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EDITORIAL

JEALOUSY

KUMAR ANIL - SHUKLA S.R.P.

Jealousy as a passion is a boon; Jealousy as an envy is a bane, the former is nature, an expression of the selfish gene, the latter is an expression of nurture, **the former is the kit for gene for propagation of species, hence normal, while the latter is an aberration, hence pathological.**

Jealousy as a passion is normal since not only inbred in human nature, but it is the most basic, all pervasive emotion which touches man in all aspects of human relationship (Buss D.M. 2000) 1. Passion is an emotional fire that propels us in our quests through life, but when it bursts into a flame, it becomes envy, i.e. abnormal. Expression of passion yields life's deepest joy but also the cruelest suffering. We correctly think of passion as a synergistic force; envy is opposed to reasoning and rationality, hence abnormal, so something to be tamed. Passion is the lever that helps lift the mundane to the extraordinary, the mediocre to the excellent. Indeed, if you have not loved or even hated with passion, you have neither reached the heights nor plumbed the depths of emotion. If you have not worked with passion you have been unfair to yourself. Investing more of yourself – body, mind and soul – into life, love, work and relationship spells the difference between boredom, excitement, mediocrity and excellence. The most successful people are those who are able to select careers matching their passion. It is far easier to announce the beginning of a love affair than to admit it has ended, all passion spent (Times News 2012) 2. When we emulate the thoughts and actions of more successful people, ideas and innovation happen better and faster because of collective learning. Working with an edge of rivalry with role model yields better results than when trying to excel in a silo, for it unleashes passion (Nangia 2012) 3.

Jealousy & Possessiveness – a nurture phenomenon is manifested as envy. Jealousy is the most childish emotion of all, hence based on wrong infantile ideas of not being good enough, in the eyes of others, culminating in impressing everybody who matters, entailing that, I – we are not worthy enough, but those who as children had a chance to build self – esteem, a deep back ground sense that they deserve love, will be aware that their worthiness does not depend upon specific other peoples choices culminating in total "SELF" indulgence that is Narcissistic Life Management. This will happen in the form of possessive controlling behavior. Jealousy is proportional and directly connected to negative self – image. Possessiveness also has a healthy side. Those who had a chance to build self –esteem as a child upto 8 years of age posses a deep back ground sense that they deserve love, will be aware that their worthiness does not depend on specific other people's choices. Then they will be able to feel good about themselves and other people even when the person they love, give's attention to other people. They would not need to feel, they will be aware that we can like different people in different ways. On the other hand **the less the self – esteem, the more one has the emptiness, fear of loss, the more he will be inclined to pathological possessiveness emanating from pathological jealousy i.e. envy.** Possessiveness towards one's intimate partner has some routes in the biology and evolution, ***the essence of pathology is the fear that we are not worthy enough*** that something is wrong with us, that somebody else, perhaps without merit, perhaps with more merit, we are afraid, receives something we dearly want. We feel that love and attention is limited, hence we still love by coercive control (Muk Kosjenka 2007) 4.

Extreme jealousy, manifesting as a delusion which has been given many names – the Othello Syndrome, Morbid Jealousy; Psychotic Jealousy; Pathological Jealousy; Conjugal Paranoia, and Erotic Jealousy Syndrome. Such delusionary manifestation is of course psychosis which destroys previously harmonious relationship rendering the hellish nightmares of daily existence. Such phenomenon answers 13% of all homicides of spousal murders. But what about genuine infidelity rage, having caught the spouse in flagrante delicate i.e. actually catching red handed, the spouse having sexual intercourse with an outside, one kills the paramour. This view of jealousy as pathological ignores a profound fact about an important defence designed to combat real threat. Jealousy is not always a reaction to infidelity that might occur... it can be an anticipatory response, a preemptive strike to prevent an infidelity that might occur, is it not emotional wisdom

then? An adaptive response expressed as control mechanism. We, every day observe a husband and a wife on a morning walk, one of the spouse appears a victor and the other the vanquished, observed more carefully there is a chasm between the level of desirability between the two and the one who is more desirable is the vanquished, more often, shall be call this as the psychologically it not physically battered spouse. This is a result of jealousy triggered by circumstance that signal a real threat to a relationship but of course not normal because normalcy is determined as an optimum psychological response as per the actual context e.g. Depression after death of emotionally significant other is mourning for about three months is normalcy, thereafter if depression hangs on it becomes a disease similarly continuous sadness without any reason or depression out of proportion to a fragile reason would be depression as a disease, shall we say Pathological. Nervousness during real uncertainty is not Anxiety Disorder whereas nervousness during no uncertainty is an anxiety disorder.

All of us know that too much or too little of normal emotions such as sadness, worry, concern, care, anger, affection are abnormal. Similarly jealousy is a normal emotion where it operates as a passion congruent with reality in pursuit of personal excellence; but too much or too little jealousy is abnormal. Normal jealousy expresses as passion. Jealousy as a continuum dilates the noumenology of normal and abnormal jealousy as follows :-

Jealousy

Too little		Normal				Extreme
-10	-5	0	+2.5	+5	+7.5	+10
Anhedonia	Lackadailism	Passion	Envy	Hate	Rage	*Delusional Jealousy *Othello Syndrome *Psychotic Jealousy *Pathological Jealousy *Erotic Jealousy *Morbid Jealousy *Conjugal Paranoia

1) Anhedonia – is expressed as absence of desire to do any thing.

2) Lackadailism – is lack of enthusiasm in life.

3) Envy – is Retroflxed Love resulting in intrusion against the adored one expressed as spying in interpersonal context.

4) Hate – is Retroflexed anger a manifestation of inferiority feelings expressed as ambivalent behaviour.

5) Rage – a manifestation of intense Hate which is a manifestation of self assumed superiority feelings expressed as episodic violence. Abnormal jealousy is expressed as Rage a function of mind forged by circumstances.

Abnormal jealousy, as enunciated above, is explained by the specific Innate Module Theory along with Social – Cognition Theory and understood by Ontogeny of Jealousy.

Let us crystallize Normal and Abnormal Jealousy, the former being Nature and the latter being Nurture phenomenon.

NORMAL JEALOUSY = NATURE

Ontogenetic Jealousy

Psycho – Physiological – Built in Neuronal Circuits ADAPTATION REPONSEBuss (2000) [1]
ONTOGENETIC – INNATE MODULE (Harris 2004)[5]

- Tolerance of infidelity for better gene transplant by superior male or female.
- Propagation of spicies
- Inherent Emotional Wisdom

NATURAL SELECTION (Buss et al 1992)[4]
EMOTIONAL COGNITION MODULE (Harris 2004)[5]

- Jealousy between genders
- Inter – paradigmatic inter personal chasm

ABNORMAL JEALOUSY = NURTURE

Phylogenetic Jealousy

Emoto – logical

AMBIVIALENT RESPONSE NURTURE PHENOMENON
SOCIAL – COGNITION (Harris 2004)[5]

- Anhedonia
- Lackadailism
- Envy
- Hate
- Rage
- Extreme Jealousy (Psychotic Syndromes)

Ontogenetically jealousy is expressed as sibling rivalry in infants for parent's resources, the nature aspect of jealousy emanating from the "Innate module – a wired in brain circuit that has different primary triggers in men and women is one of the most celebrated application of an evolutionary approach in psychology. Yet recent evidence suggests , it is not (Harris CR 2004) 5 such jealousy, in the form of infant siblings rivalry as well as rivalry amongst intra – paradigmatic peers is innate thus not pathological. The emotional – cognitive module makes men innately predisposed to jealousy over mates *sexual* infidelity, it makes women innately predisposed to jealousy over mates *emotional* infidelity (Buss D.M. et al 1992) 6. This is natural thus normal.

Since ontogeny recapitulate's phylogeny, jealousy between inter – paradigmatic interactions is normal e.g. jealousy between the Poor and the Rich; Professionally Educated and the semi literates; between intellectuals and the politicians; management and non-management, ruler and the ruled; between different religious groups, such Chasm is an expression of appreciation, thus is normal but when retroflexed it becomes Envy; when the inter-paradigmatic chasm yields anger it is normal but when retroflexed it becomes Hate, which when abreacted becomes Rage. When Envy, Hate and Lust are amalgamated as happens with mind influencing agents Rage is aroused, thus all these are abnormal phenomenon, without being a delusion. Envy, Hate and Rage can be explained in one shot by "Nurture Fault" which can be appreciated by Social – Cognition Theory which states that Mentality is forged by Societal Impact. "Jealous Mentality" expressed as Envy, Hate and Rage on the preponderant side leads to homicide, rape, murder, violence, husband or wife battering, family fracture, commune combats in spurts expressed as unleashed violence in the form of religious discord or fanaticism. While Anhedonia and Lackadailism on the deficit side are manifested as inability to cope with social reality. These are all pathological phenomenon thus elaborate entry in DSM/ICD would be prudent.

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THIS ISSUE

Shukla S.R.P.; Kumar Anil

This issue enables the mental health professionals to dwell upon Nature – Nurture dialectic,. the Psycho pharmacological as well as Psycho therapeutical aspects of mental aberrations.

REVIEW ARTICLES:

The first review article deals with genetics, the nature substrate, captioned "understanding Genomics of Psychiatric Disorders: the expanding horizons" by Basu P and Majumdar PP who cover the molecular aspects of psychiatric disorders and its nuances, thus enabling us to understand the racial differential for appropriation of psycho- pharmacological intervention as also do research accurately by sampling according to Gene Pools. This article also equips all of us with comprehensive references for pin pointed research in this emerging field.

The second article captioned "Childhood Bipolarity – A Review by Soren S, Hembram M, Purty P, Vijay and Bakhla A.K. is a comprehensive review of management of Bipolar Disorder in Childhood, full of erudition, the article kneads out the differential diagnosis of Bipolarity as also co-morbid disorders occurring with bipolar childhood disorder. A compact psychopharmacological as well as psychotherapeutic game plan for the management of childhood bipolarity has been given.

The third review article "cognitive rehabilitation: current trends" by Shivani; Sachcher; Sayeed Neha & Sarkar S, provides us with the methodology of managing cognitive faults due to central nervous system insults.

The fourth review "Agomelatine – A clinical review & role in management of depression by Shah A; Thukral P; Nair D; Palsetia D; Desouza A and Shah N deals with the neuro physiology of melatonin and it's role in remodeling of hippocampal formation as also substantiating the neuro plasticity hypothesis of major depression as a nature defect.

The fifth review article in this section on "Oppositional Conduct Disorder – A brief review by Prasad Aishwarya is of current interest because of escalating incidence of conduct disorder amongst youth due to weakening of family fabric and societal regression culminating in nebulous value system amongst generation "Y". In this paper, Prasad has kneaded out the differential diagnosis and co-morbidity of oppositional conduct disorder in particular and defiant behavior in general, along with needed appropriate therapeutic intervention in such cases.

ORIGINAL ARTICLES:

- The first original article makes us understand that attitude is a function of perception. The caption of this article is "Attitude towards Auditory Hallucinations among schizophrenic patients: Meta Analytic Perspective" is by Ranjan J. Kumar et al covers the differentiation between malevolent and benevolent attitude towards hallucinations, the former being found in schizophrenia but not the latter.

- The second in this category on ADHD subtypes and co-morbid behavioural disorders, in a school based sample by Pandey et al has dealt with the behavioural manifestations of attention deficit hyper activity expressing as inattention, aggression and conduct disorders most commonly in children between 5 – 18 years of age..

- Then comes "Correlation between Emotional Intelligence and Cognitive Symptoms in Schizophrenia by Kumar et al has dealt with social aspects of schizophrenic phenomenology, highlighting inter – personal awareness and interpersonal relationship paucity in schizophrenia.

- The next original article "Perceived Social Support in Female Patients withBipolar Affective Disorder: Impact of Prolonged Hospitalisation on marriage by Mishra P et al deals with the social, cultural, economic and demographic matters in manic depressive psychosis. This paper reflects that factors like economic dependents, frequency of episodes and rural back ground are the markers for impowerish social support in female patients with bipolar affective disorder.

- The next original article is on "Identification of Bipolar Spectrum Disorders in patients with unipolar depression using spectrum diagnostic scale – A pilot study from Eastern India by Mehta V.S. and Das K educates us not to compartmentalise Bipolar and Unipolar as bipolar 1 and 11 disorder but perceive otherwise bipolar disorder at the soft end of the spectrum. Such disorders appear as "mood disorder".

- The 2nd last original article "The cost of the opioid dependence syndrome by Soren S, Lal R, Tripathy B.M. and Anand K. apprises us with the fact that heroin, prescribed opioids and raw opium dependence is most found in the age group of 31 – 40 years, the peak productivity age range, wherein the opioid dependence decreased productivity culminating in decreased wages and earnings as also the economic burden was passed on to the family with obvious negative impact. Treatment of opioid dependence lead to 50% decrease in expenditure with beneficial consequences, for both, the patients and more so for the family. Thus treatment of opioid dependence syndrome would result in improvement of the socio-economic status of opioid dependence population. Further research is warranted since this has a bearing on per capita human productivity, deaddiction centres would help the drug dependents to achieve success as well as improve the quality of life for themselves as well as their family.

- The last original article captioned "Executive Functions in Patients with single and multiple episodes of Mania on CTMT by Yadav Sujit Kumar, Sengar K. S. and Singh Amool Ranjan examines the use of Comprehensive Trail Making Test which probes in to the problems with Psychomotor speed, visual search, sequencing, attention and set shifting appropriatenesh. This research enables the reader to appreciate that Bipolar Disorder with an upswing and Schizophrenia are two sides of the same coin.

CASE STUDY:

- Super sensitivity psychosis – A case report by Das and Sinha enunciate's limbic kindly as the cause of super sensitivity psychosis, hence Gaba agonists have a role to play in schizophrenics relapsing in spite of adequate appropriate ante psychotic medication.

- Neuro-Psychological Profile of Velocardiofacial Syndrome- A case report by Shukla Priyanka, Padhi Debasish and Sengar K.S. describes in detail the congenital anomaly, the Velocardiofacial Syndrome and examines the bio-psycho-social aspects of this rare syndrome. This case study bespeaks of research rigour.

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Review Article :

Understanding the Genomics of Psychiatric Disorders: The Expanding Horizon

Basu Priyadrshi[1], Majumder Parthap P[2]

ABSTRACT:

Genetic factors play a major role in the etiologies of most psychiatric disorders. Psychiatric disorders caused by defects in a single gene that segregate within the family (following a Mendelian inheritance pattern) are easy to screen and hence used in molecular diagnosis routinely. However, a vast majority of psychiatric disorders are caused by the interaction of multiple genetic and environmental factors. The understanding and treatment of these complex psychiatric disorders pose many challenges, because of the clinical overlap of symptoms as well as genetic heterogeneity, which creates a problem in classification of these disorders. Advancements in DNA technologies have enabled scientists to study these disorders in increasing detail. As research progresses, there has been a recent reevaluation of diagnostic criteria and their usefulness in treatment and classification. This is based on the observation that there is more etiological overlap between psychiatric disorders than previously appreciated. As new information on genetic and epigenetic risk factors in psychiatry grows, this review takes a look at how genetic dissection of such disorders has evolved and progressed over the years.

