson's symptomatology.

Two otherneurotransmitters implicated in the pathophysiological condition of Alzheimer's diseaseare the neuroactive peptides somatostatin and corticotropin; decreased concentrationsof both have been reported in persons with Alzheimer's disease.

Oxidative stress and mitochondrial hypothesis: Over-accumulation of byproducts of the electron transport chain inmitochondria such as hydrogen peroxide radicals, hydroxyl radicals,and superoxide radicals cause oxidative stress and may induce oxidativecell injury and cell death in AD. Mounting evidence suggeststhat Aβ plaques directly interfere with the electron transport chainand produce free radicals, thus increasing oxidative stress. Oxidative stress has been reported to causeoxidation and glycation of certain proteins and lipids and could lead tothe formation of advanced glycation end products, which further intensify oxidative stress and neuroinflammation. The neuronspresent in the entorhinal cortex, hippocampus, frontal cortex andamygdala are more prone to damage from oxidative-nitrosative stressand further progression of AD.

Inflammatory hypothesis: Duringthe progression of AD, amyloid plaques and NFT have been reported toactivate microglia and astrocyte cells. Further, activation of microgliaincreases the expression of pro-inflammatory cytokines andchemokines such as interleukin-1β, interleukin-6, tumour necrosisfactor-α and interleukin-8. However, in the recent studies,inflammation in AD has been linked to the innate immune system, unlikethe typical neuro-inflammatory diseases such as multiple sclerosis andencephalitides.

Epigenetics hypothesis of Alzheimer's disease: Recent research has shown the epigenetic modifications, namelyDNA methylation and histone acetylation which regulates gene expressionat the transcriptional level, play a crucial role in AD pathologies. The involvement of DNA methylation has been well characterized inneuropathological mechanisms leading to AD. Folate, Vitamin B12, and theirend product S-adenosylmethionine (SAM) are important molecules incarbon metabolism in AD and SAM is the primary methyl donor forDNA methylation. Reports have shown that the level of folate, VitaminB12 and SAM are decreased in AD patients; therefore the DNA methylationis also altered.

New therapeutic strategies for the treatment of Alzheimer's Disease

Indeed, researchers have made substantial progress in finding newtherapeutics for the treatment of AD[7, 9]. However, clinically, there existonly two classes of compounds in the market for the treatment of AD:AChEIs and NMDA receptor blockers. In addition to this, the accessibilityof the newer atypical neuroleptics and serotonin-modulating antidepressants has raised optimism for effective management of AD. However, despite their use clinically, the therapeutic effectivenessof these compounds remains limited. Thus, during the last decade,the focus has been shifted to developing new therapeutic strategies forthe treatment of AD

Antioxidants[5]

Mounting evidence suggests the potential role of oxidative stress inthe pathogenesis of AD, so the therapeutic focus has been shifted towardthe use of anti-oxidants as the target for curative as well as prophylacticmanagement of AD. Clinically, Vitamin E, a potentialanti-oxidant moiety, has been reported to slow the decline, and thereforedecrease in caregiver burden, but only in mild to moderate AD. In addition to this, chronic Ginkgo biloba treatment has beenreported to attenuate an age-dependent decline in spatial cognitionwithout altering Aβ levels in a transgenic mouse

model of AD.Ubiquinone, a synthetic analogue of an endogenous antioxidantcoenzymeQ10, has shown moderate improvements in cognitive functionsin AD patients. However, researchers have not found anytherapeutic benefits of omega-3 fatty acids in the mild to moderatecases of AD. Although anti-oxidants have shown beneficial effectsin various clinical studies in AD patients, further clinical studies arerequired to develop effective pharmaceutical products for the treatmentof AD.

Other plant-based treatment (Ethnographic treatment) [2]

Ginseng is broadly used as an additive for dietary supplementsor medicines. It serves as an adaptogen, which is a substancepromoting homeostasis and protecting against various biologicalstressors. A significant reduction of the amyloid-b40 and amyloid-b42 levels were reported after the ginsenoside Rg3 treatmentin the brains of transgenic mice. In summary, ginseng constituents are suggested tomodulate a number of dementia-related mechanisms, suchas amyloid-b metabolism, oxidative stress, neuroinflammation,and acetylcholine signalling.

The genus Curcuma (commonly termed as Turmeric) comprisesaround 80 species. A large epidemiological Indo-USCross-National Dementia study showed that the peasant Indianpopulation has a low prevalence of AD and AD-associateddementia compared to the US population, and that maybe linked to the high curcumin consumption in the Indianpopulation.

Genus Glycyrrhiza, also known as liquorice, is amember of Fabaceae family and consists of about 30 species. Due to their antioxidative properties, several species ofGlycyrrhiza was investigated for possible therapeutic effects asneuroprotectants against neurodegenerative disorders such asPD, AD, and dementia.

Camellia sinensis Kuntze (green tea) brew is one of the mostextensively consumed beverages in the world. Consumption of green tea-related compounds [e.g. (-)-epigallocatechin-3-gallate] improves cognitive functionsand prevents memory impairment in

animals and humansa large number of plants havebeen used for dementia treatment worldwide.

The mechanisms of action of the reviewed five prominent representatives (including Gingko)plants generally involve anti-inflammatory, antioxidative,and antiapoptotic activity that is mainly associated withthe neuroprotective effects of these plants or their bioactiveconstituents. Some of such naturally occurring compounds exhibit promising potential as alternative therapeutic strategies

Anti-inflammatory agents[8]

The inflammatory hypothesis has been strongly supported as a keycomponent of the pathogenesis of AD, and consequently, non-steroidalanti-inflammatory drugs (NSAIDS) have been studied but later on failedin the clinical studies for the treatment of AD . The R-enantiomerof flurbiprofen, an NSAID, has shown promising results in improvingcognitive, behavioural and psychiatric dysfunctions in AD. Thishas also been reported to modulate γ-secretase and is in the phase-IIIclinical trials for the management of AD. However, recent reportsprovide an indication for a failure of this NSAID, due to very weakpharmacological activities against γ-secretase. Overall, R-flurbiprofenhas failed to show any clinical benefits in its phase-III clinicaltrials. This failure is generally attributed to the inability of the drug topenetrate BBB and show sufficient pharmacodynamic properties. Since NSAIDs would probably be the safest drug option for AD (ascompared to other agents), a higher level of resources should be useddedicated to the development of these agents as a novel therapy, andfurther clinical studies are required to test and validate their efficacy in AD patients.

Atypical antipsychotic

Atypical antipsychotic drugs have been widely used to treat behaviouraland psychological symptoms of dementia occurring in AD patientsincluding delusions, aggression/agitation,

hallucinations, sleepdisturbances, oppositional behaviour and wandering. In clinical studies, both olanzapine and risperidone, at low doses, significantlydecrease psychological symptoms associated with dementia of Alzheimer'stype. However, the clinical use of antipsychotics isassociated with serious adverse effects such as somnolence, urinarytract infection, oedema and abnormal gait.

Antidepressants

Recently antidepressants show significant potential for the treatmentof AD patients with depression symptoms. A number ofclinical studies are ongoing for the development of antidepressantstherapies to treat symptoms associated with AD. In clinical studiesconducted on AD patients, the most prominent results have been obtainedby citalopram, a selective serotonin reuptake inhibitor treatmentwhich significantly reduced neuropsychiatric symptoms, primarilyagitation, as compared to placebo control group. Yet, not much research has been conducted using these drugs in AD; hencemore clinical studies are required for the development of antidepressantsas a potential therapy for the disruptive and aggressive behaviour seen with AD.

HMG-CoA reductase inhibitors

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is arate-controlling enzyme that converts HMG-CoA to mevalonate in apathway that produces cholesterol. Multiple epidemiologicalstudies demonstrate a link between elevated plasma cholesterol leveland AD progression. In addition to this, AD-like pathology hasbeen observed in rabbit brains, when fed to a high cholesterol diet.Multiple pathological hallmarks such as Aβ deposits, neurofibrillarytangles, apoptosis, microglial activation, and increased ventricular volumewere seen in a cholesterol-induced AD like pathology in these rabbits.Therapeutically, lowering circulating cholesterol has been found todecrease Aβ production and AD progression in rabbit's that were fedwith high cholesterol diet. Further, statins, and HMG-CoA reductaseinhibitors, resulted

in decreased Aβ production through decreasedcholesterol synthesis-dependent manners. In addition to this,studies also provide new postulated mechanisms by which statins reducethe severity of AD including improved endothelial function, enhancedcerebral blood flow, immune modulation with anti-inflammatoryaction, decreased platelet aggregation, and antioxidantactivity. Atorvastatin has been reported to show mild improvementin AD-associated cognitive and behavioural symptoms, while,

Simvastatin, has also shown slight cognitive improvement in randomized,double-blind, placebo-controlled trials in AD patients. More clinical studies are required with new HMG-CoA inhibitors fordevelopment of a new drug therapy for AD treatment.

Hormone replacement therapy

During the last decade, hormone replacement therapy showed abeneficial effect in AD treatment. Androgens modulate various brainfunctions such as visual-spatial memory and behaviour. Testosterone treatment showed significantimprovement in cognitive functions (such as spatial, verbalmemory, and constructive abilities) in male AD patients. Althoughhormone replacement therapy showed beneficial effects in a fewclinical studies, further, mechanistic clinical studies are required inrelation to androgens and AD.

Methoxytacrine derivative

It is well known that AD is a complex and multi-factorial neurodegenerativedisease affecting many pathological pathways that arelinked to each other. Lack of efficacy associated with single targetapproach lead researchers to examine the design of ligands that canattack multiple targets against complex and multi-factorial disease likeAD. Tacrine was the first AChEI to get approval by the Food andDrug Administration (FDA) agency in 1993 to treat mild to moderatesymptoms associated with AD. Despite the somewhat successful pharmacokineticproperties, it was withdrawn from the market due to poorselectivity towards AChEI resulting in adverse drug reactions.Thereafter, efforts had been made for the synthesis of

tacrine derivativeswhich could be free of fatal adverse effects found initially. Thus, 7-MEOTA, a tacrine analogue, was developed, with equal pharmacologicalactivity as the parent molecule but without spared toxicity associatedwith tacrine. Following the idea of MTD (Multi-target drug) strategy forAD, Korabecny et al. combined 7-MEOTA with p-aniside through analkyl tether containing thiourea or urea. The hypothesis behind addingthiourea or urea into the linker was that this might increase the inhibitoryactivity of AChEI . In the same line of MTD strategy baseddrug therapies of AD, tacrine-trolox and tacrine-scutellarin hybridswere developed. These hybrid compounds were found to be highlyeffective in both inhibiting AChE and showed low in-vivo toxicity.

CONCLUSION

AD is a multi-factorial disease characterized by extracellular depositionof Aβ, intracellular deposition of NFT, oxidative stress, neuroinflammationand neurotransmitter deficit. It has been concluded thatextracellular deposition of Aβ and intracellular deposition of NFT arethe main factors leading to further oxidative stress, excitotoxicity,neuroinflammation, and neurotransmitter deficits during AD. In additionto this, epigenetics could be a new factor that alters gene functionduring the development of AD pathology. Therefore, new studies should bedesigned specifically to target genes that play a role in cognition and toexamine the impact of environmental stress on these genes during theprogression of AD. Taking into consideration that AD is a multi-factorialdisease, the new drug design strategy should be focused towards themulti-target directed ligands instead of single target ligands as singletarget ligands target strategy based drugs failed to show pharmacodynamiceffects during large-scale clinical trials on subjects with AD. The7-MEOTA derivative has been developed based on this multi-targetdirected ligand theory and has raised new hope in the treatment of AD.

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Treatment of Dementia beyond Cholinesterase inhibitors

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ABSTRACT: *Dementia refers to a group of disorders which are characterized by common features such as loss of one or other acquired cognitive skills, changes in behaviour/personality and impairment in functioning. With advancement in genetic and imaging techniques,much is now known about etiopathogenesis of dementia. Depending on different etiology and pathology involved, dementias have been classified into different types. One way of classifying isbased on the reversibility of dementia, i.e. dementia can be either reversible or irreversible. Classifying on this parameter has an advantage from the treatment point of view in that, patients with reversible dementias can lead somewhat better life. The irreversible dementias, on the other hand, cannot be cured and causes therapeutic nihilism in the clinician as well as in the patient. The prototype of the irreversible dementias is Dementia in Alzheimer's disease. It accounts for around 50% of the dementia cases. A lot of research has gone into understanding the exact mechanism of cognitive decline in Alzheimer's dementia, albeit with partial success. In order to treat the deficiency of Acetylcholine (Ach) in Alzheimer's dementia, Choline-esteraseinhibitors are available in the market. But as per the evidence, their effect is not satisfactory because of some obvious reasons. When patients with Alzheimer's dementia come to a clinician, it would already have been too late to intervene because a lot of destruction of cholinergic neurons would have already taken place. After all, choline-esterase inhibitors need viable neurons to act upon. Secondly, choline-esterase inhibitors try to provide symptomatic treatment, while the underlying pathogenetic mechanisms such as deposition of amyloid plaques and neurofibrillary tangles in the brain remain untouched. Thus, it becomes immensely important to think beyond*

choline-esterase inhibitors for treating dementia as a whole and Alzheimer's dementia in particular.