Key words: ***Genomics, Epigenetics, Complex disorders, Schizophrenia, Autism***

Introduction

It is now well established that genetic factors are important in the etiologies of most psychiatric disorders. However, the vast majority of psychiatric disorders do not follow simple patterns of inheritance within a family. This implies that psychiatric disorders are probably caused by the interaction of multiple genetic and environmental factors.

Advancements in DNA technologies have enabled scientists to study complex psychiatric disorders in increasing detail. Coupled with this, the identification and localization of DNA variants throughout the human genome has resulted in a rapid increase in molecular genetic investigations of major psychiatric disorders. Molecular genetics is concerned with the search for the DNA variants, which are responsible for a disorder or which influence its development or outcome.

There are over 300 identified psychiatric disorders. With continuing research, more psychiatric disorders are being identified each year, and many are being re-categorized/re-classified based on DNA and other evidence. It is beyond the scope of this review to cover the entire spectrum of research on psychiatric genetics. We have, therefore, restricted ourselves to such psychiatric disorders that have major genetic underpinnings. We have also discussed, in the following sections, how such genetic knowledge can be useful in diagnosis and in providing mechanistic insights into these disorders.

Molecular genomics of psychiatric disorders

Classical approaches to study genetic disorders

To investigate genetic contribution to the etiology of a disorder, classical approaches have used family and twin studies. In family studies, sets of related individuals are studied. The idea is that if a disorder has a genetic component, the relatives of the person with the condition (proband) are expected to have the disorder more frequently than the general population. Hence, morbidity risk among relatives increases with genetic proximity to the proband. For example, family studies have consistently demonstrated that schizophrenia runs within families. A first-degree relative (parents, offspring, siblings) of an affected individual has a 10% lifetime risk of developing schizophrenia in contrast to a risk of 1% in the general population.(1) Similarly, in such relatives of patients suffering from manic depression the risk is 8% compared to 0.5% in the general population.(2)

In twin studies, a pair of twins is said to be concordant for a condition if both members are affected, and discordant if only one member of the pair is affected. A genetic contribution is indicated if the concordance rate in monozygotic twins (MZ) is significantly greater than the concordance rate in dizygotic twins (DZ). For example, MZ and DZ concordance rates in schizophrenia are ~55% and 15% respectively, indicating a high genetic component.(3) Similarly, in manic depression, MZ twins show disease concordance of up to three times than DZ twins, which again indicates high genetic contribution.(2)

Simple monogenic psychiatric disorders

Genetic models are defined by the observed pattern of inheritance of a disorder or a trait within families. There are three such simple Mendelian models for inheritance. If the inheritance pattern is Autosomal Dominant (AD), only one copy of a mutation is required to express the disease. The risk is equal between sexes, with a morbidity risk of 0.5 in first-degree relatives of a proband and a morbidity risk of 0.25 in second-degree relatives. For example, Huntington's disease is caused by a mutation in one copy of a gene on chromosome 4.(4) If the inheritance pattern is Autosomal Recessive (AR), affected individuals require two copies of a mutation in the same gene, one from each parent. Individuals with one copy of the mutation are carriers. In AR inheritance, siblings have a morbidity risk of 0.25. In the X-linked Recessive model, a mutation on the X-chromosome causes disease in males, while females are usually protected by having two X chromosomes. An example is Fragile-X syndrome, where over 75% of males carrying the mutation have severe mental handicap compared to only 10-20% of females.(5) **Table 1** gives a list of some monogenic psychiatric disorders. Although in some cases, multiple mutations is the same gene might give rise to the disease phenotype, with the advent of modern technical advancements, it is relatively easier and cost-effective to screen larger stretches of DNA encompassing a single gene.

Table 1. List of some Mendelian psychiatric disorders with their causal genes

Disease	Inheritance pattern	Gene location	Primary pa/ MIM#	Gene symbol	Symptoms	References
Huntington's Disease	AD	4p16.3	143100	HTT	chorea, dystonia, incoordination, cognitive and behavioral decline	The Huntington's Disease Collaborative Research Group 1993
Epilepsy, X-linked	X-linked recessive	Xp11.23	300491	SYN1	Epilepsy, with variable learning disabilities and behavior disorder	Garcia et al. 2004
Velocardiofacial syndrome/ D. George syndrome	AD	22q11.21	192430	TBX1	Cleft palate, cardiac anomalies, typical facies, and learning disabilities	Carotte-Cormier et al. 2004
Wolfram	AR	4p16.1	222300	WFS1	Diabetes mellitus, optic atrophy, diabetes insipidus, deafness, renal abnormalities, ataxia, dementia or mental retardation, and diverse psychiatric illnesses	Strom et al. 1998 synonymous
Metachromatic leukodystrophy	AR	22q13.33	250100	ARSA	Psychiatric signs may lead to a diagnosis of schizophrenia	Berger et al. 1999
Myoclonic Dystonia	AD	7q21.3	159900	SGCE	Myoclonic jerks, Dystonia, psychiatric	Zimprich et al. 2001 abnormalities
Cerebral arteriopathy (CADASIL)	AD	19p13.12	125310	NOTCH3	Migraine, strokes, white matter lesions with resultant cognitive impairment	Joutel et al. 1996
Spinocerebellar ataxia 17	AD	6q27	607136	TBP	Ataxia, pyramidal and extrapyramidal signs, cognitive impairments, psychosis, and seizures	Gao et al. 2005
Infantile onset Spinocerebellar ataxia / SCAE	AR	9q34.3	271245	C10orf2	Hypotonia, ataxia, ophthalmoplegia, bowing feet, seizures, and sensory axonal neuropathy	Hakak et al. 2001
Familial early onset Frontotemporal dementia	AD	17q21.31	600274	MAPT	Difficulties in social and personal conduct with loss of volition, executive dysfunction, loss of abstract thought, and decreased speech output	Hutton et al. 1998
Fragile X syndrome	X-linked dominant	Xq27.3	309550	FMR1	Progressive neurologic disorder with cerebellar ataxia and/or tremor, short-term memory loss, executive function deficits, cognitive decline, parkinsonism, peripheral neuropathy and autonomic dysfunction	Jacquemont et al. 2003

Complex psychiatric disorders

Understanding complex disorders

The understanding and treatment of complex neuropsychiatric disorders pose many challenges to medicine, since the most common clinical diagnoses are not defined on the basis of etiology but rather on the basis of clinical classification, behavior and cognition. In most common psychiatric disorders, it is usually rare to have a definite mode of genetic inheritance, because of genetic heterogeneity. In other words, while one gene may contribute nominally to several different disorders, one disorder may be caused by several different underlying genes as well. For example, variations in the brain-derived neurotrophic factor, BDNF, gene have been associated with schizophrenia, bipolar disorder, major depression, anorexia nervosa and bulimia nervosa.(15-19)

To expand, a disease may be caused by one major defective gene with additional modulation by other minor genetic effects or environmental factors. However, in most cases no major gene effect is observed, and the disease is thus truly polygenic. Such traits are determined by a combination of effects from several genetic loci as well as many environmental factors with small, independent and additive effects. Thus, a fundamental question regarding allelic anatomy of complex disorders revolves around how big the effect of the mutation is. Usually, genetic variations that have very large effects on disease tend to be rare in the population. Conversely, common genetic variations associated with a disease tend to carry relatively small risks. Over the past decade, one of the leading theories regarding the allelic architecture of common disorders (affecting more than 1% of the population) is the "Common Disease, Common Variant" (CDCV) hypothesis.(20, 21) The CDCV hypothesis proposes that disease alleles for common diseases were common in our ancestral population, and disease alleles for rare diseases were rare. Due to rapid population expansion, common disease alleles massively increased in proportion. Rare disease alleles have also increased in proportion, but not as much as the commoner alleles, since they were rare in the original population. Another key aspect of the CDCV hypothesis is that new alleles are constantly introduced into the population, with the result that novel variations will substitute both rare and common disease alleles. However, the rate of introduction of new mutations is a relatively slow process. Thus, the fraction of new mutation in the population is predicted to be small compared to common variants, but may represent a considerable proportion of the disease burden for initially rare disorders.(20, 21)

Genetic Approaches for studying complex disorders

The Candidate Gene Approach: If there is an a priori reason to suggest the involvement of a gene in the pathophysiology of the disorder, it forms the basis of a candidate gene study. Once identified as a candidate gene, it is systematically studied to ascertain disease liability.

Linkage and Association Approach: Two different but related methods for investigating the relationship between candidate genetic markers and disease are association and linkage. Linkage is said to occur when two genetic traits are co-inherited rather than independently inherited as predicted by Mendel's second law. If the traits are encoded by genes that exist close together on the same chromosome, then recombination between them will occur very rarely during meiosis. Under these circumstances, the two genetic traits will be passed on to subsequent offspring simultaneously. Linkage analysis requires the study of families in which there are multiple affected individuals and its aim is to detect genes of major effect. Using modern technology, segregation of single nucleotide polymorphisms (SNPs; present throughout the human genome) in the DNA within a family can be determined and compared with their co-segregation with the disease. If they co-segregate, then the disease gene is located close to the polymorphic marker.

An alternative method is the genetic association study. This method looks for an association between one allele of a genetic polymorphism and the disease. For an association study, one requires a large number of unrelated patients and a large number of unrelated unaffected individuals. SNPs very close to the causal genetic mutation are unlikely to be separated because there is very little chance of recombination occurring between them. Thus certain alleles/SNPs will also occur more frequently in patients than in controls. Genetic association studies do not require any major assumption and is capable of detecting even minor susceptibility loci. Nowadays, with the appropriate statistical methods, genetic wide association studies (GWAS) can be used to screen for association of variants at the whole genome level.

Copy Number Variations (CNVs) in Psychiatric disorders

Chromosomal deletions and duplications or rearrangements (translocations, inversions, etc.) have been associated with psychiatric disorders, often caused due to genome instability. Deletion in chromosome 22 (22q11–12), often associated with psychotic and behavioural symptoms, is well-known in psychiatry.(22-24) Recently, genomic hybridization arrays have allowed cytogeneticists to go beyond the microscopic level of resolution and to detect chromosomal alterations at the molecular level, termed as Copy Number Variations (CNVs). A CNV is a segment of DNA greater than 1000 base-pairs with variable copy number compared with the reference genome. CNV regions contained hundreds of genes, disease loci and functional elements. Some studies indicate that these variations are 2 to 3 times more important in scope than the SNPs that are used in genome-wide association studies.(25, 26) Interestingly, a large number of these submicroscopic CNVs were found to be widespread in the genome of otherwise healthy humans. The main challenge is to determine which of these CNVs are pathogenic. Usually, if a CNV co-segregates with the disease in the same family, it is very likely that this CNV is pathogenic. Reports of studies on many psychiatric disorders (e.g., autism, attention-deficit hyperactivity disorder, schizophrenia) support the possibility for a role of CNVs in these disorders.(27, 28)

Major findings from recent genetic studies

Although family-linkage and twin studies have indicated that genetic factors often play an important role in the development of psychiatric disorders, reliable identification of specific genetic susceptibility factors to particular disorders, through linkage or association studies, has proven difficult. This is possibly due to overlap of symptoms, inadequate clinical classification introducing biases, complexity of interactions between genes, environment and early development.(29) Recent research has increasingly focused on links between genes and endophenotypes, that is, specific traits like neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive, or neuropsychological characteristics, rather than disease categories.(30) We shall discuss the inherent vast variability in common psychiatric disorders in the light of modern genomic advances, particularly autism spectrum disorder (ASD) and schizophrenia. Some of the other complex psychiatric disorders are represented in **Table 2**.

Autism Spectrum Disorders (ASD)

Autism is a of development disorder in children which includes deficiency in social functioning and language development, repetitive and ritualistic behavior, tantrums and aggressive behavior.(31) Autism is the most prevalent syndrome among a spectrum of disorders currently grouped under Autism Spectrum Disorders (ASD), including Rett's syndrome (0.006% prevalence), Asperger's syndrome (0.025%), Pervasive Developmental

Disorder Not Otherwise Specified (PDD-NOS, 0.15%), and Childhood Disintegrative Disorder (CDD, 0.001%).(32, 33) ASDs have a world-wide prevalence of approximately 0.1 percent. However, considering the entire spectrum of disorders, it may be as high as 1/150, which may be due to changes in modern diagnostic criteria.(32)

ASD is a common, highly heritable neuropsychiatric condition marked by genetic heterogeneity. It is one of the most familial of all psychiatric disorders, with approximately 90% heritability.(34) The risk to siblings of autistic individuals is at least 20 times higher than among the general population.(35) Over the past decade, large-scale gene discovery efforts have clearly shown that autism is not a simple/Mendelian disorder.(36) Thus it represents an etiologically heterogeneous disorder in which the various genetic or environmental risk factors affect common molecular pathways/ networks in the brain.(37-39) At the same time, despite very strong evidence for a genetic contribution(40, 41), the rate of progress in gene discovery has been slow. However, it is also the case that studies of the genetics of complex disorders, including ASD, have just begun to reach maturity. Over the last five years, with the rapid evolution of genomic tools and methodologies, a tremendous amount of data has been generated and recent findings are offering the first glimpses of the biology underlying common disease conditions.