Keywords-*Alzheimer's, Acetylcholine, Amyloid, Behavioral and Psychological Symptoms*

INTRODUCTION

The term "Dementia" or "Major Neurocognitive disorders" stands for a group of disorders characterized by the core symptom of cognitive decline. The cognitive decline is acquired and not present since birth. Lastly, the cognitive decline should interfere in activities of living and should not be present exclusively during delirium.[1] Loss or decline in cognition may occur in many mental illnesses such as Schizophrenia, Depression etc. but cognitive decline is neither the chief feature nor the only symptom of these disorders.[1]

With the improvement in medical care, there has been a tremendous increase in the life expectancy in India. Now more and more people are living beyond 60-70 years of age. As a result, elderly now constitute 8.5% of India's total population (103.9 million) and it is projected that by 2026, there will be 173 million (12.4%) geriatric population in the country. [2]

Rising geriatric population has led to a silent epidemic of dementia. It is estimated that dementia affects around 5% of elderly who are above 65 years of age. The prevalence keeps on increasing with each decade and it reaches 20% in those over 80 years of age. [3] This high number of cases poses a huge burden on family, society and economy of the country. It is one of the important causes of years lived in disability worldwide. In order to escape from the repercussions of this silent epidemic, it is necessary to identify and treat dementia as early as possible.

Dementias are classified according to different etiology and pathogenetic mechanisms involving the brain. Dementia in Alzheimer's disease (AD)is the most common type of dementia accounting for around 50-60% of all cases. Vascular dementia (VD), dementia with

Lewy bodies (DLB), frontotemporal dementia (FTD), dementia in Parkinson's disease are other common types of irreversible dementia. [3]

What are Cholinesterase inhibitors?

The chief hypothesis for the pathogenesis of AD is based on the fact that there is a progressive loss of cholinergic neurons and resulting lower levels of Acetylcholine (Ach) in the brain. This, a low level of Ach is responsible for cognitive deficits. [4]

Choline-esterase inhibitors are a group of drugs which act by inhibiting cholinesterase enzyme responsible forthe breakdown of acetylcholine. By doing so, these drugs increase levels of acetylcholine in the brain and improve cognition. Three such drugs are approved for use in the treatment of AD, namely:Donepezil, Rivastigmine and Galantamine. [5, 6]

Why there is a need to look beyond cholinesterase inhibitors?

Unfortunately, Choline-esterase inhibitors (CEI) have not been of much success in the treatment of dementia due to the following reasons:

1. **Dementia other than AD**- Apart from the AD, there are other dementias which have different aetiology and pathogenetic mechanisms involved. For e.g. Frontotemporal dementia. It is natural that CEI will have limited or no role dementias where deficiency of Ach is not the cause.[7]
2. **Intervening too late in AD-** AD has an insidious onset and gradual progression. Often the early symptoms of cognitive decline are not taken seriously and are thought to be age-related. As a result, by the time the patient of AD presents to the clinician, a lot of cholinergic neuronal loss would have already taken place. After all, CEI needs sufficient amount of Ach in the brain to save it from degradation, which in turn needs a sufficient number of viable neurons to be produced from.[8]

3. **Doesn't treat the underlying cause of AD-** While the cholinergic neuronal loss is the end result of the neurodegenerative process, underlying mechanisms of this fate is somewhat different in the AD.[9] Amyloid plaque formation and deposition of neurofibrillary tangles are the two underlying pathogenetic mechanisms by which neurons keep on dying. CEI neither prevent their deposition nor they help in their clearance from the brain.[10,11]
4. **Not effective probably:**
   A Cochrane review involving all three CEI and including 10 randomized controlled trials (RCTs), demonstrated that treatment over 6 monthsproduced improvements in cognition, activities of daily living (ADL) and behaviour. However, the effects size was small. [12]

   A recent systematic review and meta-analysis of RCTs (including 16,106 patients) found the benefit of CEI in improving cognition and ADL as compared to placebo but not in behavioural and psychological symptoms. [13]

Now, what to do?

After knowing that CEI is not of much help in the treatment of dementia, new management strategies need to be thought of. The first and most important step is to deconstruct the phenomenology of dementia into the ABC **model**. Here, "**A"** stands for Activities of Daily Living (Personal and Instrumental), "**B"** stands for Behavioral and Psychological symptoms and "**C"** stands for Cognition. This deconstruction is important for two reasons. First, although disturbance in A and B is because of decline in C, it is important to know here that caregivers of patients of dementia are more troubled by disturbance in the A and B and are more concerned about their treatment. [14, 15]Secondly, if we run after treating only C, we will soon be frustrated and this will create therapeutic nihilism. By deconstructing dementia according to this model, we will have something to intervene or manage in each of these domains and this will be a more holistic approach to treatment.

Management on ABC Model

***Management of* Activities of daily living**

Activities of daily living (ADL) comprises personal activities of daily living such as brushing, bathing, dressing, toileting, ability to move around independently and instrumental activities of daily living such as: ability to use telephone, shopping,cooking, housekeeping, Laundry, Mode of transportation, responsibility for own medications, and ability to handle finances. [16, 17] ADL mainly depends on Cognition and treatment of cognition subsequently improves ADL. The treatment of ADL per se is chiefly non-pharmacological. However, pharmacological measures are important in managing orthopaedic disorders; Parkinson's and other movement disorders; frailty;diabetes, congestive heart failure, anaemia and visual disorderswhich confound the worsening of ADL.[18, 19]

***Management of* Behavioral and Psychological Symptoms in Dementia (BPSD)**

Behavioural and psychological symptoms of dementia (BPSD) are very common and can present in any stage of dementia. They include a wide range of difficulties such as Delusions, Hallucinations, Agitation/Aggression, Depression, Anxiety, Elation/Euphoria, Apathy, Disinhibition, Irritability/lability, Motor-disturbance (repetitive behaviour), Nighttime behaviours, and Appetite/eating behaviour. [20]These symptoms are present in morethan 90% of patients with dementia. [21]

Management of BPSD is bothNon-Pharmacological and pharmacological approaches.

Pharmacological management

Behavioural and psychological symptoms in dementia (BPSD) are one of the prime reason for which caregivers seek treatment. This is one class of symptoms which disturbs others.Treating those leads to improvement in the quality of life of patients and their caregivers. [14, 15] Thus, it is not wise to run after not so effective CEIs.

Many of the symptoms mentioned in BPSD are amenable to drugs. Many of the existing drugs in our pharmacological armamentarium are effective against BPSD, provided, the clinician understands the phenomenology of symptoms knows the neurochemical basis and knows the precipitants of a particular BPSD. The use of these drugs is in addition to CEIs.

Anti-Psychotics

This group of drugs helps in the treatment of Delusions, Hallucinations, controlling aggression and elation. Both first generation (FGA) and second-generation antipsychotic (SGA) drugs have been found effective in treating these symptoms. However, it should be kept in mind that duration of treatment of these symptoms is not like primary psychiatric disorders. The use of antipsychotics should be for minimum duration possible and in the lowest dose possible. FGAs have increased the tendency to cause extrapyramidal side effects (EPS) while SGA are also associated with poor tolerability.[22-26] The only antipsychotic drug licensed for use in dementia patients is risperidone.[27]However, Olanzapine, Quetiapine, Aripiprazole and Haloperidol can also be used judiciously.[28-36]

Antidepressants

Anti-depressants are an important class of drugs in treating BPSD such as depression, Anxiety, Apathy, Disinhibition, Irritability, repetitive behaviour, Nigh-time behaviour and sleep. Depression is highly comorbid with AD and they can co-occur in 30-50% cases. [37] Antidepressants not only treat depression but also improve cognition. [38]Again, their use should not be prolonged and the dose required is lower than the recommended dose in primary mood disorders.

SSRIs are the most common group of antidepressants used in dementia because of their good tolerability. [39]The fact that SSRIs increase levels of Serotonin in the brain leadto improvement in many symptoms in which it's deficiency is implicated. These

symptoms are depression, anxiety impulsive aggression, repetitive behaviours, Disinhibition etc. Trazodone can be used for treating sleep complaints. [40, 41]Tricyclic antidepressants (TCAs) should be avoided because of poor tolerability and anticholinergic side-effects[42]

Benzodiazepines

Benzodiazepines are widely used drugs for treating agitation, elation, and sleep problems. However, their use in dementia patients is not advisable and should be avoided. They cause anterograde amnesia which hampers already compromised new learning in dementia. [43, 44]They may also lead to frequent falls and fractures. [44, 45]

Mood stabilizers

Among the anticonvulsant mood stabilizers, carbamazepine has maximum evidence for use in dementia for treating elation and aggression/agitation. [46] The doses of anticonvulsant mood stabilizers needed in the treatment of BPSD are less as compared to the doses needed for treatment of primary mood disorders. For e.g. the dose requirement of valproate for treating BPSD is 7-12mg/kg body weight and serum valproate level 40-60 microgram/L usually suffice. [47]

Melatonin

Since it is advisable to avoid benzodiazepines for correcting sleep in patients of the AD, melatonin emerges as a viable option. It is safer, corrects the altered sleep-wake cycle and has shown to be effective in inducing sleep. However, it is also advisable to follow sleep hygiene methods for best results. [48, 49]

Promethazine

Given that BZDs are not safe for use in dementia, Promethazineis often used to sedate the patient and control aggression. But since it also has anticholinergic property its use

should be for a very short period. [50]

Other medicines

Often the cause of the abnormal behaviour and emotional disturbance in dementia is because of unmet needs. Since patients of severe dementia can't express their needs they express it in the form of BPSD. One such unmet need is relief from pain. In such a case prescribing an **analgesic** such as paracetamol will cause significant relief in abnormal behaviour.Many a time it is not unwise to prescribe analgesics even when there is no history of any pain for control of behaviour. [51]

Electroconvulsive therapy (ECT)

ECT remains the cheapest and effective treatment for controlling abnormal behaviours and psychosis, even in patients of dementia. However, one should be cautious about an increased incidence of cognitive adverse effectsin such patients. [52]

***Management of* Cognition**

Non-Pharmacological management:

The benefits of non-pharmacological methods in the treatment of cognition cannot be undermined when there is lack of effective pharmacological options. Non-pharmacological methods of enhancing cognition such as cognitive exercises/cognitive stimulation techniques, Reminiscence therapy and Validation therapy play an important role in the treatment of mild to moderate dementia. [53]

Pharmacological management

There is a tendency in medical science that whenever effective treatment doesn't exist for a disease/disorder, researchers/clinicians try everything under the sky for treatment. Let us have a look at some of the tried drugs/products in the treatment of dementia.

Gingko Biloba

Gingko Biloba is one product which offers so much theoretically in the treatment of cognitive and other disorders of the central nervous system because it improves blood flow to the brain, protects against oxidative stress and blocks platelet aggregation. However, although it is safe to use there is no evidence for its effectiveness. [54]

Supplements

Vitamin B12, Folate, Vitamin D and Vitamin E have been tried in dementia. While vitamin E and D have been found not at all efficacious, there is scope for Vitamin B12 and folate supplementation provided a deficiency is found. [55] In irreversible dementia, they have not been found statistically beneficial. [56] Another supplement **omega 3 fatty acids** are also widely prescribed; however, research evidence doesn't support its use. [57]

Other compounds

Ginsengand Dimebon (a nonspecific histamine blocker with weak CEI, Butyl CEI property and NMDA blocking property) have not been found effective in treating any domain of dementia. [58-60]Hirudin (thrombin inhibitor) has been found effective in improving cognition but is poorly tolerated. [61] Another compound Huperzine A (an alkaloid from herb Huperzia serrata), has potent CEI property and is effective for treatment of cognition. [62, 63]

Cerebrolysin

It is a pig-brain derived protein similar to human brain neurotrophic factors. Administered by the intravenous route, it has been found effective in improving cognition as well as global functioning in the AD. [64] The beneficial effect was observed for uses both as monotherapy as compared to placebo and as augmentation of CEI as well. [65]However, similar encouraging results were not found for patients with vascular dementia. [66] In conclusion, cerebrolysin may prove to be an important modality in

the treatment of Alzheimer's dementia.

Statins

Hypercholesterolaemia is one of the causative factors for the treatment of vascular dementia. In cases of vascular dementia, use of statins might help in preventing further deterioration of cognition. It is not clear whether statins would be helpful in improving the already lost cognition. [67]

Anti-inflammatory drugs

With the rise in inflammatory theories for most of the psychiatric disorders, it was too tempting not to try anti-inflammatory drugs such as Indomethacin, naproxen, the coxibs, prednisolone, atorvastatin in treatment of dementia. However, even a large number of RCTs didn't show evidence for its use. [68]

Disease-modifying agents

Two existing compounds Trazodone and dibenzoylmethane (DBM)have been found to have disease-modifying property in dementia. Trazodone is a Serotonin antagonist and reuptake inhibitor (SARI) while dibenzoylmethane is a constituent of liquorice. Effect of trazodone in controlling BPSD because of its antidepressant, anxiolytic and sedative effect is well known but no study has examined its role for cognition in humans. In animal models, however it has been shown to reduce tau-proteins in brains of FTD. Similarly, DBM has been found to reduce tau proteins in mice. As aresult, both drugs have neuroprotective functions. [69]

Curative treatments

It is well known that deposition of amyloid plaques in extracellular spaces is prime pathology involved in the AD. In normal conditions, amyloid precursor protein (APP) is first cleaved bythe alpha-secretase enzyme (AS) and then by gamma secretase (GS). As a result, soluble smaller subunits of amyloid are formed and then they are cleared from the brain. In pathological condition,

APP is first cleaved by the Beta-secretase enzyme (BS) instead of AS and in the second step when it is cleaved by GS the resultant subunits of amyloid are insoluble and they get deposited in the brain. Deposition of amyloid further leads to the formation of neurofibrillary tangles in the brain. Now, a more sensible approach will be developing those drugs which either help in preventing the formation of amyloid plaques or if amyloid plaques are already formed, they should be able to remove them. Drugs which inhibit GS and BS will help in preventing formation of amyloid plaques. Similarly, there are vaccines under development which can remove already deposited amyloid.[70]Three such drugs reached upto phase 3 trial stage of drug development but failed to show promising results. They are:

Semagacestat- a γ secretase inhibitor [71]
Solanezumab- a humanised monoclonal antibody that binds insoluble forms ofamyloid and promotes its clearance from the brain [72]
Bapineuzumab- a humanised anti-amyloidβ monoclonal antibody [73]

CONCLUSION

Treatment of dementia is challenging owing to multiple pathologies involved, delay in diagnosis and lack of effective treatment available. In such a scenario, utilizing non-pharmacological management strategies for improving ADL, BPSD and Cognition is very important. From the pharmacological point of view, it is wise to put more focus on treating co-morbid physical illnesses complicating impairment in ADL; BPSD; and exploring the unmet needs of the elderly demented patients. By doing so, we will be more able to give relief to the caregivers of patients with dementia. Form cognition point of view, CEI remains the most effective, most tolerable and most cost-effective option among various agentsavailable. Time is right to put more efforts in search of novel pharmacological agents which are disease-modifying

and which can target the underlying pathology. Till then, continue serving patients of dementia holistically ratherthan relying only on pharmacotherapy.

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Pharmacotherapy for Insomnia in the Elderly-Z-drugs and beyond: An updated review

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ABSTRACT: *Prevalence of sleep problems, particularly insomnia is very high in the elderly along with various physical and psychiatric comorbidities. For decades, sedative hypnotics like various benzodiazepines and sedative psychotropics are prescribed to the elderly for treatment of the same, often with serious consequences like fall and trauma, cognitive deterioration, coordination deficits and others. Growing realization of the same among the medical fraternity along with availability of newer agents like Z-drugs and others have prompted a slow but steady shift towards the newer molecules over the last couple of decades. However, there is still inadequate data, both empirical and clinical on the uses and adverse effect profiles of the newer generation molecules used for treating insomnia. The average clinician is often aware of the existence of the newer molecules but lacks the knowledge base and experience regarding the appropriate use of these drugs. There is a dearth of literature compiling the available data on these drugs. This review attempts to focus on the psychopharmacology, uses and adverse effects of Z drugs (zolpidem, zopiclone, eszopiclone, zaleplon), approved melatonergic (ramelteon, exogenous melatonin) and orexin antagonistic drugs (suvorexant) particularly in relevance to the elderly, followed by a brief discussion of other non-approved melatonergic treatment options (Tasimelteon, agomelatine) for sleep problems in the elderly population and intends to help clinicians choose the appropriate molecule for an individual patient.*

Keywords: *Z-drugs, ramelteon, suvorexant, elderly insomnia*

INTRODUCTION

The prevalence of chronic sleep problems is quite high in the elderly population, as is depression, anxiety and various medical comorbidities.[1-2] Moreover, the higher the number of

comorbidities, higher the number of sleep problems.[1] Subsequently, a significant number of elderly individuals are prescribed different psychotropic medications, likeantidepressants (e.g., trazodone, doxepin, mirtazapine), antipsychotics (e.g., quetiapine, clozapine, chlorpromazine), anticonvulsants (e.g., gabapentin, tiagabine), higher-dose antihistamines (e.g., diphenhydramine) etc. with existing literature reporting use of psychotropics in more than half of inpatients and around a fourth of outpatients in tertiary care centers.[3,78] However, convincing evidence for the efficacy of these molecules in the treatment of chronic insomnia is lacking for all of the above compounds.[79] Additionally, the significant safety issues associated with each of these approaches with risks like falls, cognitive decline, increased mortality etc. are well known.[4-5]In June 2005, a US National Institutes of Health (NIH)-sponsored panel reviewed the published evidence regarding chronic insomnia treatment and concluded that current evidence (as of 2005) supported only cognitive behavioural therapy and the US Food and Drug Administration (FDA)-approved benzodiazepine receptor agonist (BZRA) hypnotic medications including the benzodiazepines and the Z-drugs.[79]Long-term benzodiazepine use has been associated with a lower latent cognitive level in the elderly, apart from other adverse effects likefall and trauma, coordination deficits, driving impairment, increased risk of infection, respiratory depression etc.[6,64-65,70]

As a result, non-benzodiazepine GABA-A BZD receptor agonists, popularly known as 'Z- drugs' were widely marketed since the 1990s as a better and safer hypnotic agent with limited side effects.[7] Evidence in their support stemmed from sleep laboratory studies proving lesser cognitive and memory impairments and markedly lesser daytime sedation compared to the traditional benzodiazepines[7]. These led to the Z drugs (particularly zolpidem) being the most widely used hypnotic in many countries.[7-8] However, this was soon followed by increased reports (both scientific and media) of hallucinations, amnesia with inappropriate behaviour with zolpidem use.[9-10] After that, novel approaches like

manipulation of the sleep-wake switch via melatonin or orexin pathways were undertaken, and melatonergic agonists and orexin antagonists were developed for the treatment of insomnia and other sleep disorders.

This review intends to focus on the psychopharmacology, uses and adverse effects of Z drugs, approved melatonergic and orexin antagonistic drugs particularly in relevance to the elderly, and a brief discussion of other non-approved melatonergic treatment options for sleep problems in the elderly population.

what are 'Z- Drugs'?

Z- Drugs refer to Zolpidem, Zaleplon, Zopiclone and Eszopiclone, which are non-benzodiazepine drugs used commonly in insomnia treatment.[11]

These are basically GABAergic drugs, which act by binding to the GABA A receptors, facilitating the increased binding of GABA with the receptors by means of allosteric modulation. This in turn facilitates the opening of the chloride channels of GABA receptors thus causing depolarization (fast phasic or tonic) or hyperpolarization, depending upon the location and subtype of the GABA A receptor.[12-14]The sites of binding of Z drugs, Benzodiazepines and GABA are different at the GABA A receptors.[11]The GABA A receptors can be broadly divided into two subtypes, BZD1 (containing α1β1-3γ2 subunits) and BZD2 (containing α2,3,5β1-3γ2 subunits) depending upon attachment properties of benzodiazepines.[11] The BZD1 receptors mediate sedation and amnesia, while BZD2 mediates sleep regulation and anxiolysis.[11]

The pharmacological properties of Z drugs are given in Table 1. Clinical efficacy of*zolpidem* for insomnia is comparable to both short-acting and long-acting benzodiazepines,in terms of time to sleep onset, duration, and quality of sleep.[15] It is approximately 90% protein bound and has a higher area under the curve (AUC), time to maximal concentration (Tmax), and half-life in the elderly, thereby necessitating dosage reduction in these patient groups.[11]

Zopiclone has the longest latency and half-life of all the Z-drugs, and its active metabolites are renally excreted, necessitating dose reduction in the renal impaired and the elderly (who usually have decreased renal clearance as part of the normal ageing process). No such reduction, however, is recommended for eszopiclone, which has a shortened onset and offset of action with decreased AUC and half-life of its active metabolite (S)-desmethylzopiclone compared to the racemic mixture.[11, 16]Both Zopiclone and Eszopiclone are helpful for treating difficulty in sleep onset and maintenance.

Zaleplon has the shortest Tmax and half-life and thus a rapid onset and offset profile. It has significant first-pass metabolism in the liver with low bioavailability, and dosage should be reduced in patients with hepatic impairment and the elderly with impaired liver functions. It'shelpful for sleep onset insomnia or middle insomnia and it can be given during waking during the night.

Drug interactions:

Pharmacodynamic: Among pharmacodynamic interactions, all the Z drug effects are potentiated by alcohol, benzodiazepines and other CNS depressants while their effects are reversed via competitive antagonism by flumazenil. Further, pharmacodynamic interactions include Chlorpromazine for Zolpidem and Zopiclone, SSRIs for Zolpidem and Thioridazine for Zaleplon. [12, 21,23-27]

Pharmacokinetic: Similarly, CYP450 inhibitors like Azole antifungals increase effects of Zolpidem and Zopiclone, as does Cimetidine for Zolpidem and Zaleplon. Ciprofloxacin, Fluvoxamine and Protease inhibitors increase effects of Zolpidem, while Erythromycin increases the effects of Zaleplon[12,21,23-27].

CYP450 Enzyme inducers like Rifampicin decreases effects of all Z-drugs, while Carbamazepine and St. John's wort decreases the effects of Zolpidem in particular[12,21,23-27].

Hence, optimum care and dose adjustment are needed while prescribing Z-drugs to the elderly population who usually present with multiple systemic and psychiatric comorbidities along with insomnia and are already on a cocktail of drugs which often includes

SSRIs, antipsychotics, antifungals and CNS depressants. Moreover, the prevalence of alcohol use is significant in the elderly population, and a proper history of the same is a must to void catastrophic outcomes.

Adverse Effects:

Generally, Z drugs are well tolerated. For any given dose, adverse effects are more common and more severe in elderly subjects.[28, 30] Some common adverse effects include headache, gastrointestinal upset, dizziness, metallic taste in mouth (only for zopiclone and eszopiclone).[28, 29] Less common adverse effects include pruritus, xerostomia, visual disturbances and daytime residual effects on cognition and psychomotor performance.[30, 31]

Serious adverse effects of Z drugs can be discussed under the following heads: Cognition, Amnesia/ Parasomnia, Psychomotor performance, Driving and Miscellaneous.

Effects of Z drugs on Cognition:

Zolpidem and Zopiclone (but not zaleplon) have a dose-dependent effect on anterograde amnesia, particularly impaired word recall and recognition.[32,33]Zopiclone at 7.5mg or higher doses, but not eszopiclone (3mg dose) show impairment in memory and cognitive testing (attention, learning etc.) using standard psychometric tools even after 8 hours of sleep[34]; however, both show impairment (eszopiclone lesser than zopiclone) when sleep restriction protocols were followed.[35] Moreover, epidemiological studiesconducted over 3-4 weeks showed the persistence of the memory and cognitive impairment even with chronic dosing raising patient safety concerns regarding falls, amnesia, and decision-making capacity, particularly in the elderly.[36, 37] This becomes even more relevant considering the aspects of age- related cognitive decline, Mild cognitive impairment and dementia in many elderly patients suffering from chronic insomnia and taking Z-drugs.

Amnesia:

Amnesia is caused by Z-drugs due to agonistic binding with BZD1 receptors (containing α1β1-3γ2 subunits) and is proportional to the dose and binding affinity. Another hypothesis is their ability to reducesleep latency and block memory consolidation (transfer of short-term memory into long-term storage).[38,39]A Taiwanese case- control study has reported an increased risk of dementia with zolpidem.[42]Adverse effects of amnesia, hallucinations and parasomnia (nightmares and terrors, sleepwalking/somnambulism, sleep-eating, sleep-talking, sleep-sex and sleep-driving) with Z-drugs, particularly zolpidem have been reported significantly more than any other drug in the decade of 2000-2010 globally.[40]Prior to 2006, 14 cases of sleep driving (a variant of sleepwalking, where the individual drives a vehicle in a semi-awake state after getting out of bed from sleep, with no memory of the act afterwards) were reported with Zolpidem (13 cases) and zaleplon (1 case).[43] Risk factors for the same include concomitant alcohol or sedative intake and pre or co-existing parasomnia. The reports of parasomnia have subsequently increased after media coverage of the same in 2007. [32] Parasomnia and neuropsychiatric adverse effects of Zolpidem have been reported more commonly in females whereas suicidality has been reported more commonly in males.[40] A Taiwanese cohort study on psychiatric outpatients found amnesia or somnambulism in over 5% of patients treated with Zolpidem. [41]These findings raise many further questions. Whether these adverse effects are really more common with zolpidem than other Z drugs, or whether zolpidem is implicated more because of its increased rate of use compared to its other class siblings. Similarly, the increased reported events in females is because they have a more sensitivity to Z-drugs or whether it's an effect of higher mg/kg dosing in females (as same doses are commonly used in both genders). Moreover, do the Z-drugs really cause an increased rate of amnesia, parasomnia or hallucinations or these findings are an indirect outcome of their increased usage in (sometimes

hidden) psychiatric populations by psychiatrists. The answer to these questions will guide whether Eszopiclone or zaleplon rather than zolpidem be chosen in a patient with predisposition for these adverse events (like the elderly); whether avoidance of zolpidem is needed in females or just a dose reduction will suffice in preventing these adverse outcomes and finally whether more screening out of psychiatric conditions in needed before prescribing Z-drugs, particularly to an elderly individual.