While the CDCV hypothesis has been a leading school of thought, there are alternate views of genetic architecture of common psychiatric diseases, and autism in particular. The "Rare Variant Common Disease" (RVCD) approach supposes that common disease like ASD may be caused by multiple rare variations in the same gene (allelic heterogeneity) or multiple genes (locus heterogeneity), that lead to a common phenotype.(42, 43) Such variation could either be transmitted from generation-to-generation or de novo. With respect to ASD, gene discovery efforts have also included study of known rare monogenic syndromes that share features with ASD, like Fragile X syndrome, neurofibromatosis, and tuberous sclerosis which show phenotypic overlap with ASD. For example, mutations in MECP2, the Rett Syndrome gene, have been found among cases of idiopathic autism without the Rett phenotype.(44) Also, studies aimed at investigating extreme outlier or rare families that transmit the phenotype in a Mendelian fashion are of special interest.(45)

Rare microscopic chromosomal abnormalities occur at a mean rate of up to 7.4% in autism versus less than 1% in the general population, the most common of which are maternally inherited duplications at 15q11-13.(46-48) De novo deletions or translocations have also been reported at Xp22.3.(49) A functional mutation at this region was reported in the gene NLGN4X, a neuronal adhesion molecule important for specifying excitatory versus inhibitory synapses.(50, 51) Genes coding for molecules that interact with NLGN4X, including SHANK3 and NRXN1 have both been strongly implicated in ASD. The convergence of findings showing multiple mutations in a relevant molecular pathway as opposed to just a single gene is important for confirmation of rare variant findings and autism.(52-55)

Candidate gene association studies have also aimed at identifying common alleles contributing to ASD. While potential flaws are found in many studies of ASD, several recent candidate gene investigations have been discovered. The genes EN2, MET and CNTNAP2 have emerged as relatively strong candidates from these recent single locus association studies. Of these, Contactin Associated Protein 2 (CNTNAP2), has emerged recently as a candidate for involvement in a range of developmental disorders including autism, language development, and seizure, based both on common and rare variant findings.(56-60)

The first large-scale genome-wide association study (GWAS) showed significant association of ASD to an intergenic region on chromosome 5 – 5p14.1, mapping between the neuronal adhesion molecules Cadherin 9 and Cadherin 10.(40) In recent years, several studies have provided additional evidence for the role of rare variation and particularly Copy Number Variations (CNVs), in Contactin 4.(41, 61, 62) In general, contactins bind to contactin-associated proteins to mediate their functions, at least in the peripheral nervous system. CNTNAP2 was first and so far most convincingly tied to ASD.(63) Also, both de novo deletions and duplications at 16p11.2 have been identified in patients with ASD.(64, 65). Weiss et al. (2008) found these in ~1% of autism case samples compared to 0.1% in the general population.(65) Marshall et al. (2008), in addition to finding support for the 16p.11 locus, identified several new candidates, including DPP6 and DPP10.(66) It is of note that this deletion was observed in other psychiatric disorders including bipolar disorder (1/420), attention-deficit hyperactivity disorder (1/203), schizophrenia (1/648), dyslexia (1/748) and anxiety, panic, depression or addiction (1/3000).(28) Newly identified genes using this method include CNTN4, BZRAP1 at 17q22 and MDGA2 4at 14q21.3.(41, 67) Recently, a number of reports have been published reporting a spate of rare de novo and transmitted CNVs in ASDs.(68-70) Levy et al. (2011) studied a large cohort of families with a single affected child with at least one unaffected sibling

(multiplex families were excluded). Apart from rare deletions and duplications, they report role of inherited "ultrarare" duplications. They also report several hundred target loci causal to ASDs, which although point to a great diversity of genetic causes, but also suggests functional convergence of the pathophysiology of the disease.(68)

Morrow et al. (2008) conducted a large-scale homozygosity mapping study in consanguineous Middle Eastern families. They found several large, rare, inherited homozygous deletions that disrupted either the coding or potential regulatory regions of brain-expressed transcripts, including DIA1, NHE9, PCDH10 and CNTN3. They also found rare amino acid changes in NHE9 in nearly 6% of patients with both autism and epilepsy compared to 0.63% of controls. The results suggest that changes in activity-regulated gene expression during brain development may contribute to ASD.(71)

Since there is not a single gene or genetic test that definitively diagnoses autism, the diagnosis of autism remains largely a clinical/syndromic one. However, this does not preclude the usefulness of genetic testing in aiding in diagnosis, family planning or prognosis.(72) There are several institutional guidelines that provide recommendations regarding genetic testing in autism.

Schizophrenia

Schizophrenia is a psychotic disorder of severely inappropriate emotional responses, with patients suffering from delusions and hallucinations. There may be impairment of cognitive function, disordered thinking and concentration, as well as erratic behavior. Schizophrenia is a common disorder with a lifetime prevalence of approximately 1%.(73)

In 1988, Bassett et al. (1988) reported a Chinese family in which members with a diagnosis of schizophrenia had a partial trisomy of chromosome 5.(74) This finding was not replicated in subsequent studies. That genetic factors play a major role is evident from twin studies that show heritability for schizophrenia to be > 80%. However, identification of susceptibility genes has been slow, because of the lack of diagnostic biomarkers (physiological, biochemical, etc.) which can be used to define the parameters of the disorder. The uncertain relationship between diagnosis and underlying etiology has created difficulties for research. For example, while schizophrenia and bipolar disorder have been historically classified into non-overlapping categories with distinct etiologies, this separation is partially artificial.(29) Despite this, there have been a few notable successes in the identification of genetic risk factors. For a list of genes that have been associated with Schizophrenia as well as some common complex disorders, see **Table 2.**

Table 2. List of some complex psychiatric disorders showing association with multiple genes (data compiled from Online Mendelian Inheritance in Man)

Disorder	Phenotype MIM#	Symptoms	Affected/Associated Genes
Schizophrenia SCZD1,	181500	Psychotic disorder, inappropriate emotional responses, delusions and hallucinations, impairment of cognitive function, disordered thinking and concentration, erratic behavior.	SC2D12, MTHFR, CHI3L1, DISC1, DISC2, SYN2, DRD3, SCZD3, DTNBP1, SCZD5, SCZD6, SCZD11, GPR48, SCZD2, DAO, HTR2A, SCZD7, DAOA, AKT1, SCZD10, SCZD8, COMT, RTN4R, APOLA, APOL2
Obsessive-compulsive disorder (OCD)	164230	Recurring obsessions and/or compulsions	BDNF, COMT, HTR2A, SLC6A4, HTT, NTRK3
Bipolar affective disorder / Major Affective disorder/ Manic Depressive Psychosis	125480	Episodes of dysphoria, episodes of mania (bipolar I) or hypomania (bipolar II) interspersed with periods of depression	SLC6A3, HTR4, ABCA13, DRD4, BDNF, CLOCK, SLC6A4, BCR, COMT, XBP1, TRPM2, MTND1, TPH2
Anorexia nervosa	606788	Eating disorder, obsessive fear of weight gain, low body weight	COMT, BDNF, MAOA-uVNTR, 5-HTTLPR
Autism Spectrum Disorders (ASD)	209850	Deficiency in social functioning and language development, repetitive and ritualistic behavior, tantrums, aggressive behaviour	NLGN4X, SHANK3, NRXN1, EN2, MET, CNTNAP2, CONTACTIN4, DPP6, DPP10, CNTN4, BZRAP1, MDGA2, DIA1, NHE9, PCDH10, CNTN3
Attention Deficit-Hyperactivity Disorder (ADHD)	143465	Childhood-onset behavioral disorder, persistent inattention and/or hyperactive-impulsive behavior results in impaired social and/or academic functioning.	DRD5, SLC6A3, HTR1B, ADRA2A, DRD4, SCN9A, SNAP25, COMT
Major depressive disorder (MDD)	608516	Major depressive episodes, changes in appetite, weight, sleep, and psychomotor activity, decreased energy, feelings of worthlessness or guilt, difficulty thinking, concentrating, or making decisions, recurrent thoughts of death or suicidal attempts, impaired social functioning.	MTHFR, CREB1, FKBP5, TPH1, TPH2, HTR2A, MDD1, MDD2, CHRM2, TORIA, DRD4, SLC6A4, BCR

Role of Epigenetics in psychiatric disorders

In recent years, there have been a large number of studies indicating the importance of the effect of the environment on genome regulation through epigenetic processes, resulting in the silencing of key regulatory genes as well as re-expression of key genes. The term Epigenetics, which literally means "in addition to genetics", has evolved to include any process that alters gene activity without changing the DNA sequence, and leads to modifications that can be transmitted to daughter cells. However, unlike genetic mutations, epigenetic changes

are potentially reversible and therefore hold the promise of being treatable or preventable through drugs, diets/ supplements and other environmental influences.

Also, since epigenetic changes may precede pre-symptomatic stages of many diseases, such changes, if detectable, can serve as important biomarkers for early disease detection and prognosis. Although DNA methylation, histone modification and small regulatory RNA (eg. microRNA) mediated regulation of gene expression are three major epigenetic mechanisms identified, most technological advancements have been achieved in the DNA methylation field. Aberrant DNA methylation (hyper/ hypomethylation) is an epigenetic change that involves the addition/removal of methyl groups to cytosine residues in the context of a CpG dinucleotide. This usually occurs in the promoter region of a gene, which contains a high density of CpG dinucleotides, termed CpG islands. The methyl group addition interferes with binding of transcriptional proteins to the gene promoter (regulatory region of a gene) resulting in long-term silencing of that gene. On the other hand, promoter hypo-methylation may result in re-expression of key genes.

In recent years there has been an explosion of data indicating the importance of the effect of environment on the genome regulation through epigenetic processes, especially in the development of cancers, systemic lupus erythematosus, cardiovascular disease (atherosclerosis, homocysteinemia), psychiatric disorders (schizophrenia, bipolar disorder, major depressive disorder), chronic obstructive pulmonary disease, reproductive dysfunction and aging.(75-81)

The correlation between psychiatric disorders and the states of genomic methylation has been under extensive investigation for a long time.(81, 82) Initially, several studies pointed to abnormal methylation of the promoter of the reelin gene (RELN) and glutamic acid decarboxylase gene (GAD67) in schizophrenia and bipolar illness.(83-87) The reelin protein is necessary for neuronal migration and synaptogenesis during brain development. Another group found three fold higher methylation in the serotonin 5-HT1A gene promoter in schizophrenic or depressed patients than in controls.(88) Mill et al. (2008) studied DNA methylation changes in the frontal cortex and germline tissues associated with schizophrenia and bipolar disorder in microarrays of gene promoters.(89) Psychosis-associated DNA methylation changes were identified in numerous genes involved in glutamatergic and GABAergic neurotransmission, brain development, and other processes functionally linked to disease etiology, and corresponded to reported changes of steady-state mRNA levels associated with psychosis (eg. BDNF).(89) Other genes that have abnormal DNA methylation patterns in schizophrenic patients include COMT, SOX10 and syt11.(90-92)

McGowan et al. (2008) studied the rRNA gene that encode ribosomal RNA in the genome of brain tissue of suicide subjects, and found hypermethylation throughout the promoter and regulatory regions, consistent with reduced rRNA expression in the hippocampus.(93) Poulter et al. (2008) demonstrated that DNMT3b gene (DNMTs; the enzymes which catalyze the addition of the methyl group on CpG sites) expression is increased in suicide subjects compared with control subjects in the brain cortex, linked with female bias, and consistent with the observation that Major Depression Disorder (MDD) is twice as prevalent in women.(94)

However, epigenetic changes being stable but reversible, there is a possibility to use suitable drugs that can amend epigenomic defects by therapy.(95) DNA methyltransferase inhibitors and histone deacetylase inhibitors are being explored for epigenomic therapy, and two types of DNA methylation inhibitors, azacitidine and decitabine, have generated much interest in cancer therapies.(75, 96)

Conclusion

Modern technical advances have accelerated progress in psychiatric genetics. Single gene Mendelian disorders are easy to screen and used in molecular diagnosis routinely. For complex disorders, the collection of large cohorts via international collaborations, together with array-based DNA technologies permitting genome-wide interrogation of variation, have resulted in major advances. More progress is expected with data coming from massively parallel sequencing (Next gen sequencing) of partial and whole genomes. Although such experiments are gradually becoming routine, interpretation of results, particularly in the context of diverse and overlapping phenotype data (as is presented in psychiatric disorders), will require major computational infrastructure and possibly new computational methods.

As etiological research into psychiatric disorders progresses, there has been a recent reevaluation of diagnostic criteria and their usefulness in treatment and classification. This is based on the observation that there is more etiological overlap between psychiatric disorders than thought previously. In fact, they might better be described as domains of disorder-related traits rather than separate categories. The view that many complex

psychiatric disorders are not separate entities but are intervals in a continuous spectrum, is supported by evidence coming from epidemiology and genetics. Also, gene-environment interactions that affect the genetic and epigenetic status of an individual are being highlighted to influence psychological traits. Such interactions may be the cause of development of certain personality and psychiatric traits. Recent epidemiological studies have revealed that the development of some traits common to psychiatric disorders, such as antisocial behavior or depression, can result from environmental insults that may have occurred prior to the onset of illness in some children that carry certain genomic variants that sensitizes them to these insults.(97)

As the list of new information on genetic risk factors in psychiatry grows, the most challenging aspect will be to understand the manner by which these changes affect the development and function of regions in the brain. It is probable that instead of looking at individual genes, genetic circuits and pathways that are disrupted by variations and are affected in disease will be targeted for therapy. With these rapidly occurring changes, it is vital for clinicians and counselors to keep abreast of these new developments. Moreover, it is important to keep in mind that many of the formal diagnostic criteria and analyses were developed prior to the recent explosion of genetic data, and consequently tend to underestimate the now-demonstrated value of these approaches. Current literature recommends that there is increased need for genetic testing with a decreasing threshold for obtaining such tests. This is well justified as more is learned about the genetic causes of psychiatric disorders and as tests become more accurate and less expensive.

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Review Article :

CHILDHOOD BIPOLARITY: A REVIEW

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ABSTRACT:

Mood disorder, in form of both depression and bipolar variant is known since antiquity though by different names at different time. Like most of the mental disorders the focus always hovered around the adult population and 'pediatric' or 'childhood' bipolar disorder remained neglected. Though, recent workers have identified 'childhood variant' as gateway to understand the pathophysiology of bipolar disorder better. Current review is an attempt to delineate the historical aspect of childhood bipolarity, highlight the difference from adult bipolarity and summarise the treatment with special reference to pediatric population.

Keyword: ***childhood bipolar disorder, pediatric bipolar disorder, treatment.***

Mood disorders have a long pedigree, traceable from classical antiquity to the modern era. Early clinical observations between the mid-19th and early 20th centuries accepted the presence of mania and clinical depression in children and adolescents, but from the 1930s to the recent past, BPD was widely considered rare before puberty. In 1838 Esquirol described three cases of prepubertal mania and melancholia. In the 1880s, Moreau de Tours described excited psychotic states in children, Ritti (1883) reported a paediatric case of circular psychosis (now BPD) starting at age 12, and Emminghaus (1887) and his contemporaries (Porot & Vicario-Kiener, 1961) noted many symptomatic similarities between adult and pediatric mania and melancholia. Between 1900 and 1910, Soukhanoff & Gannouchkine (1903) found an onset before age 15 in 18% of 84 BPD patients, and Friedman (1909) distinguished three types of pediatric BPD:

-periodic psychosis with brief alternating episodes of depression and manic excitement and short euthymic intervals;

-isolated episodes of depression or excitement, sometimes related to stress;

-and brief episodes of mild depression or excitement progressing to more typical cyclic BPD in adulthood.

Other authors, (Baruk & Gevaudan, 1937; Rumke, 1928; Ziehen, 1911) anticipating recent studies of secondary mania, (Baldessarini, *et al.*,1996) observed isolated episodes of mania in medical conditions such as fever or neurological disorders (epilepsy, chorea, mental retardation). In his seminal early textbooks, Ziehen (1911) classified BPD in children as involving single or recurring episodes of mania, or circular (bipolar) insanity, more commonly the latter. In the 1920s, Rumke (1928) described mania as the most frequent psychosis in children; and Homberger (1952) noted the frequent occurrence of anxiety and of mixed mood states in children with BPD. Since midcentury, several series of early onset BPD cases have been reported. In 18 cases of major mood disorder before age 16 years, Campbell (1952) found that a third represented BPD, that mild depression or mania were often misdiagnosed as other illnesses, and that many children severely ill with BPD had been diagnosed as schizophrenic. In children under age 11 with BPD, Spiel (1961) reported rapid mood shifts, irritability, anxiety or apathy, and disturbed sleep to be common, and Stutte (1963) found episodes to be shorter than in adults.