Psychomotor performance:

Residual psychomotor effects from Z-drug use are more common in the elderly and include ataxia, postural instability, dizziness and falls. Falls are associated with significant morbidity like fractures, head injuries, even death in the elderly.[32] In studies from Korea and New Jersey, zolpidem use was associated with nearly two times increased risk of hip fractures, which was notably higher than benzodiazepine use.[44,45] Zolpidem and zopiclone have a significant dose-dependent effect on body balance and postural sway even in young adults in the first few hours after intake.[46] These effects are worse in the elderly due to increased sensitivity to peak drug action and altered pharmacokinetics.[47]Many Z drugs using elderly awaken and mobilise in the middle of the night a few hours after ingesting the Z-drug, resulting in increased chances of instability and fall. Zolpidem even at 5 mg dosing (recommended dose for elderly), caused 'induced middle of the night tandem walk' failures in older subjects compared to younger ones and controls in an RCT, moreover, the effect lasted upto 30 mins. [37]Similar impairment was noted with 20 mg, but not 10 mg zaleplon at peak plasma levels (around 1 hr. post ingestion).[33,48]

Driving impairment

A UK study found nearly two times increased the risk of a motor vehicle accident with zopiclone, while a Norwegian study found increased risk with zolpidem and zopiclone (OR greater than 2).[49,50]Similarly, zopiclone was the most frequently encountered

hypnotic drug in post-mortem samples of Norwegian drivers.[51] A French study found an increased risk of a motor vehicle accident with zolpidem only at inappropriate dosages, like taking more than one tablet per day.[52] The risk of driving impairment has been found to be more common in women than men after 10 mg zolpidem dosing.[53]

Most consistent association of driving impairment is found with zopiclone.[54] 'On-the-road-driving-test' (the gold standard for driving impairment testing) experiments found that nocturnal dosing of 7.5 mg zopiclone impairs driving 'the morning after' (i.e. after 10-11 hours of nighttime dosing), and the impairment was double that of subjects with alcohol having BAC (Blood alcohol concentration) of 0.03%.[55] With increased dosing (15 mg of zopiclone), the impairment persisted till the afternoon (16 hours after nocturnal dosing).[54]However, there was no significant driving impairment 4 hours after nocturnal dosing of 10- 20 mg zaleplon or 10 hours after 3 mg eszopiclone.[55-56] Zolpidem 10mg nocturnal dosing resulted in impaired driving ability in older adults (55-65-year age group) even at 10 hours after drug ingestion, in comparison to minimal impairment of such in healthy adults.[59-60] However, taking 20 mg zolpidem at bedtime or 10 mg taken in the middle of the night resulted in impaired driving even in healthy adults, and more so in the elderly.[33,58]

The International Council on Alcohol, Drugs and Traffic Safety (ICADTS) has classified prescription medications, including Z-drugs, into three categories based on their likelihood of driving impairment.[61] These loosely correspond to BAC as follows: category I(unlikely to impair driving or no effect, BAC<0.05 %),category II (likely to produce minor-moderate effects,BAC 0.05–0.08 %),and category III (likely to producesevere or dangerous effects, BAC>0.08 %). ICADTS hascategorized zopiclone as category III, while zolpidem andzaleplon are assigned to category II (may be considered category I if taken at 10 mgand driving occurs after 10 and 5 h post-dose, respectively).[62-63]

Risk of Infections:

Few observational studies have reported associations between Z-drug use and community-acquired pneumonia, with adjusted hazard ratios of 4.24 of influenza-like illnesses and 20.69 for influenza-like illness related mortality for current users.[64-66]They also reported a dose-response trend with hazard ratios generally trending higher from 'non-users' to 'past-users' to 'current-users'. A meta-analysis of published studies found 25–64% increased the risk of infection (various types) in those exposed to Z-drugs over placebo. The data was statistically significant for eszopiclone and zolpidem with adjusted hazard ratios of 1.48 (95% CI 1.25–1.74) and 1.99 (95% CI 1.21–3.26). [67] However, the absolute eventrates were low at 6.86% in the hypnotics group and 4.56% inthe placebo group.[67]These factors become even more relevant for the elderly subpopulation as they already have a significantly higher comorbidity burden putting them at a substantially greater risk for infections.

Pancreatitis

There have been a few reports of acute episodes of pancreatitis with Z drugs use, incidentally, both are from Taiwan. One of them reported a confounding adjusted odds ratio of 2.36 (95% CI 1.70–3.28) with use of zopiclone within 30 days of pancreatitis and the same of 7.20 (95% CI 1.60–2.66), with use of zolpidem within 7 days of pancreatitis diagnosis compared to never users of the drugs. [68-69]Moreover, they also reported a dose-response trend with a greater association for doses greater than 10mg (OR 8.7) compared to less than 10 mg (OR 6.76).[68-69]

Respiratory disease exacerbation:

Benzodiazepines have been postulated to diminish respiratory functions by reducing airway smooth muscle tone and increasing arousal threshold for desensitizing neurons in airway obstructed sleep states.[70] However, Z-drugs didn't show any significant effect on either CNS control of breathing or ventilation in either normal

subjects or those with mild to moderate chronic obstructive pulmonary disease.[70] Similarly, two metanalyses failed to find any worsening of sleep-disordered breathing parameters in subjects of obstructive sleep apnea.[72-73] However, in a review by Stege et al, studying the results of drug effects (benzodiazepines vs. Z-drugs) on oxygen saturation, inspiratory flow rate and other objective respiratory parameters in COPD patients, the findings were inconclusive as four out of six studies found no difference in respiratory changes between benzodiazepines and z-drugs.[71]

Cancer risk

Observations studies have raised alarms on cancer risks with Z-drugs and benzodiazepines.[74-76]A metanalysis of 18 case-control and 4 cohort studies published in 2016 concluded an estimated 19% increased cancer risk with significant dose-response trend among benzodiazepine/ Z-drug users over non-users.[77] However, the statistical analysis was skewed with higher associations between oesophageal, brain and pancreatic carcinoma with lorazepam, clonazepam and zopiclone compared to cancers at other sites and other drugs. The odds/risk ratio of 2.08 (CI 1.77–2.44) for brain tumours was significantly greater than other types of cancer in the metanalysis. [77]

Summary of Z drugs

Though deemed safe, particularly in COP and OSA, Z-drugs, particularlyZopiclone and Zolpidem (including higher than recommended doses) impairs psychomotor performance, cognition and memory particularly in the elderly. They do have residual effects in the morning and are often responsible for falls, hip fractures and driving accidents in the elderly. A risk-benefit analysis often may not favour treatment. Z-drugs and hypnotics, in general, have a small beneficial effect with a number needed to treat (NNT) of 13 for improved sleep versus a number needed to harm (NNH) of 6 for any adverse event (146). The drugs should be judiciously used by the clinician after factoring in multiple issues like time to bed,

time to wake up, comorbidities, co-prescribed drugs, the presence of psychiatric symptoms, hepatic and renal functions of the elderly, etc.

So what are the other pharmacological options for insomnia management in the elderly?

Since the 1990s, various research groups started working on different aspects of the sleep physiology other than GABA agonism as alternate strategies for insomnia treatment. Some degree of success was achieved in the manipulation of melatonin/ Suprachiasmatic nucleus activity and that of the orexin/ lateral hypothalamus activity. In 1996, Takeda and others developed TAK-375, now known as Ramelteon, to act as a melatonin receptor agonist. It underwent all stages of clinical trials and was approved by the US FDA in 2005 for insomnia treatment.[78]Ramelteon and exogenous melatonins are the two melatonergic agents approved currently for the treatment of insomnia.

Ramelteon

Structurally, Ramelteon ((S)-*N*-[2-(1, 6, 7, 8-tetrahydro-2*H*-indeno [5, 4-b] furan-8-yl) ethyl] propionamide) is the single (S)-enantiomer of a tricyclic indan derivative, which acts on MT1 and MT2 melatonin receptors. [78, 81]The pharmacokinetic properties of ramelteon are given in Table 2. It is 82% protein bound and readily absorbed from the GI tract, but undergoes extensive first-pass metabolism by the liver, with resultant mean plasma concentrations of less than 2%.[78,80,81]There is a large degree of intersubject variability in the peak concentration and total systemic exposure resulting in unpredictable drug response in many subjects. Taking ramelteon with food increases the AUC, delays Tmax and decreases the Cmax and hence, it is not recommended to be taken with or just after a heavy meal. [78,81]It is metabolized by the cytochrome p450 system into four metabolites: M-I, M-II, M-III, and M-IV of which M-II is the only active metabolite with around one-tenth potency of ramelteon and elimination half-life of 2-4 hours.[78,80,81]

Ramelteon binds with the MT1 receptors and MT2 receptors, with binding affinity around 3-16 times that of melatonin. [80] It exerts its direct sleep-inducing effects through MT1 receptors located at the hypothalamic SCN, while its phase shifting effects are exerted through MT2 receptors.[82] Ramelteon seems to promote sleep by regulating the sleep/wake cycle rather than by generalized CNS-depressant effect. It apparently accelerates the sleep onset by influencing the hypothalamic "sleep switch", downstream from SCN, similarly but more efficiently than melatonin.[80,82] The sleep switch model was proposed by Saper and colleagues describing a flip-flop mutually inhibitory pathways among sleep promoting activities in the ventrolateral preopticnucleus (VLPO) and wakefulness-promoting activities in the locus coeruleus (LC), dorsal raphe nucleus (DRN) and tuberomammillary nucleus (TMN).[83-86]The phase shifting effects by MT2 receptors are yet to be fully clarified in humans.[80,82]

Drug Interactions

Since ramelteon is metabolized by the CYP enzyme system in the liver, their antagonists like fluvoxamine, ciprofloxacin, mexiletine, norfloxacin, tacrine, zileuton, fluconazole, ketoconazole significantly increase the plasma concentrations of ramelteon, and hence co-prescriptions of such drugs with ramelteon is to be avoided. [87, 88]An example of the magnitude is that CYP1A2 antagonist Fluvoxamine if co-prescribed raises the plasma concentration of ramelteon by 100 fold.[88] On the other hand, CYP inducers like rifampicin substantially decrease the plasma concentrations of both ramelteon and its metabolite M-II. [87]

Efficacy

Two polysomnography studies conducted on acute insomnia patients reported significantly shorter sleep latency and increased total sleep time.[89,90]Numerous studies of varied designs including double-blind, placebo-controlled RCTs conducted over variable durations were conducted on ramelteon in different age groups and

insomnia subtypes, including in the elderly, which found reduction of sleep onset latency (eitheras latency to persistent sleep (LPS) or as subjective sleep latency (sSL).[80]Improvement in sleep duration (with limited extent) has been reported with ramelteon in many but not all studies. Other sleep parameters, such as wake after sleep onset (WASO), subjective WASO (sWASO) andsleep efficiency (SE), are only slightly influenced by ramelteon. These studies were beautifully reviewed and tabulated (Table 2) by Pandi-Perumal and colleagues. [80]

Adverse effects

No significant next morning residual sedation or cognitive impairment (tested using the digit symbol test and other similar psychometric assessments) or discontinuation withdrawal symptoms were observed in numerous preclinical and clinical trials.[78] Adverse events (compared to placebo) reported were somnolence (5% vs. 3%), dizziness (5% vs. 3%), and fatigue (4% vs. 2%).[78]

Safety studies: No clinically relevant changes were observed in vital signs, clinical chemistry, urinalysis, heamatology, endocrine or ECG trends except a slight transient decrease in free and total testosterone levels in older males.[93,95]Three studies have confirmed the absence of any balance difficulties (even in elderly subjects with insomnia) with ramelteon (like placebo) and lesser than active comparators like zopiclone, zolpidem or triazolam.[91,92,94] They also involved studies in laboratory settings where subjects were awakened, and balance tests conducted 1.5-2 hours after drug ingestion.[91,92,94]This is particularly relevant, more so in the comparative context of benzodiazepines and Z-drugs in avoiding fall and subsequent trauma in the elderly, which is often a preventable cause of morbidity and mortality.

Special Populations

No respiratory depressant effects (measured by hourly oxygen saturation)were observed with ramelteon versus placebo in a double-blind two-way crossover study on mild-moderate COPD patients.