To expand and accelerate research on mood disorders, the National Institute of Mental Health (NIMH) (NIMH, 2001) developed a project to formulate a strategic research plan for mood disorder research. One of the areas selected for review concerns the development and natural history of these disorders. Expanded knowledge of pediatric-onset bipolar disorder identified was as a particularly pressing issue because of the severity of the disorder, the controversies surrounding its diagnosis and treatment, and the possibility that widespread use of psychotropic medications in vulnerable children may precipitate the condition. The Workgroup recommends that NIMH should establish a collaborative multisite multidisciplinary Network of Research Programs on Pediatric- Onset Bipolar Disorder and identify several pressing questions and three high-priority recommendations

for better understanding early-onset bipolar disorder. The first of these recommendations, to establish a Collaborative Network of Research Programs on Paediatric-Onset Bipolar Disorder, judged the most important of the seven recommendations made by the Workgroup. Questions identified include the following: How common is bipolar disorder in children? How does it differ from adult-onset bipolar disorder? What are the earlier signs and symptoms of paediatric bipolar disorder? What is the relationship of ADHD and other disruptive disorders to paediatric-onset bipolar disorder (Costello, 2002)?

While it is clear that relatively few children have a classic adult-like presentation of bipolar disorder (BD), children with severe irritability, hyperactivity and distractibility are exhibiting a "broad phenotype" of PBD (Leibenluft, Charney, Towbin et al., 2003; NIMH, 2001). Nonetheless studies of children with either classic BD symptoms or the "broad phenotype" suggest that PBD is both markedly impairing and treatment-resistant, increasing the demand for relevant information and research (Biederman, Faraone, Wozniak et al., 2005a)

Clinical Presentation

The Course of Bipolar Youth (COBY) study in the USA recruited 263 children with clearly episodic bipolar illness (Axelson, Birmaher, Strober et al., 2006). Of the children in the COBY study, 92% had euphoria and 84% had irritability, indicating that most youth with PBD have both symptoms. Over 2-year follow-up, patients (n = 152) had mixed mania or rapid cycling 29% of weeks, significantly more than BD adults (Birmaher, Axelson, Strober et al., 2006). In another sample of 90 children with clearly episodic BD, 86% had elevated mood, while 92% had irritability; also, 50% had a rapid cycling course, and periods of euthymia were identifiable but brief (Findling, Gracious, McNamara et al., 2001).

Thus conclusions can be drawn from the literature on the phenomenology and course of PBD. First, data from the COBY study and Findling, Gracious, McNamara et al. (2001), contradict frequent statements in the literature that children with BD do not have euphoria, because almost all patients in these studies experienced euphoria, in addition to irritability. studies support the contention that early-onset BD is associated with high episode frequency (Birmaher, Axelson, Strober et al., 2006; Findling, Gracious, McNamara et al., 2001. The data do not indicate that children with BD have a non-episodic illness, because several investigators have recruited sizable samples of children with clearly defined episodes meeting DSM-IV duration criteria. And consistent with the observation that children tend to cycle more frequently than adults with BD, all studies agree that PBD is a very impairing illness, leaving affected children symptomatic most of the time.

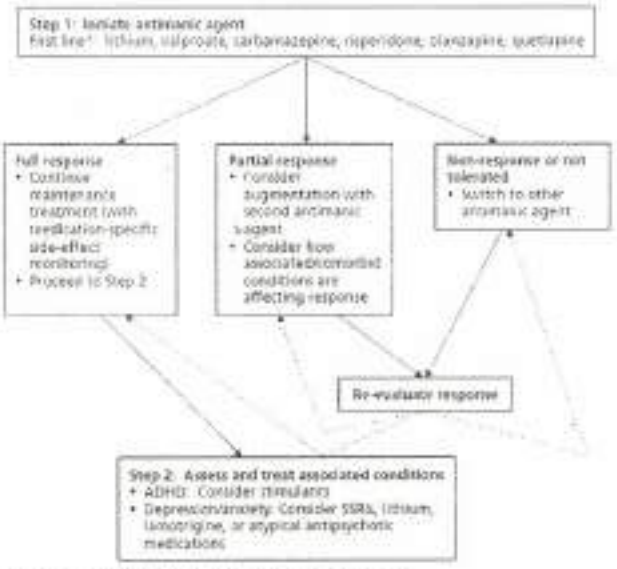
Assessment

When assessing comorbid illnesses, clinicians should diagnose such illnesses only if symptoms are present when the patient is not in an acute mood episode (Axelson, Birmaher, Strober et al., 2006; Dickstein, Rich, Binstock et al., 2005b). For example, a child with BD should be diagnosed with ADHD only if ADHD symptoms are present when he or she is euthymic or subsyndromally ill. Conversely, for a symptom such as distractibility to count toward the diagnosis of mania in a child with ADHD, the distractibility must worsen significantly during the putative manic episode. ADHD can be distinguished from mania in those children with ADHD alone do not have distinct episodes of mood change accompanied by DSM-IV-TR "B" criteria of mania. Similarly, BD youth with associated ADHD and oppositional defiant disorder (ODD) may have severe irritability, but irritability resulting from ADHD or ODD is distinct from manic irritability in that only the latter occurs, or worsens, during distinct time periods that last days or weeks and during which "B" mania criteria also occur. (DSM-IV-TR "B" symptoms of mania or depression (e.g., sleep and activity changes, increased distractibility)) adolescents should be assessed for substance abuse, because cocaine, amphetamine and a number of other illicit substances can cause symptoms resembling those of mania.

Treatment Guidelines For Paediatric Bipolar Disorder

These treatment guidelines arose out of a need first voiced by members of the Child and Adolescent Bipolar Foundation (CABF), who noted that clinicians who treat children and adolescents with bipolar disorders (BPDs) are in desperate need of guidelines regarding how to best treat these patients. In July 2003, a group of 20 clinicians and CABF members met over a 2-day period to develop these guidelines. There were four work groups: diagnosis, led by Mary Fristad; comorbidity, led by Boris Birmaher; and treatment, in two groups led by Karen Wagner and Robert Findling, respectively. These guidelines are not intended to serve as an absolute standard of medical or psychological care but rather to serve as clinically useful guidelines for evaluation and treatment that can be used in the care of children and adolescents with bipolar disorder. (Findling et al., 2005)

Clinicians attempting to prescribe evidence-based treatment for PBD are confronted by a dearth of randomized placebocontrolled trials (RCTs) that precludes designating any psychopharmacological or psychotherapeutic treatment as having "strong" evidentiary support. Given the paucity of pediatric data, clinicians often rely on data from adult BD. However, caution is urged in basing treatment on adult data, because youth sometimes respond differently from adults. children clearly meeting DSM-IV-TR criteria for bipolar disorder who, like adults with the illness, are typically too severely impaired to benefit from psychotherapeutic approaches without initial stabilization with pharmacotherapy. This is the population that is generally targeted in RCTs of medications. In children exhibiting the "broad phenotype" of PBD, whose major presenting problem is non-episodic irritability, psychosocial approaches, including interventions with the child, family and school environment, may be particularly important.



Pediatric bipolarity psycho-pharmacology algorithm. Kowatch *et al.* (2005a).

Pharmacotherapy of Mania

Mania should be the initial treatment focus in BD, because antimanic medications not only reduce manic symptoms but may also prevent activation secondary to antidepressants or psychostimulants. Currently available antimanic medications include: Lithium, Antiepileptic medications (AEDs, e.g. valproate and carbamazepine) and atypical antipsychotic medications. In general, relatively weak support exists concerning the efficacy of any of these agents in PBD. This complicates efforts to select any one agent as a first-line treatment and emphasizes the importance of thorough discussions with patients and their families concerning the available data on each agent's efficacy and safety. The detailed discussion of individual agent is beyond the scope of this review.

Pharmacotherapy of Depression in PBD

No RCT has targeted bipolar depression in children or adolescents.RCTs in adult bipolar depression demonstrate efficacy for lamotrigine, quetiapine and the combination of olanzapine plus fluoxetine (Altshuler, Suppes, Black et al., 2003). Of note, some evidence suggests that the risk of antidepressant-induced mania is higher in pre-pubertal children than in older adolescents or adults (Martin, Young, Leckman et al., 2004; Rey & Martin, 2006).

Treatment Of Comorbid Psychiatric Disorders

Most children and adolescents with BPDs have other coexisting (comorbid) psychiatric disorders, particularly ADHD, oppositional defiant disorder, conduct disorder, anxiety disorder, and, during adolescence, substance abuse. The treatment plan should be modified to include treatment of each disorder because comorbid conditions worsen the prognosis of BPD. Before treating the comorbid disorder(s), it is important to first stabilize the symptoms of BPD. Once the bipolar symptoms are stabilized, the need for treatment of comorbid disorders should be reviewed. If the symptoms of the comorbid condition(s) are negatively affecting the child's psychosocial or academic functioning, then treatment is warranted. Whenever appropriate, using psychosocial therapies to treat coexisting disorders is recommended (e.g. using CBT to manage depression).

Although it is important to treat most of the impairing comorbid symptoms as soon as possible, it is best to begin treatment for each comorbid disorder sequentially, one at a time after the BPD has been adequately treated. It is recommended to introduced medications one at a time, if possible, to discern the benefits and side effects of each agent.

Attention-Deficit/Hyperactivity Disorder

ADHD is one of the most common comorbid conditions, occurring in 70% to 90% of prepubertal children

and 30% to 40% of adolescents with BPD (Kafantaris *et al*, 1998;). Currently, the medications used to treat ADHD include the stimulants (methylphenidate and derivatives of amphetamine) and nonstimulants (atomoxetine, bupropion, the tricyclic antidepressants), and to a lesser extent the a2-agonists (clonidine and guanfacine) (Biederman *et al*, 2004). Of all these medications, stimulants are the agents of choice for ADHD uncomplicated by BPD. Apha 2-agonists are helpful for the aggressive behavior in children with ADHD (Connor *et al*, 2002).

Oppositional Defiant and Conduct Disorders

If a child has BPD and the behavior problems appear to be secondary to the mood disorder (mania, depression, or both), the panel recommended first optimizing the treatment of the BPD. medications used for the treatment of BPD such as lithium and divalproex (Steiner *et al*, 2003), the first generation of typical antipsychotics, and the atypical antipsychotics have been found useful for the management of behavior disorders, Importantly, many children with behavior disorders have ADHD; in these cases, the use of the stimulants may be warranted, particularly in the reduction of aggression. (Biederman *et al*, 2004).

Anxiety Disorders

Comorbid anxiety disorders can be treated using psychotherapy and/or pharmacological interventions. The SSRIs have also been found to be efficacious for the treatment of these disorders, but caution should be used because these agents may trigger manic, mixed, or rapid cycling episodes. Therefore, in most cases, particularly in patients with BPD-I, before attempting to use SSRIs to alleviate the anxiety disorder, it is advisable to first stabilize the BPD. The benzodiazepines have been shown to be efficacious for the treatment of adult anxiety disorders, but only a few studies with small samples have been conducted in children with anxiety (Bernstein & Shaw, 1997).

Substance Abuse

It is important to determine whether the mood symptoms were present before substance abuse began or if the mood changes are the result of substance abuse. If it is clear that the person has both substance abuse and BPD, both conditions need to be treated simultaneously without delay. A placebo-controlled trial in adolescents with comorbid BPD and substance dependence disorders showed that lithium was an efficacious treatment for both disorders (Geller *et al*, 1998). A number of family-related factors, such as parental alcoholism or other substance abuse, poor parent–child relationships, low parental support, inconsistent or ineffective discipline, and poor parent supervision and management of the teen's behavior, have been identified as risk factors for the development of substance abuse among teens.

Management of Suicidal Behaviors

First step is to evaluate whether the child is safe and whether the treatment needs to be carried out in an outpatient or inpatient setting. The data regarding long-term use of lithium are compelling: It is associated with an eightfold reduction in suicide and reported attempts in adults with BPD (Baldessarini & Jamison, 1999). Specific psychosocial therapies for the management of ongoing suicidality such as dialectic behaviour therapy, if available, should also be considered (Rizvi & Linehan, 2001).

Pervasive developmental disorders (PDD)

Patients with paediatric bipolar disorder and PDD should be initially treated with an atypical antipsychotic (e.g. risperidone), and mood stabilizers should be added as necessary. The use of other medication to target other PDD symptoms should be considered, taking into account that some medications may destabilize mood. Patients should be referred to an appropriate PDD programme when available.

Migraine or epilepsy

For those with paediatric bipolar disorder and seizures or migraines, the mood stabilizer chosen should be an anti-migraine agent (eg. carbamazepine, valproate).

Other Psychiatric and Medical Conditions

Youths with BPD who are experiencing significant tics and who have behavioural symptoms associated with PDD should be initially treated with an atypical antipsychotic, and other mood stabilizers should be added as necessary. For youths with seizures or migraines in addition to BPD, medications that target both disorders, such as divalproex, carbamazepine, and oxcarbazepine should be tried first. Female patients with significant premenstrual dysphoria may be offered SSRIs after mood stabilization with lithium, divalproex, or other mood stabilizers.

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Cognitive Rehabilitation: Current Trends

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ABSTRACT:

Cognitive rehabilitation (CR) is a therapeutic approach designed to improve cognitive functioning after central nervous system insult. It includes an assembly of therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem solving, and executive functions. There have been evidences to prove that cognitive rehabilitation plays a major role in restoration of the cognitive functioning. There are various approaches for this but nowadays various new techniques are added so that the success rate increases. Various Indian studies are being carried on this area.

Key words: ***Cognitive rehabilitation, cognition.***

INTRODUCTION

The care of people with mental and behavioral disorder has always reflected prevailing social values related to the social perception of mental illness. Impairment cognitive functions are a significant cause of disability after brain injury and stroke which often leads to residual deficits in the physical and psychological spheres. Cognitive rehabilitation (CR) is a therapeutic approach designed to improve cognitive functioning after central nervous system insult. It includes an assembly of therapy methods that retrain or alleviate problems caused by deficits in attention, visual processing, language, memory, reasoning, problem solving, and executive functions (Sohlberg & Mateer 2001). CR consists of tasks designed to reinforce or re-establish previously learned patterns of behavior or to establish new compensatory mechanisms for impaired neurological systems. Cognitive rehabilitation may be performed by a physician, psychologist, or a physical, occupational, or speech therapist. Cognitive rehabilitation can be defined as an intervention in which patients and their families work with health professionals to restore or compensate for cognitive deficits hereby improving the patient's everyday functioning

APPORACHES IN COGNITIVE RHABILITATION

Cognitive rehabilitation is a systematic, goal – oriented treatment program aimed at improving cognitive functions and to increase the level of self-management and independence after brain damage.. Here described some of the earlier approaches to cognitive rehabilitation.

Goldstien (1942) proposed behaviour therapy as a way of managing cognitive deficits. In which patients were treated by training discrete behaviours related to the cognitive areas of memory, perceptual ability, language, and motor skills. Token economy served as a supplementary strategy for motivating the patient to continue the program.

In 1986, Prigatano put forth a four step process which combines psychosocial and neuropsychological interventions for cognitive recovery. The steps were:

1) Reducing the generalized cognitive confusion by systematically helping patients to improve their attention skills.
2) Through individual and group counselling patients are made aware of their strengths and weakness.
3) Patients are helped to recognize the need for compensatory behaviours and in final step, cognitive deficits are addressed, and followed by that there emerged some programs like General Stimulation Approach, Functional Adaptation Approach, Restorative approach or Compensatory approach.

A small description is provided in the following table;

APPROACH	TECHNIQUES USED	PRINCIPLE
General Stimulation Approach	Cognitive retraining workbooks or microcomputer programs etc	Stimulation of cognitive processing will result in improvement in mental functions

Functional Adaptation Approach	Training provided in a naturalistic or living situation	Cognitive functioning cannot be improved with specific retraining hence it should be carried out in a wholly functional context
Restorative Approach (AHRO, 1999)	Auditory, visual and verbal stimulation and practice, number manipulation, computer-assisted stimulation and practice, performance feedback, reinforcement, video feedback	Repetitive exercise serves as restorative function. Mainly targets the improvement of internal cognitive processes with a goal of generalizing improvements in real-world environments.
Compensatory Approach	Visual cues, written instructions, memory notebooks, watches, beepers, computers and other electronic devices to trigger behaviour	It aims at developing external assistance and encourages and reinforces an individual's remaining strengths.

Besides this there are some other approaches or techniques that are used in cognitive rehabilitation, such as environmental interventions, which mainly focuses on changing aspects of the injured individual's environment so as to reduce behavioural and functional impairments (Sohlberg & Mateer, 2001).

NEW TECHNIQUES

There are some new techniques that have found their way in the rehabilitation programs

A) Virtual Reality- Virtual reality (VR) can be viewed as an advanced computer interface that allows the user to interact and become immersed within computer-generated simulated environments. Although media hype may have oversold it's potential at this early stage in the technology's development, a uniquely suited match exists in its application to cognitive assessment and rehabilitation. Through its capacity to create dynamic multisensory, 'real-life' stimulus environments, within which all behavioral responding can be recorded. Its importance has now been recognized as a new tool for the study, assessment, and rehabilitation of cognitive processes (Rizzo and Buckwalter, 1997)

B) Drama technique - The use of drama techniques in the therapy of individuals with traumatic head injuries is a new addition to cognitive rehabilitation. The success of a pilot programme using drama techniques as a means of developing the social-communication, cognitive and motor skills of individuals with head injuries points the way to a new and useful cognitive rehabilitation tool (Stensrud et al., 2006)

C) Posit science's Brain fitness program- The Brain Fitness Program features six computer-based exercises for use on a PC or Mac. These exercises speed up and sharpen how the brain processes and remembers sounds. Scientific studies show the Brain Fitness Program helps you in a) Remember more of what you hear b) Keep up with conversations (even in noisy places) with friends and family, at work, while volunteering, etc. c) Pick up more details in conversation, music, movies, and every sound-rich setting d)The exercises adapt to individual level, and give constant feedback about progress. The program is easy to use, even for computer novices.

D) Music therapy: It consist of using music therapeutically to address physical , psychological, cognitive or social functioning for patient of all ages. Because music therapy is a powerful and non-invasive medium, unique outcomes are possible. Available European literature suggests that music therapy is capable of alleviating poor executive functioning in schizophrenia (Glicksohn & Cohen 2000) music induced reduction in arousal enabling patients to allocate more attention to task in hand.

E) Direct instruction (DI): Instruction is an essential component of effective cognitive rehabilitation, which requires teaching or re-teaching a variety of skills and concepts to people with compromised learning. Currently, the field lacks a cohesive set of principles to guide clinicians' instructional behaviours. A review of the literature in related fields, in conjunction with findings in neuropsychology, reveals evidence-based principles that lead to effective instructional design and implementation (Sohlberg et al., 2000). Case studies suggest that Direct Instruction is a promising approach for teaching both academic and behavioral skills to students with TBI.

EVIDENCE BASED STUDIES OF EFFICACY IN VARIOUS DISORDER:-

Traumatic Brain Injury (TBI): Various studies was done where cognitive rehabilitation was used in.

Cicerone (2004) conducted a nonrandomized, controlled intervention trial to evaluate the effectiveness of an intensive cognitive rehabilitation program compared to a standard neuro-rehabilitation program for patients with TBI. The Intensive group exhibited a significant treatment

effect compared to the standard neuro-rehabilitation program group. The Intensive group patients were more than twice as likely to show clinically significant improvement in community integration. Salazar et al. (2000) worked with moderate-to severe closed head injury people to an intensive eight-week inpatient cognitive rehabilitation program or a limited home rehabilitation program that included weekly telephone support from a psychiatric nurse. Outcome measures used included return to gainful employment and fitness for military duty at a one-year follow-up. They concluded that the overall benefit of in-hospital cognitive rehabilitation for patients with moderate-to-severe TBI was similar to that of home rehabilitation. Ninety percent of the hospital group was able to return to work compared to 94% of the home group. Fitness for active military duty was 73% for the hospital group and 66% for the home group. Patient-selection criteria (relatively young, previously healthy, well-oriented military personnel) make it difficult to generalize these findings to a broader population.

Cerebrovascular Accident (CVA)/Stroke: Several Cochrane systematic reviews have evaluated the effectiveness of cognitive rehabilitation following stroke. Lincoln et al. (2001) evaluated the use of cognitive rehabilitation for attention deficits following stroke indicated that cognitive rehabilitation may improve alertness and sustained attention, although the evidence could not support or refute its use to improve functional independence. A Cochrane review on cognitive rehabilitation for spatial neglect following stroke concluded that, although there is a growing number of cognitive rehabilitation approaches that show promise on standardized neglect tests, there is insufficient unbiased evidence to support or refute the effectiveness of either bottom-up or top-down approaches. It was stated that, although the number of neglect rehabilitation trials is rising, there are insufficient high quality randomized controlled trials with appropriate functional outcome measures tallow confident recommendations for clinical practice (Bowen et al., 2002).

Dementia: Clare and Woods(2007), reported on the effectiveness of cognitive training (guided practice on a set of tasks that reflect particular cognitive functions) and cognitive rehabilitation (developing strategies and methods of compensating based on individual needs and goals) interventions on patients with Alzheimer's disease and vascular dementia. Nine randomized controlled trials (RCTs) were identified for cognitive training, and no RCTs were identified for cognitive rehabilitation. They reported no significant differences between cognitive training and control were found. To conclude, it was stated that, based on the evidence reviewed, there was no evidence supporting the efficacy of cognitive training and insufficient evidence to evaluate the effectiveness of cognitive rehabilitation in Alzheimer's disease and vascular dementia.

Alzheimers Disease: In a meta-analysis of the literature regarding cognitive training (CT) and Alzheimer's disease, Sitzer et al. (2006) reviewed 19 controlled trials, 14 of which were RCTs. A small effect size for CT in general was reported but, more specifically, there were negative or minimal effects on visuospatial functioning and language, small effects on motor speed and visual learning, medium effects on executive functioning, and large effects on verbal and visual learning. Only a few studies reported follow-up data suggesting that gains may be maintained an average of 4.5 months after discontinuing treatment. Many limitations in the studies were identified such as: the limited number of well-controlled studies, small sample sizes, and the variable outcome measures and techniques used. They concluded that CT may improve the cognitive and functional abilities of patients with Alzheimer's disease, but further research is needed, including effectiveness studies in various settings and the use of performance-based measures to evaluate the effects of treatment on daily functioning.

Schizophrenia: McGurk et al. (2007) conducted a meta-analysis of 26 randomized controlled trials that evaluated the effects of cognitive remediation on cognitive performance, symptoms and psychosocial functioning in 1,151 patients with schizophrenia. It was found that impact of cognitive remediation on function was moderated by several factors including the addition of adjunctive psychiatric rehabilitation, cognitive training method, and patient age. It was concluded that cognitive remediation may have a moderate effect on cognitive performance and when combined with psychiatric rehabilitation, may improve functional outcomes. Velligan et al. (2006) examined research findings on the eight evidence-based approaches to cognitive rehabilitation. The eight approaches included: attention process training, integrated psychological therapy, cognitive enhancement therapy, neurocognitive enhancement therapy, cognitive remediation therapy, the neuropsychological educational approach to remediation, errorless learning approaches, and attention shaping. According to them, the studies that were included varied considerably in areas such as criteria for study inclusion, the conceptual organization of studies, and interpretation of findings. They stated that few approaches had more than three data-based studies

supporting their efficacy in schizophrenia and that there are no agreed upon guidelines for levels of intensity or duration of training. They findings of this review were not uniformly positive but encouraging, which is what they would expect at this stage of cognitive rehabilitation development.

COGNITIVE REHABILITATION IN CHILDREN AND ELDERLY: A FRESH OUTLOOK

Children with brain injuries- It is not uncommon to see children with brain injuries worsen cognitively and behaviourally as they grow into the late adolescence and young adulthood unless they receive cognitive rehabilitation therapy throughout their developmental years. In one study, 33 post-secondary students with learning disabilities proofread self-generated written language samples under three conditions: (1) using a speech synthesis program that simultaneously highlighted words on a monitor and audibly "spoke" them; (2) having text read aloud by another person; and (3) receiving no assistance. Subjects detected a significantly higher percentage of errors when using speech synthesis compared to either of the other conditions. In particular, subjects detected a significantly higher percentage of capitalisation, spelling, usage, and typographical errors with speech synthesis. Subjects may have detected more errors with computer assistance than with human assistance because a person reading the text aloud may subconsciously correct errors when reading aloud; the novelty of the computer may have increased motivation in that condition; and the visual highlighting may have provided an additional benefit unavailable with the human assistant (Raskind et al., 1999).

Elderly population- New frontiers of cognitive rehabilitation in geriatric age: the Mozart Effect (ME). The ME was described for the first time in 1993. Subsequently other studies with similar designs were performed. The present study, therefore, proposes: (i) to verify the existence of the benefits of exposure to music in elderly subjects with mild cognitive impairment (MCI), (ii) to explore whether it is possible to find any lasting improvement after training, conducted for a long period of time, with such musical pieces, in the measurable cognitive performances. The study conducted showed that the ME is present in geriatric patients with MCI; the influence on spatial-temporal abilities remains constant in time if the stimulation is maintained. The continuation of this study will consist of increasing the number of individuals examined and in having them listen to music during the study of ECG rhythms and during the acquisition of cerebral functional magnetic resonance imaging (fMRI), and, at the same time, testing them by neuropsychometric methods (Cacciafesta et al., 2010).

DOES COGNITIVE REHABILITATION PLAY ANY PROPHYLACTIC ROLE?

There have been evidences to prove that cognitive rehabilitation plays a major role. Consistency of behavioral and neural changes after focused cognitive rehabilitation in patients with mild cognitive impairment was seen. These focused interventions have significantly improved the accuracy of memory and reaction time for the trained associations, with the benefits persisting for at least 1 month. Analysis of the fMRI data has consistently revealed increased encoding-related activation within a widespread cerebral cortical network primarily involving medial frontoparietal and lateral tempoparietal areas (i.e. portions of the default network). Additionally, training has resulted in increased effective connectivity between many of these regions. In a study of the benefits of a multi-component cognitive rehabilitation program in patients with mild cognitive impairment it was found that these people showed significant improvement on activities of daily living, mood, verbal and non-verbal episodic memory performance(Kurz et al., 2008). Rozzini et al(2006) reported that subjects without treatment maintained their cognitive functional and behavioural status after one year; patients treated with only cholinesterase inhibitors improved in depressive symptoms whereas those treated with a combination of cognitive training and cholinesterase inhibitors showed significant improvements in different cognitive areas, such as memory, abstract reasoning and in behavioural disturbances particularly depressive symptoms , in regard to efficacy of cognitive rehabilitation in patients with mild cognitive impairment treated with cholinesterase inhibitors.

FACTORS AFFECTING REHABLITATION OUTCOME:

Neurological symptoms: The location, size and type of lesion are the critical determinants of cognitive consequences and the likelihood of recovery. The natural history of TBI recovery depends on whether the head injury is diffuse or focal, with recovery from diffuse injury following a more stereotypic course (coma, posttraumatic amnesia (PTA), post acute recovery from focal injury being more dependent on the lesion location and size (Katz and Mills 1999). Coma severity, coma duration and PTA duration have been identified as significant predictors of functional outcome from diffuse TBI.

Neuropsychological status; A comprehensive neuropsychological evaluation is recommended to determine which skills have been compromised and need to be rehabilitated versus which skill survive and can be recruited to compensate the lost functioning (Caetano & Christensen, 1997). Deficits in executive functioning and sustained attention pose particular challenges for the patient's ability to engage in effortful, extended cognitive rehabilitation and to reintegrate in social and vocational activities. Nevertheless it must be noted that most standard neuropsychological tests assess cognitive impairment rather than disabilities. Hence, they are poor predictors of functional outcome, particularly when neuropsychological functioning is assessed in the post –acute stage of recovery. More ecological neuropsychological tests have been devised in recent years are more predictive of everyday functioning (Burgess et al 1998 ; Schwartz and Macmillon 1989; Wilson 1991).

Psychosocial factors; It is widely known that psychosocial status and lifestyle affect cognitive function in vulnerable population and that such factors are taken into account in developing treatment programs. Prigatano (1999) has conducted considerable research on the importance of patient's awareness of their functional disabilities and on the relationship between awareness and their ability to benefit from rehabilitation. Poor awareness can lead to passive or resistant behaviour in therapeutic setting. Different approaches have been taken to help improve awareness and motivation. Patients and family education about common squeal of brain injury (Anderson 1996), record of patient's behaviour (through logs or videotape)to provide the patient with a more objective view of the behaviour (Mateer, 1999) psychotherapy to help patients cope with their disabilities(Ben-Yishay & Diller, 1993;Prigatano 1999) and psychological problems, including worry, anxiety, depression are commonly associated with brain injury (Morton & Welmon, 1995, Prigatano, 1999). It is well established that emotional problems negatively effects cognitive functions (Fields et al., 1998), but cognitive deficits has also been shown to relate with social functioning, satisfaction with lifestyle and optimism (Dawson et al., 1999).These findings led to widespread agreement that problems with these need to be addressed as part of a comprehensive cognitive rehabilitation programme (Prigatano 1999; Wilson 1995).

Background history and support: The patient's background characteristics and social supports play an important role in rehabilitation outcome, yet, with the exception of patient's age, they are rarely integrated into rehabilitation therapies or outcome evaluation in a objective way. A recent study demonstrated the importance of premorbid patient's characteristics found that patient with poor outcome following mild TBI were likely to have had past neurological and psychiatric problems and other life stressor (Ponsford et al., 2000). Similarly, a number of study has documented reduction in patients social support network following TBI (Morton & Welman, 1995) ,reduction that may negatively affect recovery outcome (Lezak, 1995). To address these needs, Ruff and Camenzuli (1991) recommended a multi-axial classification system to help identify factors that may influence rehabilitation outcome. It includes premorbid and current emotional, psychological, and vocational status, factors that should be considered prior to establishing outcome goals and expectations.

INDIAN EXPERIENCES:

Cognitive rehabilitation is implemented as a treatment program for patients with head injury, since past fourteen years in our country. It was started by attempting restoration of function. In an experience with over two hundred patients, it has been found to be effective for improving post concussion syndrome, memory deficits and even frontal lobe deficits following head injury (Rao et al.,1995). In NIMHANS, home based cognitive remediation program was developed, which incorporates the functions of attention and memory. In this program, the therapist would teach a task to a care giver on a weekly basis. The patient's relative or friend would administer these tasks to the patients at home(Sarkar et al., 1996) Methods of restoration on detoxified alcoholics with residual memory deficits have been tried. Patients showed improvements in their planning ability and in their memory (Mathai et al., 1994)

In children with attention deficit hyperactivity disorder cognitive rehabilitation has been used to improve their functioning. As a result, it was seen that their attention span increased, impulsivity reduced and school performance also improved (Aggarwal, 1992). In a study conducted on the role of cognitive and vocational retraining in chronic schizophrenic patients it was found that there were significant differences in the pre and post assessment in the areas like attention, memory, executive functioning and problem solving but no significant difference in vocational part (Pandey, et al., 2006). Various studies are still in progress in India and work is been carried out to see the effect of cognitive rehabilitation in various fields.