[96,100]A similarly designed study on mild-moderate OSA patients failed to find any exacerbation of sleep-disordered breathing or fall in oxygen saturation.[101]No adverse effects of any kind were noted in patients of mild, moderate or severe renal impairment, including patients on dialysis, and therefore, no dose adjustment of ramelteon was needed or recommended in renal impairment.[98] However, in accordance with the extensive hepatic metabolism of ramelteon, increased systemic exposure of ramelteon was observed in mild to moderate hepatic impairment.[99]Thus, caution is advised in using ramelteon in patients of moderate hepatic impairment and its use is contraindicated in those with severe hepatic impairment. [97]These studies are supportive of the safety of ramelteon use in the elderly who often have comorbid COPD or OSA and at least mild to moderate renal impairment. It is advisable, however, to screen for hepatic impairment (at least an LFT) before prescribing ramelteon in elderly subjects.

Melatonin

Structurally, melatonin is N-acetyl-5-methoxy tryptamine, secreted naturally from the pineal gland and shows diurnal variations.[102]It plasma concentrations at nighttime is around 10 times that of its daytime plasma concentrations.[103]Exogenous melatonin is synthetically produced and classified by US FDA as a food supplement, therefore, out of the purview of its regulations and approval. It is, however, approved by the European Medicines Agency for the treatment of insomnia in adults above 55 years of age. [104]The pharmacokinetic properties of exogenous melatonin are given in table 2. It is around 60% protein bound, mainly to albumin, a1-acid glycoprotein, and high-density lipoprotein. [105]It binds to the MT1 and MT2 receptors, like ramelteon, and exerts its actions via similar pathways.[80,82,105]The binding affinity for the MT1 receptor is 8 fold greater than that of MT2 for exogenous melatonin.[106]Its primary metabolite is 6-sulphatox-y melatonin [aMT6s] which is biochemically inactive.[104]

Drug interactions

In humans, co-administration of melatonin with thioridazine, imipramine and zolpidem showed pharmacodynamic interaction in the form of increased sedation, impairment of attention, memory and coordination with no pharmacokinetic interaction, while coadministration with cimetidine showed increased plasma melatonin concentration but no pharmacodynamic interaction.[105]Melatonin metabolism is mostly mediated by CYP1A2, a Cytochrome P450 isozyme inhibited by fluvoxamine, ciprofloxacin and other quinolones, and induced by caffeine, carbamazepine, omeprazole and cigarette smoking.[105]CYP1A2 substrates such as theophylline and clozapine may also give rise to drug interactions. Melatonin, on the other hand, inhibits CYP 1A (with 48% inhibition from control) and doesn't induce CYP 1A, 3A or 2C. [105]

Efficacy

Studies have suggested a relationship between sleep, pineal function and melatonin levels. Melatonin levels naturally decrease with increase in the age which correlates with poorer sleep quality in elderly individuals compared to young adults. [103]Nocturnal melatonin levels were also found reduced in primary insomnia. [107]It is thus obviously logical that exogenous melatonin is tried in the treatment of such. Four good quality studies with 845 total participants tried to assess the effectiveness of melatonin in promoting better sleep in insomnia patients.[108-111]Three of those, including the study with the largest sample size of 791 participants found that melatonin significantly improved sleep time and sleep quality compared to placebo.[109-111]One of them even recommended that melatonin is effective in maintaining good quality sleep in the elderly while weaning off from benzodiazepines.[110]The other one, with a sample size of 10 participants didn't find any beneficial effects of melatonin over placebo.[108]Another study done on 10 elderly individuals with mild cognitive impairment found 6 mg melatonin, administered two hours before habitual bedtime significantly

decreased sleep onset latency, along with improvement in mood and memory, but had no effect on total sleep time.[112]

Safety

Acute toxicity of melatonin in animals and humans has been found to be extremely low. In animal studies, LD50 (lethal dose for 50% of the subjects) could not be established even with 800 mg/kg bodyweight.[113]In humans, experimental doses upto 6.6 gm. /day followed by an elaborate battery of biochemical tests to detect any potential toxicity concluded no adverse effects at the end of study period other than somnolence.[114,115]In clinical studies involving humans,the most common adverse effects reported are headache and somnolence.[109-111,117.118,121]Palpitations and abdominal pain have been reported as an adverse effect in two studies[117,119,120] Infrequent adverse effects, reported in only one of many studies include- nasopharyngitis, arthralgia, tachycardia, dizziness, nausea, vomiting, nightmares, difficulty swallowing and breathing, hypnotic activity, heavy head, heartburn, flatulence, swelling of arms/legs, sweating/hot flash, exanthema, sleeping difficulties, depression and sleepwalking.[109,117,119-123]

Cause of concern?

Though as of now, melatonin appears to be safe as far of adverse effects are concerned, there are some isolated reports and animal studies doubting otherwise. Some animal studies suggest melatonin can downregulate the pituitary-gonadal axis with downstream consequences.[102]There have been reports of melatonin reducing sperm motility in rats and inhibiting testicular aromatase levels in men on long-term use.[124,125]However, other studies found no alteration of testosterone or luteinizing hormone with chronic low dose melatonin administration in men.[126]Similarly, a phase 2 clinical trial of 1400 men treated with 75 mg melatonin nightly didn't report any damage to the female reproductive system.[127] Animal studies suggest melatonin may accelerate autoimmune conditions and there has been a case report showing transient

exacerbation of neurologic symptoms in one patient of multiple sclerosis with melatonin.[128,129]Some animal studies reported light-induced damage to retinal photoreceptors with moderate-high doses of melatonin (about 30 mg human dose equivalents) and others reported increased atherosclerosis in the aorta in hypercholesterolemic rats with melatonin.[130,131]

Another important area of concern is the timing of melatonin administration. If melatonin is given throughout the day or at such a time that it unduly prolongs the nocturnal melatonin rise, it can worsen the seasonal affective disorder, bipolar or classic depression.[132,133]Moreover, though melatonin is considered a potential adjunct for treating cancer and immune deficiency, a poorly timed administration can have opposite effects. For example, a melatonin injection given in evening reduces tumour growth, but has no effect when given mid-afternoon and stimulates the tumour growth when given in the morning.[102,134,135]

Also, long-term exogenous melatonin administration (and probably those of the MT1, MT2 agonists like ramelteon etc.) results in desensitization and internalization of MT1 and MT2 receptors in the SCN. The potential consequences of the same in the long term are still undetermined and under investigation. [80]

Other melatonin agonists

There are other drugs (Agomelatine and Tasimelteon) acting on the MT1 and MT2 receptors which are, however, not approved by the FDA for treatment of insomnia.

Agomelatine

It is approved by the European Medicines Agency for the treatment of a major depressive disorder in adults less than 75 years of age[136]. Its pharmacokinetic characteristics are given in Table 2. Agomelatine is 95% protein bound, undergoes extensive hepatic first-pass metabolism, and binds to MT1 and MT2 receptors as agonists and 5HT-2C receptor as an antagonist (this property is postulated for its antidepressant action)[104,136]It binds to both MT1

and MT2 with equal affinity.[104,136]It has no active metabolite. It's reported adverse effects are Nausea, dizziness, headache, somnolence, insomnia, migraine, diarrhoea, constipation, abdominal pain, vomiting, hyperhidrosis, back pain, fatigue, anxietyand increases in liver enzymes [136]. It is usually recommended to perform a liver function test before prescribing agomelatine.

Tasimelteon

Tasimelteon is approved by FDA (2014)and European Medicines Agency for treatment of a CRSWD (non 24hrs) in blind adults. Its pharmacokinetic characteristics are given in Table 2. It is almost 89% protein bound and binds to the MT2 receptor with four-fold greater affinity than MT1.[137,138]It has 6 very weak active metabolites (M9, M11, M12, M13, M14, and M3) which are not considered clinically significant for exerting its actions. [139]It is recommended to be taken at bedtime without food.[104] Its common reported adverse effects are Headache, increased ALT level, nightmares or unusual dreams, upper respiratoryinfection, urinary tract infection, though these are rare in clinical practice. [137,138]

Orexin receptor antagonist

Suvorexant is a medication recently approved by FDA (2014) for treating insomnia that blocks orexin-mediated wake signalling. It is the first of DORA: Dual Orexin Receptor Antagonist, a newer generation of drugs which target and selectively block the binding of neuropeptides orexin A and B to receptors OX1R and OX2R, thereby inhibiting wakefulness.[140,141]It is approved at doses of 5mg, 10mg, 15 mg and 20mg by the FDA for insomnia treatment.[142] Higher doses have been reported to have side effects and moreover, the drug is scheduled as a controlled substance in the United States due to its reported abuse potential.[142,143]It should be taken 30 mins before bedtime without a meal (as food ingestion can delay Tmax by upto 90 mins) and shouldn't be taken if intended sleep time is less than 7 hours.[141]Its pharmacokinetic properties are given in Table

2. It is extensively protein bound and caution is recommended during dose increase in obese females.[141]Its common side effects include somnolence, fatigue, and headache and rare side effects include diarrhoea, xerostomia, upper respiratory tract infections, dizziness, abnormal dreams and cough.[142,145]There have been some concerns regarding unconscious nighttime activity, sleep paralysis, hypnagogic hallucinations, mild cataplexy, and suicidal ideation with suvorexant use.[144]It improves sleep onset and maintenance and is usually tolerated well by the elderly. Studies report no difference in suvorexant efficacy or safety between elderly (65 yrs. and above) and non-elderly (18-64 yrs.), apart from noted balance impairment 90 mins after 30 mg suvorexant administration in the elderly [140,141]. The only contraindication of suvorexant use is narcolepsy [141]. However, caution and dose adjustments are advised on co-prescription with hepatic CYP inhibitors like ketoconazole, diltiazem etc. and CYP inducers like rifampicin. [141]

Summary of hypnotics not acting on the GABA-A receptor:

The melatonin receptor agonists appear relatively safer in the short and intermediate term compared to GABA-A agonists, however, their safety in the long term remains to be ascertained, and probably will become clearer over the next decade once their use increases in routine clinical practice and subsequently more clinical research is done on them. Another important limitation of melatonin agonists is that they are not powerful CNS depressant like GABA-A agonists, and therefore, appears less effective/ ineffective, particularly in individuals with a long history of sedative use/ abuse. However, in those in whom it remains effective, the melatonergic agents significantly improve the quality of sleep without any residual hangover. The orexin rector antagonists are comparatively more potent and sedating than melatonergic agonists, and subsequently, have more side effects and risk of toxicity and abuse. Their use and safety in the elderly remain to be ascertained as of now, and more clinical experience and research is needed for the same, which will increase once the availability of this drug increases in different countries.

Table 1: Z-Drugs Pharmacology [11, 17-22]

Z drug	Chemistry	Receptor binding	Tmax (h)	Oral bio-availability	Elimination t½ (h)	Dose range	Metabolism
Zolpidem	imidazopyridine	Alpha1+++ Alpha2,3 + Alpha5 -/+	1–2	65–70 %	2.5–3	5 – 10 mg	CYP 3A4, 2C9, 1A2
Zolpidem ER (Extended Release)			1.5 – 2.5			6.25 – 12.5 mg	
Zaleplon	pyrazolopyrimidine	Alpha1+++ Alpha2,3,5 -/+	0.7 – 1.4	30 %	~1	5 – 20 mg	Aldehyde oxidase, CYP 3A4
Zopiclone	cyclopyrrolone	Alpha1++++ Alpha2,3,5 -/+	1.5–2	75–80 %	5–6	3.75 – 7.5 mg	CYP 3A4, 2C8
Eszopiclone	Cyclopyrrolone (S-enantiomer)	Alpha1+++ Alpha2,3 ++ Alpha5 -/+	1–1.5	75–80 %	6–7	1–3 mg	CYP 3A4, 2E1

Table 2: Melatonin agonist's pharmacology:

Drug	Chemistry	Receptor binding (agonist)	Tmax (h)	Oral bioavailability	Elimination t½ (h)	Dose range	Metabolism
Ramelteon	tricyclic indan derivative	MT1, MT2	0.5–1.5	84%, (effectively)<2%	1-2	8-16 mg	CYP1A2, CYP2C, CYP 3A4
Exogenous melatonin	N-acetyl-5-methoxy tryptamine,	MT1, MT2, MT3	0.75–3	15%	3.5-4	2-5 mg	CYP1A1 CYP1A2 CYPC19 (possible)
Agomelatine	N-(2-(7-Methoxynaphthalen-1-yl)ethyl) acetamide	MT1, MT2, 5HT-2C antagonist	0.5-1.3	3.3 +/- 1.1 %	1-2	25-50 mg	CYP1A1 CYP1A2 CYP2C9
Tasimelteon	N-[[(1R,2R)-2-(2,3-dihydro-1-benzofuran-4-yl)cyclopropyl]methyl] propanamide	MT1, MT2	0.9-1.7	38.3%	0.5-3	20mg	CYP1A2 CYP3A4
Suvorexant	(7R)-4-(5-chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl]-[5-methyl-2-(triazol-2-yl)phenyl]methanone	OX1R, OX2R	0.5-6	82%	13.5	5-20mg	CYP3A4 (Major) CYP 219 (Minor)

CONCLUSION

To conclude, we're still far away from finding the perfect hypnotic for the elderly, which will cause optimum sleep without daytime residual sedation and without negatively interacting with the elderly individual's many comorbidities and their medications. However, a lot depends on the intent and expertise of the clinician in selecting and prescribing the appropriate hypnotic to the elderly patient, considering his/her physical comorbidities and psychiatric symptoms and the drugs treating them. It is vitally important for the clinician to listen attentively into the symptoms, problems and daily routine of the elderly patient before prescribing a hypnotic and is imperative for him to describe the potential adverse effects that may occur and discuss the preventive options for the same with the patient. With the correct attitude and approach on behalf of the clinician, and good tailoring of the available molecules with the individual patient's needs, we may successfully treat and manage the chronic and nagging problem of insomnia in the elderly patients.