CONCLUSION

The development of cognitive rehabilitation interventions reflects a growing recognition that cognitive recovery is possible. At the same time, there is little evidence for the effectiveness of existing interventions that goes beyond the demonstration of small effect sizes,

let alone for cognitive rehabilitation's durability or generalizability. We argued that in order for the field to advance, cognitive interventions must incorporate a number of other features. It must also be recognized that significant cognitive recovery can occur through the use of structured interventions, and living and treatment environments in general, and possibly through medication. Therefore, a focus on maximizing cognitive recovery through whatever means (or combination thereof) are possible should replace a focus on single interventions in future research and practice. Paradoxically, in moving ahead in these ways, the future of cognitive rehabilitation will be making use of insights that date back to Kraepelin but that have yet to to be used for systematically promoting cognitive change.

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Review Article :

Agomelatine : A Clinical Review and Its Role in the Management of Depression

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ABSTRACT:

The present review article looks at the role of Agomelatine as an antidepressant drugs while elucidating its unique mechanisms of action compared to other traditional antidepressants. The article examines the present literature on agomelatine and provides the busy clinician an overview of this drug along with its pharmacodynamic and pharmacokinetic properties. Clinical trials and studies involving agomelatine have been reviewed and the analysis presented.

Key words: ***Agomelatine, antidepressant.***

INTRODUCTION

Major depressive disorder (MDD) carries an enormous personal, social, and economic burden. Despite a better understanding of disease mechanisms and neurobiological consequences of treatments, the effectiveness and tolerability of currently available antidepressants remain suboptimal [1-2]. The current search for therapeutic targets has shifted from selective monoamine systems to monoamine and non-monoamine networks [3]. Although many individuals experience the disorder, only a small proportion of patients with MDD present for treatment. Older antidepressants such as the tricyclic antidepressants (TCAs), although effective, have significant and sometimes life-threatening adverse effects that limit their use. The newer antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) tend to be better tolerated, but still have significant adverse effects, e.g. sexual dysfunction and nausea, which may limit compliance. Among the various strategies to help patients with new, more effective and better tolerated treatments, the re-synchronization of biological rhythms appears to be particularly attractive given that a disruption of circadian rhythms is characteristic of a large number of mood disorders [4-5].

Agomelatine is a new antidepressant that is a potent agonist of melatonin receptors and an antagonist of the serotonin 5-HT_{2C} receptor subtype. It is in late-phase trials for the treatment of major depressive disorder.

AGOMELATINE : A MELATONIN AGONIST

Melatonin is a pineal hormone which has a fundamental role in the synchronization of circadian rhythms [6-7] that are disorganized in central nervous system disorders such as depression [8-11]. There are three types of melatonin receptors: MT-1, MT-2 & MT-3. The MT-1 and MT-2 receptors belong to the super family of G-protein coupled membrane receptors linked to the inhibition of the adenylyl cyclase and the subsequent decrease of cAMP [12]. These two receptors are expressed by almost all structures of the CNS, especially hypothalamic suprachiasmatic nucleus. The SCN is an endogenous clock which controls the rhythmic secretion of melatonin in our body with low circulating levels during the day, and high plasma concentrations of hormones at night [13]. It is now clearly recognized that disorganized internal rhythmicity is characteristic of a large variety of affective disorders, including unipolar and bipolar depression, mania, seasonal affective disorder and premenstrual dysphoric disorder [14-18].

MECHANISM OF ACTION OF AGOMELATINE

Agomelatine, a naphthalene derivative of melatonin, potently binds to melatonin receptors MT-1 and MT-2, suppresses cAMP formation and mimics the actions of melatonin by dose dependent inhibition of suprachiasmatic neurons [19]. Agomelatine possesses sleep wake cycle regulating properties, and as affective disorders involve a disorganization of circadian rhythms, agomelatine is suggested to play an important role in the pathophysiology of major depression.

5-HT2C receptors are present in the suprachiasmatic nucleus (SCN), ventrotegmental area, locus ceruleus and limbic system. A polysynaptic circuit runs from the SCN to the ventrotegmental nucleus, the origin of mesocortical and mesolimbic dopaminergic pathways [20]. Also, 5-HT2C receptors cause excitation of GABA interneurons. GABA excitation via 5-HT2C receptors leads to inhibition of adrenergic and dopaminergic pathways resulting in depressive symptoms. 5-HT2C antagonists hence improve the depressive symptoms by increasing dopaminergic and adrenergic transmission.

5-HT2C receptors are also concentrated in limbic structures such as the frontal cortex, the amygdala, the hippocampus and the septum, which have major roles in the control of mood and in the aetiology of anxio-depressive states [21-22].

Activity at 5-HT2C receptors seems to be enhanced in depression. Being a selective 5-HT2C antagonist, agomelatine displays antidepressant and anxiolytic properties. It also promotes slow wave sleep [23-24] and libido [25-26]. Collectively, these observations suggest that 5-HT2C receptor antagonists such as agomelatine should favourably influence mood, circadian synchronization and sleep quality, while preserving sexual function.

PHARMACODYNAMICS

As already mentioned agomelatine is a potent melatonin receptor agonist at MT1 and MT2 receptors in the SCN. It also antagonises the serotonin 5 HT2C receptors with weak action on 5 HT1A and 5 HT2A with negligible activity on other serotonergic receptor subtypes [27]. It is important to note that agomelatine has a dual phased action. Its melatonergic sleep promoting action prevails during the night, whereas during the day its antidepressant action via 5HT2C inhibition is uncoupled from its nocturnal action (this may also be considered as an advantage of agomelatine versus the other classes of antidepressants) [28]. Agomelatine does not directly affect the uptake of serotonin, norepinephrine, or dopamine. By inhibiting 5 HT2C receptors, however, it secondarily increases norepinephrine and dopamine in the frontal cortex of the brain. [27]. This effect might contribute to its antidepressant activity. Agomelatine does not bind to adrenergic, cholinergic, or histamine receptors.

The dentate gyrus of the hippocampal formation is a site of continuous neurogenesis during adult life. Chronic stress can result in decreased neurogenesis (nerve cell growth) [29]. Remodelling of hippocampal formation may be a factor in development of depression and is the basis for neuroplasticity hypothesis of major depression [30]. A recent study published has shown that chronic treatment with agomelatine increased cell proliferation and neurogenesis in the ventral dentate gyrus, a region implicated in response to anxiety and emotion. This implies the antidepressant and anxiolytic effects of agomelatine may be partially due to effects on the ventral dentate gyrus [31].

The animal studies demonstrate that agomelatine is able to resynchronize a disrupted circadian rhythm. Agomelatine shows regulation of sleep wake rhythm, increasing the duration of slow wave sleep and normalizing its distribution throughout the night [32]. In contrast, it does not change rapid eye movement (REM) latency, amount of REM or REM density [33].

PHARMACOKINETICS

Agomelatine is rapidly and well absorbed after oral administration, from the gastrointestinal tract [34]. However, its absolute bioavailabilty is relatively low due to high first pass metabolism [35]. With maximum plasma concentration being observed between 1 and 2 hours after administration, the absorbed fraction is greater than 78 % [34].

Agomelatine is moderately distributed throughout the body with a volume of distribution at a steady state of about 35 L. It is highly protein bound (its plasma protein binding is greater than 95%) [36].

Agomelatine is almost entirely metabolized through the liver, and it undergoes extensive first pass hepatic metabolism. The major cytochrome P-450 (CYP-450) enzyme involved in the metabolism of agomelatine is CYP-1A2 (accounting for about 90% of its metabolism), with minor metabolic contributions by CYP-2C9 and CYP-2C19 [37]. Agomelatine has at least four main metabolites. None of the metabolites have any known toxic effects. Agomelatine and its metabolites are mainly excreted through the kidneys. The elimination half-life of agomelatine is very short (about 2–3 hours) [34]

AGOMELATINE AS AN ANTIDEPRESSANT

The efficacy of agomelatine as an antidepressant has been demonstrated in many animal (preclinical) and human (clinical) trials. Various behavioural models in animals are based on the reversal of the deleterious effects

caused by stress situations, be it acute, sub-chronic or chronic [38]. These preclinical models have shown almost equal efficacy of agomelatine with other antidepressants such as fluoxetine and imipramine.

However, an important point to note is the role of agomelatine in the chronic mild stress paradigm. The chronic mild stress paradigm is considered the most relevant animal model for providing evidence of antidepressant properties of a drug because it focuses on anhedonia, one of the key symptoms of depression. Agomelatine reverses the anhedonia seen in this model, irrespective of the time of day of its administration. There is no withdrawal relapse even one week after cessation of treatment [39].

Agomelatine, in addition to its antidepressant activity, exerts a clear-cut anxiolytic action in various animal models, and mechanistic studies in rats provide compelling evidence for a role of 5-HT2C receptor blockade in this anxiolytic action.

Clinical trials have demonstrated efficacy and safety of agomelatine for the treatment of depression and anxiety. A meta-analysis of the severely depressed subpopulations, using increasing cut offs of the HAMD scale at inclusion, showed agomelatine was also effective in management of severe depression [40]. The antidepressant efficacy of agomelatine is associated with an early improvement in depressive symptoms (approximately 2 weeks) and an excellent acceptability [41]. Patient oriented evidence suggests better improvement on subjective getting to sleep and on subjective quality of sleep compared to venlafaxine [42]. Agomelatine is as effective as paroxetine and venlafaxine when compared with respect to response to treatment as well as remission after treatment [43-45]. Agomelatine is more effective than placebo and as effective as paroxetine or venlafaxine in reducing depressive symptoms correlated with symptom relief in terms of HAM-D reduction [44-46].

Agomelatine also appeared to be effective in anxiety associated with depression as demonstrated by reductions in Hamilton's Anxiety Rating Scale (HARS) when compared to placebo [41].

TOLERABILITY AND SAFETY OF AGOMELATINE

A dose-ranging multinational study, double blind and randomised study examined the antidepressant efficacy of three different doses of agomelatine (1, 5 or 25 mg) in more than 700 patients with MDD. The antidepressant efficacy of 25 mg agomelatine was demonstrated in both the mean efficacy criterion (decrease in the HAMD-17 total score) and in secondary outcome measures (MADRS, CGI-S, number of responders). The most common side effects associated with agomelatine are headache, nausea, dizziness, dry mouth, diarrhea, somnolence, fatigue, upper abdominal pain, and anxiety. The most common serious adverse events were suicide attempts (agomelatine 0.6% versus placebo 0.4%), depression (agomelatine 0.5% versus placebo 0.8%), and falls (agomelatine 0.3% versus placebo 0.3%) [47].

Inspite of these effects, agomelatine has a relatively benign side effect profile. A notable advantage is the lack of clinically significant weight gain, the low risk of sexual dysfunction, the low incidence of gastrointestinal symptoms, absence of ECG abnormalities and the absence of discontinuation symptoms. In this manner, agomelatine compares favourably to SSRI and SNRI drugs.

Comparative studies with venlafaxine show that sexual dysfunction with respect to desire-arousal factor, and orgasm dysfunction occur in a lower percentage of patients treated with agomelatine than treated with venlafaxine. However these results were found not to be statistically significant [47].

When the overall tolerability of agomelatine in head-to-head comparisons with other active drug comparators was done; results showes that agomelatine was not substantially better, as evidenced by the roughly similar rates of discontinuation. Of special concern with the use of agomelatine, is liver function. Significant elevations of liver enzymes are common, at times including rare and serious cases of hepatitis. Monitoring of liver enzyme levels of all patients has been recommended before starting treatment, after 6, 12, and 24 weeks of treatment, and thereafter based on clinical judgement. For this reason, agomelatine is contraindicated in patients with any degree of liver impairment. The liver precautions and the need for laboratory monitoring are a distinct disadvantage for the use of agomelatine compared to many other antidepressant drugs. Agomelatine however, does not significantly affect renal function [47].

As per one study, no statistically significant difference in the number of emergent discontinuation symptoms was seen one week after treatment interruption between patients discontinuing agomelatine and those who continued it [47]. This was in contrast to patients

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Review Article :

OPPOSITIONAL CONDUCT DISORDER

Aishwarya Prasad*

ABSTRACT:

Oppositional Conduct Disorder is labelled as Oppositional Defiant Disorder (ODD) according to American Academy of Child and Adolescent Psychiatry (AACAP) A childhood Psychiatric disorder manifesting itself in prepurberty in males and post puberty in females in the form of uncooperativeness, defiant and hostile behaviour towards authority figure(s), seriously interfering with youngster's day to day functioning and inter-personal relationships thereby affecting the child's social, family and academic life. ODD evolves form the phenomenon of "terrible two" in families with at least one parent having or having had psychiatric problem.

Key words: ***Oppositional Conduct, Defiant, Terrible Two***

Oppositional conduct disorder (ODD), is a child psychiatric disorder. Children diagnosed with ODD show a pattern of uncooperative, defiant and hostile behavior towards authority figure. It is usually severe enough to seriously interfere with the youngster's day to day functioning. A diagnosis of ODD cannot be given if the child presents with conduct disorder (CD)

According to the American academy of Child and Adolescent psychiatry (AACAP), ODD is present in 5-15 percent of all school aged children. Some statistics say that the rate of ODD is higher in boys before puberty, and is the same in boys and girls after puberty. With this kind of prevalence we can easily expect to encounter many children with oppositional defiant disorder around us and it will be a lot easier for us if we know how to deal with such children.

All children are oppositional from time to time, more so when tired, hungry, stressed or upset. Oppositional behavior is often a normal part of development for two to three year olds and early adolescents. However it becomes a reason of serious concern when it is so frequent and consistent that it stands out as compared to other children of the same age and developmental level and/or it affects the child's social, family and academic life.

It is not easy to distinguish ODD from age appropriate normal oppositional behavior. Children with ODD very frequently lose temper, argue with adults, defy rules, refuse adult requests and deliberately annoy others. This behavior persists throughout different settings and is not targeted against a particular parent or teacher. A diagnosis is made when the symptoms persist beyond six months. Other patterns of behavior include the child being touchy, angry, resentful, spiteful or vindictive. They have a tendency to blame others, show mild physical aggression but language is usually extremely obscene and aggressive. Symptoms of ODD are seen to be enhanced with co morbidities like ADHD, anxiety or depression.

Children who are later diagnosed with ODD are found to be fussy, colicky and difficult to soothe as infants. As toddlers/preschool, they throw temper tantrums over small things like eating, toilet training, homework and sleeping. They have an intractable power to struggle and are in a habit to procrastinate. They do not follow rules and instructions and when questioned, claim to forget/ fail to hear, often leading to hearing tests which are normal. Winning in an argument is most important aspect of the struggle

The child typically has little insight and ability to admit to difficulties. He tends to blame his troubles on others or external circumstances. They are always questioning rules and are constantly attempting to change those that they find unreasonable.

CAUSES

According to "Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) in Children and Adolescents: Diagnosis and Treatment", children of alcoholic parents or parents who often run into trouble with the law have an 18 percent chance of developing ODD. It appears that ODD arises out of a circular family dynamic. The more a child acts in defiant provocative ways the more negative feedback is elicited from the parents. In an attempt to achieve compliance, the parent or authority figures remind, lecture, berate, physically punish, and nag the child. But

far from diminishing oppositional behavior, these kinds of responses toward the child tend to increase the rate and intensity of non-compliance. There may be a vicious cycle in which the parent and child bring out the worst in each other leading to the phenomenon of "terrible twos". ODD appears to be more common in families in which at least one parent has a history of a Mood Disorder, Oppositional Defiant Disorder, Conduct Disorder, Attention-Deficit/ Hyperactivity Disorder, Antisocial Personality Disorder, or a Substance-Related Disorder. In addition, some studies suggest that mothers with a Depressive Disorder are more likely to have children with oppositional behavior, but it is unclear to what extent maternal depression results from or causes oppositional behavior in children.

HOW TO RESPOND

The earlier this disorder can be managed, the better. Treatment can help restore the child's self-esteem and rebuild a positive relationship between the parents and the child as well as relationships with other important adults in his or her life — such as teachers and care providers.

Interventions can be made at various levels. Preventive measures such as developing a good relationship between an authority figure and child, creating a predictable environment and practicing emotional neutrality can go a long way. Once ODD has been diagnosed, the child and adolescent psychiatrist or other professional may recommend a combination of therapies for ODD. Initial interventions include educating the family about ODD and how to deal with patients diagnosed with ODD. Behavioures that diminish power struggle should be used. Such behavioral patterns include listening, privacy and simple directive and choices. When the child starts to get aggressive he/she should be reminded of a funny moment to distract him/her. Since ODD occurs in the context of the family and is heavily influenced by the health of family interactions, Therapists working to treat this disorder may thus recommend marital therapy, or substance abuse treatment to parents and caregivers if they believe such interventions will improve the overall health of family interactions. Medications have not been proven effective in treating Oppositional Defiant Disorder, so they are generally only used if a child has a co-morbid (co-occurring) disorder that responds to medication, such as Major Depression or ADHD. Other approaches to the treatment of ODD, include parent training programs, individual psychotherapy, family therapy, cognitive behavioral therapy, and social skills training. According to the American Academy of Child and Adolescent Psychiatry, treatments for ODD are tailored specifically to the individual child, and different treatment techniques are applied for pre-schoolers and adolescents.

DEALING WITH RELAPSE

During a period of good adjustment, the patient and his family and the therapist should plan what steps to take if signs of relapse appear. Such a plan should also include what specific symptoms are warnings of relapse. The therapist should direct the parents that he/she should be called immediately if those specific symptoms occur. They should also be told at the same time to notify friends and other people who can help. Specific plans and a more predictable and consistent daily schedule should be made for the child.

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Attitude toward Auditory Hallucinations among Schizophrenic Patients: Meta-Analytic Perspective

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ABSTRACT:

Background: *Verbal auditory hallucinations are subjective phenomena or internal cognitive events. The auditory hallucination is misattributed by the schizophrenic patients to internal or external sources, which lead to deterioration in their psychosocial functioning, and lead to development of delusions, suicidal ideation and suicidal acts. There is a dearth of meta-analysis in the area of attitude toward auditory hallucinations among schizophrenic patients.* ***Aim:*** *Aim of the present meta-analysis was to undertake the first quantitative review of attitude toward auditory hallucinations among schizophrenic patients.* ***Methods:*** *PubMed, PsycINFO and ERIC databases were searched for reviews that examined the schizophrenic patients' ascription toward auditory hallucination. Nine studies were eligible for inclusion in the meta-analysis.* ***Results:*** *Schizophrenia patents have "malevolence" attribution, not "benevolence" attribution towards auditory hallucinations. Schizophrenic patients behaviourally resisted the auditory voices to prevent them. Schizophrenic patients did not have "engagement" feeling and "engagement" behaviour with auditory voices. Further evaluation is required to know about "resistance" feelings toward auditory hallucination among schizophrenic patients, because generated effect size (95% CI= 0.428-0.558, Z= -0.202, p>0.05) is in question.* ***Conclusions:*** *Schizophrenic patients attribute auditory hallucinations as wicked, and behaviorally attempt to prevent hallucinatory voices. Schizophrenic patients do not have view of engagement and they do not engage behaviorally with hearing voices.*

Key words: ***Attitude, Auditory hallucination, Schizophrenia***

INTRODUCTION

Hallucinations make up one of the central themes in the history of psychopathology. Jasper [1] has defined hallucination as "false perceptions which are not in any way distortions of real perceptions, but spring up on their own as something quite new and occur simultaneously with and alongside real perception". Hearing voices is, of course, core characteristic of schizophrenia [2, 3]. Phenomenologically auditory hallucination is the most common and important disorder of perception [4]. Recently, Baethge et al. estimated that the cross-sectional prevalence of hallucinations among inpatients with schizophrenia is 61.1% [3]. Prevalence of auditory hallucinations was present among 47% to 98% schizophrenic patients [5, 6, 7]. The prevalence of auditory hallucinations was found 64.3% in Indian schizophrenia samples [4].

Affect and behaviour arising from hallucinations may be understood as activating events, whose significance is appraised by the individual's belief system and which largely give rise to characteristic emotional and behavioural consequences; such as emotions of fear, guilt, depression, sometimes elation, and the behaviour of appeasement [8, 9]. Attitude toward hallucinations, the emotional reaction to hallucinations, and the degree of control to cope with hallucinations, are also associated with social context [10].

Attribution for hallucinations in the 'schizophrenia' spectrum disorders have been subject to investigation. However, no meta-analysis has been reported in this intent. The aim of the present meta-analysis was to provide the first quantitative review of attitude toward auditory hallucinations among schizophrenic patients.

METHOD

Identification of studies

To identify relevant studies, we ran searches on PubMed, PsycINFO, and ERIC up to January 2012. We used the key words "attitude" or "attribution or belief" combined with "auditory hallucination" and "schizophrenia". Articles were retrieved for further assessment if the title or abstract suggested that reference will give sufficient information about attitude toward

auditory hallucinations among schizophrenic patients. Subsequently, relevant references were searched manually for full article.

Inclusion Criteria

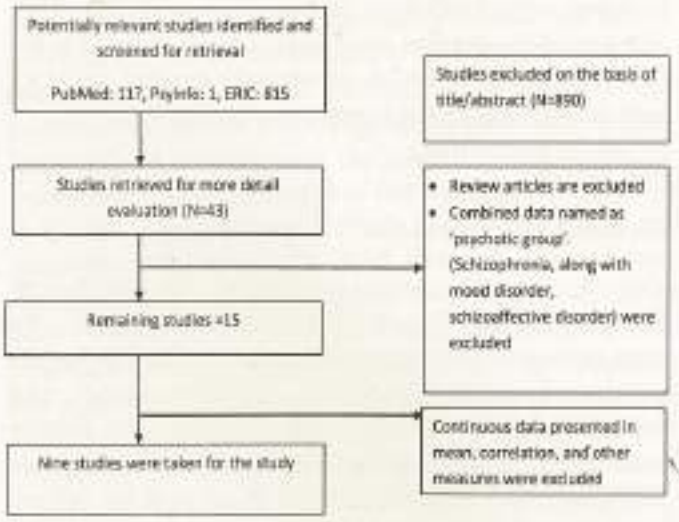
Manuscripts were included if they met the following criteria:

1. Inclusion of article of participants with schizophrenia according to ICD-10-DCR
2. In article data are presented on numbers or frequency
3. Entire article is in English

Review Search Strategy

The references search process has been done as recommended by the Quality of Reporting Meta Analysis (QUOROM) as shown in Figure-1 [11]. The initial search yielded 117 reference titles in PubMed, 1 in PsyINFO and 815 in ERIC. On the basis of title, abstract and full text, 43 titles were identified as having a possible relevance to know attitude toward auditory hallucinations among schizophrenic patients. Out of 43 references 28 were review studies and were left out from analysis. Studies, where data of schizophrenic group was merged with schizoaffective disorder and mood disorder and collectively termed as 'psychotic group', were excluded. Results of six other references were presented in mean, standard deviation and correlation format, and thus were excluded. Finally nine studies were included in present meta-analysis.

Figure 1: Flow chart (diagram) of studies included and excluded for Meta-Analysis as recommended by The Quality of Reporting of Meta Analysis (QUOROM) [11]



Data extraction and Selection procedure

Initially selected references were coded in the domains of year of publication, total number of patients included and the number of patients reporting a particular kind of attitude toward hallucination. Data presented in percentage was converted into numbers. Data presented in mean, standard deviation and correlations, cannot be converted in to numbers or frequencies and therefore were excluded from present meta-analysis. Included references were classified into six divisions according to classification given by Birchwood and Chadwick [8]. Classification of different domains for attitude toward hallucination is explained in Figure-2.

Figure-2

Parameter of attitude toward hallucination	Description
Benevolence	Voices are enhancing positive self concept, helping or protecting, having positive attitude, blessing, react positively and adjusting well with voices.
Malevolence	Voices are punishing, controlling, react negatively, had forced of command, abusing and threatening, poorly adjusted with voices.
Resistance Feeling	Negative feeling, makes me feel anxious, interrupting thinking process and suppression of voices in mind, feeling fear.
Resistance Behaviour	Do things to prevent voices, reluctant to obey the voices, negative and hostile reactions to stop it, resistance in work and self care.
Engagement Feeling	Voices entertain, positive companionship, express emotions, delusions as explanation, reassure me and debate the voices.
Engagement Behaviour	Voices enhance performance, do things to be contact with voices, engaged friendly, conversation, excessive religiosity due to voices, and take guidance.

Statistical Analysis

For conducting meta-analysis, a computer software Comprehensive Meta-Analysis (CMA) 2.0 version was used. In a systematic software review for meta-analysis, Bax et al. found that CMA 2.0 is identical, and it has only minor numerical inconsistencies [12]. CMA 2.0 scored

highest on usability and also had the most complete set of analytical features [12]. Statistical testing was carried out at the 5% level of significance (two-sided tests). Fixed effects model was used in meta-analysis because all the included references were conducted by different researchers, in different places, using different tools, and so forth [13].

RESULTS

Table -1: Characteristics of Benevolence Attribution of Auditory Hallucination among Schizophrenic Patients

Studies	Events	Sample Size	Event Rate (LL -UL)	Logic Event Rate	Standard Error	Z-Value	P value	Event rate and 95%CI
Singh, et al., 2002 [16]	53	75	0.667 (0.553-0.764)	0.693	0.245	2.830	0.005	
Ranjan et al., 2010 [18]	30	50	0.500 (0.367-0.613)	0.000	0.236	0.000	1.000	
Benjamin, 1989 [14]	10	14	0.714 (0.439-0.889)	0.916	0.592	1.548	0.121	
Garret, 2003 [20]	4	32	0.125 (0.048-0.288)	-1.946	0.535	-3.640	0.000	
Lowe, 1973 [21]	9	15	0.600 (0.348-0.806)	0.405	0.527	0.769	0.442	
Ramanathan, 1983 [15]	9	11	0.818 (0.493-0.954)	1.504	0.782	1.924	0.054	
Fallon et al., 1981 [19]	26	40	0.650 (0.492-0.781)	0.619	0.331	1.867	0.062	
Chadwick et al. 1994 [8]	12	26	0.462 (0.284-0.650)	-0.154	0.393	-0.392	0.695	
Chadwick et al. 2000 [17]	63	75	0.863 (0.764-0.925)	1.841	0.340	5.407	0.000	
Total full model (95% CI)	219	338	0.611 (0.554-0.665)	3.798	0.000			

Meta-analysis of references (Table 1) that applied for benevolence attitude toward auditory hallucinations among schizophrenic patients, achieved significant overall effect size (95% CI=0.175-0.272, Z= -8.813, p<0.001) indicates significant number of schizophrenic patients were not having benevolence attitude toward auditory hallucinations. All the references included in present meta-analysis [8, 14, 15, 16, 17, 18, 19, 20, 21] too reported that schizophrenic patients do not have benevolence attribution toward hallucinatory voices. However, the reported number of patients was not statistically significant in the study of Benjamin et al. [14].

The meta-analysis result of malevolence attitude toward auditory hallucinations is presented in Table 2. Overall generated effect size (95% CI= 0.554- 0.665, Z=3.798, p< 0.001) indicates significant number of schizophrenic patients had malevolence attitude toward auditory voices. Heterogeneity among findings of included references was found; some references [15, 16, 17] reported that significant number of schizophrenic patients have malevolence attitude toward auditory hallucinations. Other included references [14, 18, 19, 21] in present meta-analysis also reported that schizophrenic patients have malevolence attribution toward voices; however, reported numbers of patients were not statistically significant in their findings. Contradictory findings were reported by Chadwick et al. [8] and Garret et al. [20].

Table -2: Characteristics of Malevolence Attribution of Auditory Hallucination among Schizophrenic Patients

Studies	Events	Sample Size	Event Rate (LL -UL)	Logic Event Rate	Standard Error	Z-Value	P value
Singh, et al., 2002 [16]	53	75	0.667 (0.553-0.764)	0.693	0.245	2.830	0.005
Ranjan et al., 2010 [18]	30	50	0.500 (0.367-0.613)	0.000	0.236	0.000	1.000
Benjamin, 1989 [14]	10	14	0.714 (0.439-0.889)	0.916	0.592	1.548	0.121
Garret, 2003 [20]	4	32	0.125 (0.048-0.288)	-1.946	0.535	-3.640	0.000
Lowe, 1973 [21]	9	15	0.600 (0.348-0.806)	0.405	0.527	0.769	0.442
Ramanathan, 1983 [15]	9	11	0.818 (0.493-0.954)	1.504	0.782	1.924	0.054
Fallon et al., 1981 [19]	26	40	0.650 0.610 (0.492-0.781)	0.331	1.867	0.062	
Chadwick et al. 1994 [8]	12	26	0.462-0.154 (0.284-0.650)	0.393	-0.392	0.695	
Chadwick et al. 2000 [17]	63	75	0.863 (0.764-0.925)	1.841	0.340	5.407	0.000
Total full model (95% CI)	219	338	0.611 (0.554-0.665)		3.798	0.000	

Result of present meta-analysis for included studies of resistance feeling toward auditory hallucinations among schizophrenic patients is presented in Table 3. Overall generated effect size (95% CI= 0.428-0.558, Z= - 0.202, p>0.05) indicated that almost 50% patient reported having resistance feeling with voices and 50% not. Included reference [8, 14, 15, 18] documented that schizophrenic patients have resistance feelings toward auditory voices. However, findings of Chadwick et al. [8] and Benjamin et al. [14] were not statistically significant. Other included references [16, 19, 20, 21] reported that schizophrenic patients do not have resistance feeling with auditory voices; however, findings of Lowe [16] and Singh et al. [21] were not statistically significant.