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Management of Anxiety in Elderly

Kshitiz Sharma, Subhash Das

ABSTRACT: *With increasing life expectancy, prevalence of geriatric disorders is increasing. Anxiety disorders are commonly seen in the geriatric population. Due to the process of ageing, homeostatic processes are impaired which may lead to greater frequency and intensity of side effects of medicines, thus close monitoring is required.Among anxiety disorders in the elderly prevalence of generalized anxiety disorder is found to be the greatest followed by phobias, panic disorder and obsessive-compulsive disorder. In the case of anxiety disorders in the elderly, thorough history and review should be conducted, which should include ruling out any physical illness, any drug or substance use and assessment of psychological risk factors.Approaches to treatment include both pharmacological and non-pharmacological methods.In pharmacological treatment, the drugs should be started at a lower dose and should be built up gradually. Research has supported the use of SSRIs and SNRIs. Benzodiazepines should be used very cautiously. Agomelatine is a newer drug which is also used in geriatric anxiety disorder. Non-pharmacological approach can include lifestyle modification, behaviour therapy and cognitive behaviour therapy. New approaches like mindfulness and yoga are also perceived to be beneficial. In the treatment of geriatric anxiety disorders physiological processes of ageing, comorbid medical conditions have to be taken into account so as to maximize efficacy and minimise side effects. Non-pharmacological management plays an important role in the management of geriatric anxiety disorders.*

Keywords: *elderly, anxiety disorders, SSRI*

INTRODUCTION

With advancements in medical technology life expectancy has increased thus leading to an increase in the geriatric population. This is a global phenomenon and countries in both developing and developed world are facing this trend of increasing geriatric population. In the coming years, the proportion is expected to rise further. It is estimated that the geriatric population comprises 11% of the total population worldwide and it is projected to increase to approximately 22% by 2050. [1]

In India,the current proportion is estimated to be around 8% and is projected to increase to 19% by 2050[1]. That means approximately 1 in every 5 Indians will belong to the geriatric age group which is those who are aged 65 years and above.

With ageing,the homeostatic mechanism of the body is impaired (for example postural control, orthostatic circulatory responses etc.). The sensitivity of receptors may be increased leading to increased incidence and severity of side effects. The therapeutic response may also be delayed. The elderly may also be more susceptible to develop serious side effects of commonly prescribed drugs (for example bleeding with SSRIs). Gut motility is reduced leading to slow absorption and the slow onset of action of drugs. It has been found that the percentage of body fat increases with age. Percentage of body water is reduced and albumin is also reduced in the elderly. This leads to a greater volume of distribution of lyophilic drugs and lower volume of distribution of hydrophilic drugs and increased amount of active free drugs(which are not bound to albumin). Renal functioning also reduces with age especially in the context of concurrent medical illnesses. Estimated GFR is an investigation of choice for assessing renal function in the elderly as creatinine production is reduced due to reduced muscle mass and debility.[2]

Anxiety is one of the most common disorders of the elderly and is more common in comparison to depression in the later life. Among older adults, in the US the lifetime prevalence of anxiety disorders is as high as 15.1% and in other countries prevalence of

anxiety disorders ranges from 4.4% to 14.2%. [3]Some Indian studies have pointed towards the overall prevalence of anxiety disorders as approximately 10%. Among anxiety disorders generalized anxiety disorder (GAD) was found to be most prevalent followed by phobias, panic disorder and obsessive-compulsive disorder. [4] However anxiety disorders especially, GAD in later life may go unnoticed and many symptoms like sleep disturbances, restlessness, poor concentration and fatigue may be thought to be due to normal ageing, physical conditions and due to medications used in later life[3].

While assessing an elderly patient with anxiety disorder certain points should be kept in mind for example presence of psychiatric or medical co-morbidity, normal concerns of ageing and whether the patient is already on any medication.

Probable causes of anxiety in the elderly	
Physical condition	• Neurological (Stroke, Parkinsonism,epilepsy, multiple sclerosis, tumours) • CVS (Angina,mitral valve prolapse, cardiac arrhythmia, acute asthmatic attacks) • GI disorders (Irritable bowel syndrome) • Metabolic /endocrine (Hypoglycaemia, hyperthyroidism, pheochromocytoma, hypo/ hyperparathyroidism, carcinoid syndrome, uraemia, hepatic failure, hypocalcaemia or hypercalcaemia) • Deficiency states (Vit. B1,B6,B12,folic acid)
Psychological Risk factors	• low educational attainment • lower economic status • being childless • being single or widowed • poor self-rated health • functional impairment • empty nest syndrome • having another psychiatric disorder

	• low self-efficacy • impaired social networks • cognitive impairment • presence of a major illness in the partner • neuroticism • poor coping skills
Drugs	• Anticholinergics (examples: benztropine, diphenhydramine, oxybutynin) • Antidopaminergics (examples: neuroleptics, metoclopramide) • Beta-agonists (example: albuterol) • Dopaminergics (examples: amantadine, L-dopa, carbidopa-levodopa) • Fluoroquinolones • Hallucinogens (example: cannabis) • Nonsteroidal anti-inflammatory drugs (example: indomethacin) • Procaine derivatives (example: lidocaine) • Selective serotonin reuptake inhibitors • Stimulants (examples: amphetamines, caffeine, cocaine,theophylline) • Steroids (examples: anabolic steroids, corticosteroids, estrogens) • Sympathomimetics (examples: ephedrine, epinephrine) • Triptans (example: sumatriptan) • Thyroid preparations
Substance abuse	• Cannabinoids, alcohol, ecstasy • Withdrawal syndromes- alcohol, benzodiazepines, barbiturates

*table has been compiled with the help of information from various sources. [4, 5]

Approaches in the management of anxiety disorders in the elderly

1. Pharmacological
2. Non-Pharmacological

Pharmacological

Antidepressants (SSRIs and SNRIs)

SSRIs and SNRIs are the first choices of management in geriatric anxiety disorders [3]. SSRIs considered to have the best safety profile in the elderly are citalopram, escitalopram, and sertraline. These have the lowest potential for drug-drug interactions based on their cytochrome P-450 interactions. Studies support the efficacy of citalopram[5], Sertraline[6] and extended-release venlafaxine.[7] A study comparing the response to venlafaxine in young patients with old patients found response to be similar in both the groups. [8]A period of 4 to 12 weeks is advised for assessing the response to treatment. Side effects have to be closely monitored especially for hyponatremia as it may lead to serious adverse consequences. [4] SSRIs such as fluoxetine, paroxetine, and fluvoxamine have higher risks of drug-drug interactions. Also, fluoxetine is generally not recommended for use in the elderly because of its long half-life and prolonged side effects. Paroxetine is also typically not recommended for use in the elderly as it has the greatest anticholinergic effect of all the SSRIs. [9]

However as often elderly patients are found to be suffering from co-morbid disorders like Hypertension, Diabetes etc so all these drugs should be used cautiously with frequent monitoring for the side-effects and drug-drug interactions. Some of these have been highlighted here. SNRIs can lead to increased blood pressure. Use of SSRIs and SNRIs can cause a greater chance of bleeding especially in patients who are already on anticoagulants e.g. warfarin. Owing to renal functioning associated with ageing, there is also an increased risk of elderly patients developing hyponatremia secondary to a syndrome of inappropriate antidiuretic hormone secretion.

Benzodiazepines

Benzodiazepines are often among the frequently prescribed drug for anxiety[3] in the elderly, but most professional bodies recommend against the use of benzodiazepines in the geriatric population. The American Geriatrics Society advice morning use of benzodiazepines in patients aged more than 65 years. [10]As per the clinical practice guidelines of Indian Psychiatric Society in the Indian Journal of Psychiatry (IJP), the benzodiazepine is to be used only in for short periods and should be quickly tapered. But benzodiazepines are still used commonly in the geriatric population which may predispose to side effects such as a risk of dependence, cognitive deficits, greater risk of falls leading to fractures and greater mortality.

For the management of insomnia, which is often present in anxiety disorders, other drugs can be considered for example trazodone, doxepin, mirtazapine and ramelteon.[10]

Other drugs

Other drugs that are used for anxiety disorders are Mirtazapine, buspirone and TCAs. Mirtazapine and bupropion are also considered to have a good safety profile in terms of drug-drug interactions, though one should be careful in using TCAs due to its cardiovascular side-effects

Studies on newer molecules like Agomelatine have found that it is more effective than placebo in reducing anxiety symptoms in patients of major depressive disorder[11, 12]. Some studies focusing on the use of Agomelatine in Generalised Anxiety Disorder (GAD) have demonstrated efficacy as well as tolerability for treatment[13] as well as relapse prevention in GAD.[14]Agomelatine has also found to be well tolerated in the geriatric age group.[15]Thus agomelatine is a good alternative for the treatment of anxiety in elderly.

Treatment End Point

As per the recent clinical practice guidelines of IPS the duration of treatment should be at least 12 months beginning from the time

of remission (and up to 2 years). While stopping the medication, the dose should be reduced over several months with monitoring for relapse. Monitoring should be done 3-6 monthly keeping two things in mind:

a) Remission/and or exacerbation of anxiety
b) Emergent cognitive symptoms.

Non Pharmacological management

Indian Psychiatric Society, in its clinical practice guidelines, advises the use of non-pharmacological methods as the first recommendation in its clinical practice guidelines.

These are:

Lifestyle modification- Adequate sleep, diet and exercise have been advised. Any triggers whether medical or non-medical need to be removed.

Behaviour therapy- Use of psychotherapy based on the principles of behaviour therapy is also suggested e.g. relaxation therapy, systematic desensitization and exposure and response prevention.

Cognitive behaviour therapy- It has been one of the most researched methods of management of anxiety in the elderly. ABC (Antecedent-Behaviour-Consequence) model of CBT has been suggested to identify and modify maladaptive behaviour.

Efficacy of CBT in GAD has been supported by meta-analytic research. [16]A meta-analysis supports the role of CBT in symptom reduction in a wider ambit of anxiety disorders including GAD, panic disorder, mixed anxiety disorders comparative to control conditions.[17]Innovative approaches to implementCBT like for example telephone-based, internet-based are other alternatives which offer flexibility and have also shown promising results in managing anxiety disorder in the elderly.[3]

Miscellaneous approaches: Other approaches like mindfulness, yoga, music and dance therapy may also have a role in the management of anxiety.

CONCLUSION

To conclude, anxiety disorders are not uncommon in the elderly and may often be overlooked. Keeping in mind the physiological changes that occur with ageing along with the co-morbid physical conditions that are often present in the elderly, the treatment approaches have to be planned in such a way so as to maximize efficacy and minimize side effects. Among pharmacological options, SSRIs are usually the first choice in the management of anxiety disorders. Most guidelines advice avoidance of benzodiazepines in the elderly, and if at all used, it should be given for a shorter period. Among non-pharmacological CBT is a widely researched modality and has shown efficacy across many anxiety disorders. Newer approaches like mindfulness yoga are also being increasingly used in the management. With further research in future too we will definitely have suitable approaches towards management of anxiety disorders.

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From Pharma to Farmers' Industry

Shyamanta Das

ABSTRACT: *The better prognosis of psychiatric disorders from India is traditionally linked to the psychosocial support. But, there is the possibility of a few other reasons for the same. Equatorial position with sunlight exposure and dietary habit that is rich in antioxidants can be them. Moreover, the chemistry of therapeutic molecules is usually found first in the vegetative forms. And in age-old Ayurveda, such an approach to deal with mental illness is available. Unfortunately, it is true that the real potential still remains not fully explored. Here may lay the future mystery for a novel therapeutic way.*

Keywords: *Prognosis, Psychosocial Support, Ayurveda.*

INTRODUCTION

In psychiatry, we have a few revolutions [1]. During the middle ages, mental illness was thought to be due to demonic possession, witchcraft, and the like. Unfortunately, in certain sections of our society, such beliefs still prevail. But, following the Renaissance, it is widely accepted that mental illnesses are brain disorders, like other medical illnesses. This is considered the first revolution of psychiatry. The second revolution coincides with the evolution of psychoanalysis. The third revolution starts with the introduction of chlorpromazine. Successful treatment of patients with pharmacotherapy helped in their movement from asylums to society. That marked the fourth revolution, in the form of community psychiatry.

If we draw a timeline, we can see a period of stagnation in modern psychiatry, between the second and third revolutions,

for almost half a century. Freud's concepts, which he proposed as abstracts, were concretized by his followers, as they remained fixated on their tangibility. The de-institutionalisation, if we can ignore the phase of trans-institutionalisation, is the result of the third revolution, i.e. pharmacotherapy of mental illnesses. It led to the fourth revolution in the community or social psychiatry. Talking about pharmacotherapy in psychiatry, it was traditionally the four groups of antipsychotic, antidepressant, antianxiety, and mood stabilizer. Certain developments in contemporary psychiatry led to a paradigm shift as far as this division is concerned.

PERSONALIZED MEDICINE

These developments worth noting include Matcheri Keshavan and his team's Bipolar and Schizophrenia Network for Intermediate Phenotype or B-SNIP in short,[2] Thomas Insel and his team's Research Domain Criteria or RDoC initiative,[3] Joseph Zohar and his team's Neuroscience-based Nomenclature (NbN),[4] as well as Stephen Stahl's deconstructing syndrome into symptoms.[5]

On one hand, there is an attempt for a brain-based diagnostic system, [6] and on the other; the attempt is to have a mechanism-based classification of treatment instead of categories. [7] We all know the fallacy of calling, for example, escitalopram, an antidepressant. Though used in a depressive episode, another patient with panic disorder may come and say that you have given him an antidepressant for his anxiety disorder!

So, the journey is from phenomenology through neurocircuitry, [8] to biological and molecular psychiatry, a corollary of which we can find in oncology. Our current diagnostic systems of ICD and DSM are comparable to TNM classification, i.e. tumour, node, metastasis. Oncology has moved from the TNM classification to Human Epidermal Growth Factor Receptor 1 (HER-1) and 2 (HER-2). Similar is this journey of ours. Treatment needs to be tailor-made according to the need of the patient, or in other words, "personalised medicine in psychiatry". [9]

Currently, we have a common brain-biology based approach

for both the diagnosis as well as treatment of psychiatric disorder. Does this signify our "entering the fifth revolution of psychiatry"? [10]

RESOURCES IN PSYCHIATRIC CARE

"If you have a cardiovascular problem, I would prefer to be a citizen in Los Angeles than in India," said Benedetto Saraceno, then Director of the Department of Mental Health and Substance Abuse at the World Health Organization's (WHO) headquarters in Geneva. "If I had cancer, I would prefer to be treated in New York than in Iran. But if you have schizophrenia, I am not sure I would prefer to be treated in Los Angeles than in India."[11]

"The better prognosis of schizophrenia spectrum disorders in India is traditionally linked to the strong supporting system in the forms of family and friends; thus, implying the role played by the psychosocial factors. But, it is often overlooked that there are too many other factors which may have an influence on such protection. Diets and role of antioxidants need to be highlighted in this context."[12] Or, maybe the even equatorial position of our subcontinent!

"The huge gap between those who require the service and the actual service users, as well as the affordability of such services which are presently in place, calls for alternative resources. This draws attention to herbal extracts. It is a fact that the chemistry of most of the molecules is first identified in its vegetative origin. Later on artificially preparing that structure which is beneficial and discarding the harmful one, we finally reach the desired molecular chemistry. A combination of diets rich in antioxidant properties and the widespread use as well as the availability of herbal extracts can lay the future mystery of molecular chemistry, for a novel treatment approach, which can have a disease-modifying effect in psychiatric illnesses."[12]

CONCLUSION

The seeds have been already sown in the traditional Hindu

system of medicine known as Ayurveda. One such medicine is the plant 'sarpagandha' (Rauwolfia serpentina), from which reserpine, a drug known to have antipsychotic effects, is derived. [13] Many such herbs are widely available in the courtyards of our villages. Currently, there is insufficient evidence to accept herbal extracts like curcumin, an ingredient of turmeric, as a possible alternative to standard therapy [14] as well as the promising preliminary reports of 'Brahmi' (Bacopa monnieri) as 'add-on' management. [15] But one thing that comes out of this is that, "Ayurvedic medication may have some effects, but has been evaluated only in a few small pioneering trials". [16]

This has the potential to replace the currently domineering pharma industry with the farmers' industry in the near future!

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Pharmaceutical Regulatory Agencies in India

Susanta K Bordoloi, Arijit Dutta

ABSTRACT: *As the pharmaceutical industries throughout the world are moving ahead towards becoming more and more competitive, regulatory agencies are being established in various countries across the globe. Regulatory agencies and organizations play a vital role to meet the requirements of legal procedures related to the drug development process in a country.In the present scenario, pharmaceuticals are considered the most highly regulated industries worldwide. The regulatory body ensures compliances in various legal and regulatory aspects of a drug. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate drug development process, licensing, registration, manufacturing, marketing and labelling of pharmaceutical products. The major challenges of these regulatory agencies and organizations around the world are to ensure the safety, quality and efficacy of medicines and medical devices, harmonization of legal procedures related to drug development, monitoring and ensuring compliance with statutory obligations. They also play a vital role to ensure and increase regulatory implementation in non-regulated parts of the world for the safety of people residing there. The present study describes a brief review of various regulatory bodies of India and the scope and challenges of such regulatory organizations in drug development and delivery of safe and effective healthcare products to individuals around the country.*

Keywords*: Regulatory agencies, Pharmaceutical industry, India*

INTRODUCTION

Regulatory affairs in the pharmaceutical industry are aimed at the protection ofhumanhealth. People and the government spend

money on drugs because ofthe role they can play in saving lives, restoring health, preventing diseasesand stopping epidemics. But, in order to do so, a drug must be safe,effective and of good quality. Since the purpose of the drug is to diagnose,prevent or treat diseases or ailments in humans, they are productsintimately linked with the advances in research and regulation. Thepharmaceutical industry has to pursue an international market and at the same time it is obligatory for them to comply with national regulations.

An agency called the Drug Regulatory Authority (DRA) develops and implements most of the legislation and regulations on pharmaceuticals. Its main task is to ensure the quality, safety and efficacy of drugs, and the accuracy of product information. This is done by making certain rules that the manufacture, procurement, import, export, distribution, supply and sale of drugs, product promotion and advertising, and clinical trials are carried out according to specifiedstandards.

The main goal of drug regulation is to--

- Guarantee the safety, efficacy and quality of drugs available to the public.
- Licensing of premises, persons and practices.
- To inspect manufacturing facilities and distribution channels.
- Product assessment and registration.
- Adverse drug reaction (ADR) monitoring.
- Control of drug promotion and information

Every country has its own regulatory authority[1], which is responsible to enforce the rules and regulations and issue the guidelines to regulate the drug development, licensing and registration.

The drug regulation consists of:

1. Drug Laws
2. Drug Regulatory Agencies

3. Drug Regulatory Boards
4. Quality Control
5. Drug Information Centres.

DRUG REGULATORY AGENCIES IN INDIA[3,4,5]

India is one of the leading markets for pharmaceutical products. Increase in the private healthcare infrastructure, widening rural markets and the inclusion of newer technologies have placed healthcare as an independent sector in India. With the privatisation of healthcare, the medical devices sector is growing too.

The Drugs and Cosmetics Act, 1940 ("D&C, Act") was introduced in India in 1940, in order to regulate the import, manufacture, distribution and sale of drugs and cosmetics. However, till date by the Government of India has been enacted any separate regulation for regulating the import, manufacture, distribution or sale of medical devices in India.

Drugs and Health are in the concurrent list of Indian Constitution. It is governed by both Centreand State Governments under the Drugs & Cosmetics Act.

MAIN BODIES:-

Central Drug Standard Control Organization (CDSCO)
National Institute ofHealth & Family Welfare (NIHFW)
Indian Council of Medical Research (ICMR)
Drug Technical Advisory Board (DTAB)
Central Drug Testing Laboratory (CDTL)
Indian Pharmacopoeia Commission (IPC)
National Pharmaceutical Pricing Authority (NPPA)

1. CDSCO[2]

In India, the Central Drugs Standard Control Organization (CDSCO) is the main regulatory body. It currently regulatesthe import, sale and manufacture of medical devices which have been notified as drugs by virtue of Section 3(b) (IV) of the D&C Act. It is the duty of the CDSCO to lay down standards of drugs, cosmetics, diagnostics and devices and issues licenses to drug manufacturers and importers. It lays down regulatory measures, amendments to Acts and rules and regulates market authorization of new drugs, clinical research in India andstandards of imported drugs etc.

It has its Headquarter in New Delhi.It is India's main regulatory body for pharmaceuticals and medical devices.The Drug Controller General of India (DCGI) isresponsible for the regulation of pharmaceuticals and medical devices. It is advisedby the Drug Technical Advisory Board (DTAB) and the Drug Consultative Committee(DCC). The licensing and classification of medical devices are handled by the Central LicensingApproval Authority (CLAA). The CLAA is also responsible for setting and enforcing safetystandards, appointing notified bodies to oversee conformity assessment, conducting post-marketing surveillance and issuing warnings and recalls for adverse events.

It establishes safety, efficacy and quality standards for pharmaceuticals andmedical devices. It publishes and updates the Indian Pharmacopeia, a list of regulatedpharmaceuticals and devices. The CDSCO appointsnotified bodies to perform conformity assessment procedures, including testing, in order

toensure compliance with their standards for all drug and device applications. The CDSCO is divided into several zonal officeswhich do pre-licensing and post-licensing inspections, post-market surveillance, and recallswhen necessary.Apart from its regulatory functions, the CDSCO also offers technical guidance, trains regulatoryofficials and analysts and monitors adverse events. The CDSCO also works with the WorldHealth Organization to promote Good Manufacturing Practice (GMP) and internationalregulatory harmony. This organization is soon to be revamped with new added responsibilities with possible name of National Drug Agency.

2. NATIONAL INSTITUTE OF HEALTH AND FAMILY WELFARE (NIHFW)

NIHFW is an Apex Technical Institute, funded by Ministry of Health and Family Welfare, for the promotion of Health and Family Welfare programs in the country through education, training, research, evaluation, consultancy and specialized services. It was established on March 9, 1977, by a merger of the National Institute of Health Administration and Education (NIHAE) with the National Institute of Family Planning (NIFP).

3. DRUG TECHNICAL ADVISORY BOARD (DTAB)

The Central Government constituted a Board called the Drugs Technical AdvisoryBoard to advise the Central Government and the State Governments on technical matters arising out of the administration of D&C, Act 1940.

4. CENTRAL DRUG TESTING LABORATORY (CDTL)

The central drug laboratory, Kolkata is the national statutory laboratory of the government of India for quality control of drug and cosmetic and established under the D&C act, 1940. Oldest quality control laboratory of the drug control authorities in India. It functions under the Director General of Health Services in the Ministry of Health and Family Welfare.

5. INDIAN PHARMACOPOEIA COMMISSION (IPC)

It is an autonomous institute under the Ministry of Health and Family Welfare, Govt.of India. It is dedicated to the setting of standard of drugs, pharmaceuticals and healthcare devices besides providing training. To develop comprehensive monographs for drugs included in IP including API, Excipients and dosage forms. To accord priority to monographs of drugs in the National Essential Drug List & their dosage forms.

6. NATIONAL PHARMACEUTICAL PRICING AUTHORITY (NPPA)

NPPA is an organization of the Government of India which was established, inter alia, to fix/ revise the prices of controlled bulk drugs and formulations. It is its duty to enforce prices and availability of the medicines in the country, under the Drugs (Prices Control) Order, 1995. It is also entrusted with the task of recovering amounts overcharged by manufacturers for the controlled drugs from the consumers. It also monitors the prices of decontrolled drugs in order to keep them at reasonable levels, implement and enforce the provisions of the Drugs (Prices Control) Order in accordance with the powers delegated to it.

CONCLUSION

The Pharmaceutical industry represents one of India's strength. There is need of reform in the regulation of India's Pharmaceutical industry. It has been the subject of many official commissions since 1995. Most commentators agree that the state should intervene to prevent untrammelled market forces leading to citizens' suffering, because adequate information about the costs and benefits of different pharmaceuticals is inaccessible to most users. But in India, a wide range of stakeholders must be considered before changes can be made to the regulatory framework.

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Understanding Polypharmacy

Vijay Gogoi

ABSTRACT: *World Health Organization defines polypharmacy as the administration of many drugs at the same time or the administration of an excessive number of drugs. Definitions used in studies are varied and based on a numerical count of medicines, time of prescribing, class of medicine, drug interactions or combinations. Contributing factors are many and can be related to patients, physicians, monitoring and disease conditions. Evidence suggests that with each increasing number of medicines prescribed, risks of complications increases manifold. Identifying patients with polypharmacy, use of screening tools, improving the discharge process, medicine reconciliation, deprescribing and regular review of prescriptions could be some of the ways to manage polypharmacy effectively.*

Key-words: Rational, polypharmacy, prescriptions

INTRODUCTION

Simultaneous use of multiple medications is common clinical practice. Different practitioners have conflicting views towards this controversial treatment approach. While some criticize this strategy, others practice and advocate polypharmacy with their justification. With time, our understanding of drug profile, their reactions, and interactions with other molecules has considerably increased. However, scientific literature on definitions, patient profile, clinical conditions, guidelines or factors contributing to the use of multiple medications is still limited. New drugs are mostly studied in isolation or with a placebo. Combination studies are limited to a few short-

term drug interactions. Systematic data on safe co-prescribing are limited which leads to the knee-jerk reaction that polypharmacy is unacceptable. [1] By the end of this chapter, we will attempt to define polypharmacy, discuss the factors leading to it, its consequences and how to effectively manage polypharmacy with particular emphasis on psychiatric medications.

DEFINITION

The term polypharmacy implies prescription of multiple medications. World Health Organization has defined polypharmacy as "the administration of many drugs at the same time or the administration of an excessive number of drugs". [2] However, the literature search for this treatment strategy indicates that there is considerable heterogeneity in the terminologies, classifications and variables used for research on polypharmacy. In a systematic review of definition for polypharmacy, a total of 138 definitions and associated terms were obtained. [3] Studies have defined polypharmacy either based on the numerical count of medicines or have used descriptive definitions.

Numerical definitions and associated terms	Descriptive definitions and associated terms
Polypharmacy	Polypharmacy
Major polypharmacy	Appropriate polypharmacy
Hyper polypharmacy	Rational polypharmacy
Excessive polypharmacy	Indiscriminate prescribing
Persistent polypharmacy	Pseudo polypharmacy
Chronic polypharmacy	

The numerical only definitions included a range from two or more to 11 or more medications. Although researchers frequently use a certain number of medication (5 or more), there is no consensus on the number of medications above which polypharmacy is considered. However, basing the definition only on the number of drugs used doesn't take into account the benefits a patient may

receive from their medications. Moreover, it has been shown by research that over the years, the proportion of patients receiving multiple medications has been steadily increasing. [4]

Some of the alternative descriptive definitions of polypharmacy take into account the drug interactions, number of diagnosis or drug combinations.

Polypharmacy: The intentional, concomitant use of two or more medications to treat either a patient with more than one pathophysiologically distinct illness or a patient with a single disorder. [1]

Appropriate polypharmacy: Prescribing for a person for complex conditions or for multiple conditions in circumstances where medicines use has been optimised and where the medicines are prescribed according to best evidence. The overall intent for the combination of medicines prescribed should be to maintain good quality of life, improve longevity and minimise harm from drugs.[5]

Problematic polypharmacy: The prescribing of multiple medicines inappropriately, or where the intended benefit of the medicines are not realized. [5]

Some researchers have classified polypharmacy based on time slots, as simultaneous, cumulative or continuous. [6]

Simultaneous polypharmacy corresponds to the number of drugs concurrently taken by a patient on a given day.

Cumulative polypharmacy is defined by the sum of different medications administered over a given period of time. Different studies uses different time periods.

Continuous polypharmacy is similar to cumulative polypharmacy but limited to medications taken for prolonged and regular periods. It only takes into account medications present in two given time periods spaced by an interval of six months, for example.

Based on the WHO ATC (Anatomical Therapeutic Chemical Classification System), certain types of medications are often excluded from research on polypharmacy, such as topical agents and local action drugs, vitamins, minerals, herbal medicines, vaccines, homeopathy or drugs classified as "diverse" in the ATC classification (contrast agents, diagnostic tests, etc.).[7]

Another classification of polypharmacy, based on the type of drug used is also known.

Same Class Polypharmacy	Use of more than one medication from the same class (*e.g, 2 SSRI*).
Multi Class Polypharmacy	Use of more than one drug from different classes for the same symptom cluster (*e.g, Atypical Antipsychotic + Mood Stabilizer*).
Adjunctive Polypharmacy	Use of one medication to treat side effects of another medication (*e.g, Anti Cholinergic + Antipsychotic*).
Augmentation Polypharmacy	Use of one medication at lower dose along with another medication in full therapeutic dose for the same symptoms.

With all these classifications and descriptions, it is apparent that there is no consensus on a single definition of polypharmacy and there are multiple variables which need consideration for a proper understanding of this common clinical practice.

CONTRIBUTING FACTORS

The proportion of adults dispensed with multiple medications has continuously been increasing over the years. [4] The Research on Asian Prescription Patterns (REAP), an international collaborative consortium for studying prescription patterns of psychotropic drugs, found differences in the prevalence of psychotropic polypharmacy across Asian countries. [8] Explanations proposed for these differences were the diverse training backgrounds of psychiatrists, local culture, availability and cost of drugs, patient characteristics, and the local health-care reimbursement system of each country. They also found antipsychotic loading and rate of polypharmacy to be significantly higher in inpatients as compared to outpatients. Some of the common factors leading to polypharmacy include:

a. An aging population with multi-morbidity which frequently demand prescription of multiple drugs.
b. More coherent adherence to treatment guidelines for chronic disorders resulting in growth of prescribing.

c. Underutilization of recommended medications.
d. Augmenting a medication to improve efficacy.
e. Tendency to achieve quick control of symptoms.
f. Minimize potential adverse effects of initial drug.
g. Imprecise diagnosis.
h. Fear of withdrawing the initial medications.
i. Patients stuck in cross titration.
j. Inadequate consideration of receptor pharmacology while prescribing medications.

From a clinician's perspective, prescription of multiple medications could be: [1, 9]

a. To treat two pathophysiologically distinct but comorbid illnesses in the same patient
b. To treat an adverse effect produced by the primary drug
c. To provide acute amelioration while awaiting the delayed effect of another medication
d. To treat intervening phases of an illness.
e. During transition from one molecule to another
f. To boost or augment the efficacy of the primary treatment.

Sheldon and Ronald [1] have proposed criteria for rational co-pharmacy in psychiatry to increase the efficacy of the primary treatment. With a relatively simple pathophysiology, well understood neuropathology, neuroanatomy and neurophysiology and involving dysfunction of a single neurotransmitter, Parkinson's disease has been used as a model for rational co-pharmacy.

Table	Criteria for rational co-pharmacy in Psychiatry
1.	Knowledge that the combination has a positive effect on the pathophysiology or pathoetiology of the disorder.
2.	Convincing evidence that the combination is more effective, including more cost-effective, than monodrug therapy.

3. The combination should not pose significantly greater safety or tolerability risks than monotherapy:
    - Drugs should not have narrow therapeutic indices.
    - Drugs should not have poor tolerability profiles.
4. Drugs should not interact both pharmacokinetically and pharmacodynamically.
5. Drugs should have mechanisms of action that are likely to interact in a way that augments response.
6. Drugs should have only one mechanism of action.
7. Drugs should not have a broad-acting mechanism of action.
8. Drugs should not have the same mechanism of action.
9. Drugs should not have opposing mechanisms of action
10. Each drug should have simple metabolism.
11. Each drug should have an intermediate half-life.
12. Each drug should have linear pharmacokinetics.

It must be mentioned here that co-pharmacy intends to produce a drug-drug interaction where one drug either accentuates or diminishes the effect of another or changes the pharmacokinetics of another molecule. However, each drug added to the regimen frequently increases the likelihood of adverse effects and expenses. Also, ironically, development of drugs with a limited mechanism of action and less side-effect profile further increases the necessity of combination treatment strategy. [1]

CONSEQUENCES OF POLYPHARMACY [10]

Increased healthcare cost

Dose related Adverse drug events

Drug-Drug Interactions

Medication Non- Adherence

Decline in functional status

Cognitive Impairment
Increased risk of Falls
Urinary Incontinence
Poor nutritional status

Prescribing Cascades is another phenomenon which occurs when a new drug is prescribed to treat symptoms arising from an unrecognized adverse drug event related to an existing therapy. Patient is then at risk for developing additional adverse effects related to the new and potentially unnecessary treatment. [11]

Examples:

Initiation of anti-Parkinson therapy for symptoms arising from use of antipsychotics, such as orthostatic hypotension and delirium Cholinesterase inhibitors, commonly used for the management of dementia symptoms in older adults, may cause diarrhea and urinary incontinence. A prescribing cascade occurs when the prescription of a cholinesterase inhibitor is followed by a prescription for an anticholinergic therapy to treat incontinence.

MANAGING POLYPHARMACY

To address the challenges posed by polypharmacy, medicine optimization is fundamental. As suggested by National Institute for Health and Care Excellence (NICE), it "requires evidence-informed decision making about medicines, involving effective patient engagement and professional collaboration to provide an individualised, person-centred approach to medicines use, within the available resources". [12]

Identifying patients with polypharmacy

Duerden and Avery, in their report for the King's Fund, outlined a pragmatic approach to identifying patients with polypharmacy and identifying 'at risk' patients using a combination of patient characteristics and the number of drugs prescribed. [5] Implementation and use of electronic health records can further improve this process of identifying patients with polypharmacy.

Use of Screening tools

Beers Criteria[1,3]: The Beers criteria, is one of the most widely used guidelines to assess inappropriate drug prescribing and help improve safety of prescribing medications. The 2015 revised Beers criteria, available through the American Geriatrics Society, includes over 50 medications designated in one of three categories:

i. those that should always be avoided.
ii. those that are potentially inappropriate in older adults with particular health conditions or syndromes, and
iii. those that should be used with caution.

The Beer's criteria are increasingly being used to monitor quality of care for older adults. The validity of these consensus-derived criteria in predicting adverse outcomes therefore is becoming increasingly more important. Studies of earlier versions of the Beers criteria found that while the criteria did predict adverse outcomes, some medications that were not on the earlier criteria correlated more closely with adverse outcomes:

MAI (Medication Appropriateness Index)[5]: The MAI was designed to assess the appropriateness of a medication for a given patient. It requires clinicians to rate the following 10 explicit criteria to determine appropriateness of medication for an individual; Indication, Effectiveness, Dosage, Directions, Practicality, Drug–drug interaction, Drug–disease interaction, Unnecessary duplication, Duration, and Expensiveness.

STOPP Criteria: The Screening Tool of Older Person's Prescriptions (STOPP) criteria

START Criteria: Screening Tool to Alert doctors to the Right Treatment is a set of 22 validated criteria, developed by a consensus process involving experts in geriatric pharmacotherapy, aimed to identify potential prescribing omissions in older hospitalized patients.

Medication Review

It is important to review patient's medication periodically to detect side effects, optimize therapy and undertake essential

laboratory tests. The National Prescribing Centre guide to medication review outlines good practice on medicine review. [14] The guide describes three types of medication review: prescription review, compliance and concordance review, and clinical medication review.

Medicine Reconciliation

It is the process of ensuring that when patients are discharged from the hospital, systems are in place to communicate any changes in medications to primary care teams. Even though the concept of reconciliation is not much applicable in our health setting, medicine discrepancies at discharge are common. Improving the discharge process by providing discharge summary, proper explanation of each medication, follow up of high-risk cases (either in person or telephone) and coordination between primary health care can reduce the risk of polypharmacy.

Deprescribing

It is the process of planned and supervised tapering or cessation of inappropriate medicines. The goal is to reduce medication burden while maintaining quality of life. Scott. et. al. [15] have proposed 5 steps for a deprescribing protocol.

1. Ascertain all drugs the patient is currently taking and the reasons for each one;
2. Consider overall risk of drug-induced harm in individual patients in determining the required intensity of deprescribing intervention;
3. Assess each drug in regard to its current or future benefit potential compared with current or future harm or burden potential;
4. Prioritize drugs for discontinuation that have the lowest benefit-harm ratio and lowest likelihood of adverse withdrawal reactions or disease rebound syndromes; and
5. Implement a discontinuation regimen and monitor patients closely for improvement in outcomes or onset of adverse effects.

Further, to improve prescribing and minimize the risks from polypharmacy, the concept of "polypill", use of artificial intelligence and clinical decision support system are being developed in recent years. Reducing medication errors, use of monitored dose systems and the development of guidelines for multi-morbidity could significantly decrease the prevalence of polypharmacy.

Figure: An original sample prescription of Polypharmacy prescribed to a 35 year old Alcohol dependent male at the time of discharge after a hospital stay of 1 month.

Medications prescribed:

1. Disulfiram,
2. Ursodeoxycholic acid,
3. Levetiracetam,
4. Clobazam,
5. Pantoprazole,
6. Liver support (L-Aspartate,, L-Ornithine, Metadoxine and Silymarin),
7. Multivitamin (Alpha lipoic acid, Benfotiamine, Folic Acid, Methylcobalamine, Pyridoxine),
8. Olanzapine,
9. Chlordiazepoxide,
10. Lorazepam,
11. Multivitamin,
12. Acamprosate.

CONCLUSION

Polypharmacy is a common phenomenon, and because of multiple factors, it is on a rising trend. In many cases, it is inevitable and improves quality of life. However, it is not without its adverse consequences and with an increasing number of drugs, the risk increases. For a better understanding of this phenomenon, systematic studies of combination drugs, standardized definitions and guidelines for management of polypharmacy should be promoted. However, a look into the sample prescription provided raises serious concerns about the intent of polypharmacy.

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