Table -4: Resistance Behaviour for Auditory Hallucination among Schizophrenic Patients

Studies	Events	Sample Size	Event Rate (LL -UL)	Logic Event Rate	Standard Error	Z-Value	P value	
Singh, et al., 2002 [16]	68	75	0.773 (0.665-0.854)	1.277	0.276	4.650	0.000	
Ranjan et al., 2010 [18]	30	50	0.600 (0.460-0.725)	0.405	0.289	1.405	0.160	
Benjamin, 1988 [14]	12	14	0.857 (0.573-0.964)	1.792	0.764	2.348	0.019	
Garret, 2003 [20]	5	32	0.156 (0.067-0.328)	-1.685	0.487	-3.464	0.001	
Lowe, 1973 [21]	10	15	0.667 (0.409-0.858)	0.693	0.648	1.256	0.205	
Ramanathan, 1983 [15]	8	11	0.727 (0.414-0.910)	0.951	0.677	1.449	0.167	
Fallon et al., 1981 [19]	29	40	0.725 (0.569-0.841)	0.969	0.354	2.738	0.006	
Chadwick et al 1994 [8]	12	26	0.462 (0.284-0.650)	-0.154	0.393	-0.392	0.695	
Total full model	164	283	0.634 (0.569-0.695)		3.939	0.000		

Meta-analysis for resistance behaviour toward auditory hallucination was presented in Table 4. Achieved overall generated effect size (95% CI=0.568-0.695, Z= 3.939, p<0.001) indicates that significant number of schizophrenic patients resist behaviourally in order to prevent auditory voices. Similar findings were documented in included references [14, 15, 16, 18, 19, 21]. However, findings of some references [15, 18, 21] were not statistically significant. Contradictory findings were reported by Chadwick et al. [8] and Garret et al. [20].

Meta-analysis for reported reviews of engagement feeling with auditory voices is presented in Table-5. Overall generated effect size (95% CI= 0.242-0.357, Z= - 6.099, p<0.001) indicates that significantly less number of schizophrenic patients had engagement feeling with auditory hallucinations. Similar findings were documented in included references [8, 14, 15, 16, 18, 19, 20]. However, in some references [8, 14, 18, 19] the reported number of patients was not statistically significant. Contradictory findings were reported by Lowe [21].

Table -5: Engagement Feelings for Auditory Hallucination among Schizophrenic Patients

Studies	Events	Sample Size	Event Rate (LL -UL)	Logic Event Rate	Standard Error	Z-Value	P value	
Singh, et al., 2002 [16]	14	75	0.187 (0.114-0.291)	-1.472	0.298	-4.967	0.000	
Ranjan et al., 2010 [18]	20	50	0.400 (0.275-0.540)	-0.405	0.289	-1.405	0.160	
Benjamin, 1988 [14]	4	14	0.286 (0.111-0.561)	-0.916	0.592	-1.549	0.121	
Garret, 2003 [20]	6	32	0.188 (0.087-0.358)	-1.468	0.453	-3.238	0.001	
Lowe, 1973 [21]	9	15	0.600 (0.348-0.808)	0.405	0.527	0.769	0.442	
Ramanathan, 1983 [15]	2	11	0.182 (0.048-0.507)	-1.504	0.782	-1.924	0.054	
Fallon et al., 1981 [19]	8	40	0.225 (0.121-0.379)	-1.237	0.376	-3.288	0.001	
Chadwick et al. 1994 [8]	11	26	0.423 (0.252-0.615)	-0.310	0.397	-0.781	0.435	
Total full model	76	283	0.296 (0.242-0.357)			-6.099	0.000	

Meta-analysis for reviews that applied for schizophrenic patients' engagement behaviour with auditory hallucination is presented in Table 6. Achieved significant overall effect size (95% CI= 0.324- 0.477, Z= - 2.519, p<0.05) indicates significantly less number of schizophrenic patients engaged behaviourally with auditory hallucinations. The findings of the present meta-analysis were homogenous with results which were also reported in included references [14, 15, 16, 18, 19, 21]. Contradictory findings were reported by Chadwick et al. [8] and Garret et al. [20].

Table -6: Engagement Behaviour for Auditory Hallucination among Schizophrenic Patients

Studies	Events	Sample Size	Event Rate (LL -UL)	Logic Event Rate	Standard Error	Z-Value	P value	
Singh, et al., 2002 [16]	2	75	0.027 (0.007-0.100)	-3.597	0.717	-5.019	0.000	
Ranjan et al., 2010 [18]	16	50	0.320 (0.206-0.460)	-0.754	0.303	-2.486	0.013	
Benjamin, 1988 [14]	2	14	0.143 (0.036-0.421)	-1.792	0.764	-2.346	0.019	
Garret, 2003 [20]	28	32	0.875 (0.711-0.953)	1.946	0.535	3.640	0.000	
Lowe, 1973 [21]	13	15	0.867 (0.606-0.968)	1.872	0.763	2.464	0.014	
Ramanathan, 1983 [15]	2	11	0.182 (0.048-0.507)	-1.504	0.782	-1.924	0.054	
Fallon et al., 1981 [19]	14	40	0.350 (0.215-0.508)	-0.619	0.331	-1.867	0.062	
Chadwick et al. 1994 [8]	14	26	0.538 (0.356-0.710)	0.154	0.393	0.393	0.695	
Total full model	91	283	0.398 (0.324-0.477)			-2.519	0.012	

DISCUSSION

The present meta-analysis extends the earlier individual research findings in terms of size (263-338 patients) of database analysis. Different cognitive models have suggested that dysfunctional attribution toward auditory hallucinations occur as the result of internal events attributed to an external source [22], meta cognition [23, 24, 25] and reduced attention [26]. In the midst of the rationale of different cognitive models, this meta-analysis has been carried out.

The majority of schizophrenic patients do not have benevolence attribution toward auditory hallucinations. Similarly, previous studies which were not included in present meta-analysis have also reported that very few voice hearers constructed voices as benevolent and majority of voice hearers perceive voices as persecuting them, and voices were out to gain control of them [9]. Overall schizophrenic patients perceive voices as powerful and omnipotent [27].

Inconclusive findings were found by us in the area of resistance feeling toward auditory hallucinations among schizophrenic patients. Other previous research studies, not included in present meta-analysis, have reported that the occurrence of hallucinations were related to the appearance of intrusive thoughts associated with anxiety, meta-cognitive beliefs concerning low self-confidence in one's own judgments and beliefs [24]. However, Qulis et al. have also concluded that auditory hallucinations give negative emotional and behavioural impact on schizophrenic patients; and have also found similar trend of negative correlation between auditory hallucinations and supportiveness and mood enhancing effect of the hallucination [28]. Schizophrenic patients resist behaviourally in order to prevent auditory voices. Findings of present meta-analysis are consistent with other previous researches [29, 30, 31]; who have also reported 60% to 94% schizophrenic patients using resistance behaviour to cope with hallucinations.

Schizophrenic patients do not have feelings of engagement with auditory hallucinations. Findings of the present meta-analysis are similar to that of Brichwood and Chadwick; who have reported that more than two third of the voice hearers were at least moderately depressed, which may be directly attributable to the interpersonal appraisal to power and entrapment by the voices [9]. Schizophrenic patients also don't show engagement behaviour with auditory hallucinations. The findings of present meta-analysis are similar to that of Sanjuan, et al. [32], who have also concluded that negative associations were found with intensity of distress and negative content with auditory voices attributed by schizophrenic patients.

We used only published data for present meta-analysis, which is a methodological limitation, along with limited detection of heterogeneity across studies and validity of results. Small sample size in some included studies also undermines the statistical power of this meta-analysis [13].

CONCLUSIONS

The meta-analysis of nine methodologically sound studies, according to our inclusion and exclusion criteria, has shown that the schizophrenic patients have malevolence attitude toward auditory hallucinations. Resistance feeling toward auditory hallucinations among schizophrenic patients is still a question but behaviorally they resist hallucinatory voices. Schizophrenic patients do not have feelings of engagement with auditory hallucinations and they do not engage themselves behaviourally with auditory hallucinations.

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Attention deficit hyperactivity disorder (ADHD) : subtypes and comorbid behavioral disorders in a school based sample.

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ABSTRACT:

Background : *There have been wide discrepancies in the various epidemiological aspects of ADHD in the reports from all over the world. Data of the same from Asian community samples too are inadequate.*

Aims and Objectives : *To estimate the prevalence of ADHD, distribution of its subtypes and association with various co-morbid behavioral disorders and aggression in various domains in school based study sample.*

Methodology : *A government aided school in Mumbai, familiar to the authors, was selected for the study. After obtaining the appropriate permissions from the authorities, students of grades 5th to 9th were screened, using Vanderbilt's ADHD diagnostic rating scale, both teacher's and parent's versions; for the presence of ADHD and its subtypes, and Children's aggression scale, again teachers and parents version; for aggressive behavior. About 500 translated sets were given to the teachers and parents for reporting. 341 completed sets were received and analyzed by appropriate statistical methods.*

Results : *The point prevalence of reported symptoms consistent with diagnosis of ADHD was found to be 14 percent in our study population, of which most common (70%) were consistent with combined type; and least common were those reported with symptoms suggestive of inattentive subtype (8%). The prevalence was 1.4 times more in boys and it decreased with increasing age in both the sexes. Symptoms suggestive of behavioral problems in form of Oppositional Defiant disorder (28%), Conduct Disorder (10%) and anxiety/ depression (6%) were co-reported in population with reported symptomatology of ADHD, all of which were significantly more than those reported in student population without reported symptomatology suggestive of ADHD; suggesting significant co-morbidity. Also, children who had symptomatology suggestive of ADHD, had reported rates of aggressive behavior than those who didn't.*

Conclusions : *Similar studies with larger sample sizes and clinical assessment of individual subjects may yield more accurate data regarding the epidemiology of ADHD that will be useful for early diagnosis and complete assessment of co-existent disorders in patients suffering from ADHD.*

Key words: ***Attention Deficit Hyperactivity : Children Aggression***

INTRODUCTION

Historically, the first description of ADHD comes from George Still, who in 1902 described children with restlessness, impulsivity, inattentiveness and severe affect and conduct problems [1]. Since then ADHD has been addressed by various names depending upon the contemporary belief of its causation or the most severe symptom [2].

Attention-deficit/hyperactivity disorder or ADHD is probably the commonest psychiatric disorder diagnosed in children [3]. It is characterized by a persistent pattern of symptoms resulting from impulsivity/hyperactivity and/ or inattention [4]. There is a wide range of prevalence of ADHD, reported from various parts of the world. A range from 3 to 7 percent of prepubertal elementary school children can be considered as a safe estimate of prevalence of the disorder [5-6]. Most of the studies on ADHD have confirmed that the disorder is more prevalent in boys, the sex ratio again displaying a wide range from 1:2 to 1:9 [7-8].

It has also been found that the occurrence of the disorder decreases with age. However, about 40-50 percent of patients continue to have at least some symptoms through adulthood [9-11]. DSM-IV TR presents an ADHD diagnosis with three subtypes: predominantly inattentive (IA), predominantly hyperactive/impulsive (HI), and combined type (C). Some studies have identified

inattention as the commonest subtype while others report that hyperactivity/impulsivity or combined type is commonest [12-15]. The existence of comorbid disorders influences the severity, treatment and prognosis of ADHD. Apart from externalizing behavior disorders such as oppositional defiant disorders and conduct disorders, and internalizing disorders such as anxiety and depression, children suffering from ADHD can have co-existing learning disorders, bipolar disorders, Tourrette's syndrome and various other co-morbidities [16-17]. Again there has been a wide discrepancy in the estimated occurrences of comorbid disorders. Some studies have reported the prevalence of comorbid disorders to be as high as 87% in the population affected with ADHD [18].

It has been shown that ADHD and oppositional defiant disorder coexist in 30 to 40 percent of ADHD patients. ADHD and conduct disorder have been reported as co-occurring in 30 to 50 percent of patients [19-22]. However, some recent have found that only 14.3 percent were comorbid for conduct disorder [23]. Earlier studies reported the coexistence of depression in patients with ADHD to range from 9 to 38 percent [21]. Anxiety disorders co-occurring with ADHD have been reported at 25 percent [21].

In view of the wide discrepancies in the available reports and dearth of Indian data on various aspects of ADHD, this study was undertaken with the following aims

1. To estimate the prevalence of ADHD
2. To assess the distribution of its subtypes
3. To establish and measure the rates of comorbid disorders with ADHD
4. To measure the frequency of aggression in ADHD.

METHODOLOGY

The students of a government aided vernacular medium belonging to 5th to 9th grades were screened using standard rating scales for ADHD, its co-morbidities and patterns of aggressive behavior. After obtaining the appropriate permission from the school authorities, the sets of questionnaire containing parents' version were distributed to the students of the above grades, in each of the sections, to be given to their parents at home. The teachers' version sets were given to the class-teachers.

Teachers and parents were counseled and educated about the study in groups. Apprehensions that might have biased reporting by them were addressed and parents as well as teachers were assured that there will be no change in attitude towards participating students, should they qualify for the diagnosis of behavioral disorders under consideration, as complete anonymity will be maintained.

Each completed set was studied by the authors and only those sets that had consistent reporting by both teacher and parent were considered for further analysis. 341 students were thus found to be eligible for inclusion in the study.

The following rating scales were used –

a) **Vanderbilt's ADHD Diagnostic Rating Scale (VADRS)** : This is a scale designed to assess disruptive problems in ADHD and is modeled on DSM-IV criteria. The scale includes all 18 criteria for ADHD, and also includes items representing DSM-IV criteria for Oppositional Defiant Disorder (ODD), Conduct disorder (CD) as well as Anxiety and Depression. The items are rated on 4 point scale with response-options never, occasionally, often and very often. It also includes performance items in 8 areas, reporting and evaluation of these were not incorporated in the study due to inadequate reporting. The scale has a reliability rate according to the Cronbach's alphas, for both parents and teachers versions and in all domains ranging from 0.79 for anxiety and depression to 0.91 for ADHD. High degree of correlation was found between diagnosis based on VADPRS/ VADTRS and diagnosis by structured clinical interview proving its validity. The scale has two versions – a parent's version to be completed by parents made up of 47 items and a teachers version to be completed by the class teacher which is a 35 item questionnaire [24-25].

a) **Children's aggression scale (CAS)** : This is a scale designed on the Overt Aggression Scale for Adults for assessment of aggressive behavior in children. It is also available in two versions i.e a parent and a teacher version. The items are rated on 5 point scale with responses. The items are recorded on 5 subscales viz. verbal aggression, aggression against animals and objects, provoked physical aggression, initiated physical aggression and use of weapons. It has good reliability between 0.62 for individual subscales to 0.90 for the total scale. There's good correlation between reported symptoms on CAS-P and CAS-T [26-27].

The scales were translated into Marathi, as it is the language spoken and understood by the majority of teachers and guardians of the population to be studied. The translated versions were rechecked by independent language experts for their correctness. Both sets contained instructions regarding completion of the items. Data such gathered was analyzed using appropriate statistical methods to calculate prevalence of ADHD with its

subtypes and record behaviors suggestive of various comorbidities which can be screened using Vanderbilt's diagnostic scale and prevalence of aggression in various domains and its association with diagnosis of ADHD.

RESULTS

There was not much differences in the number of boys and girls across various age groups. There was a total of 341 students who were a part of the study of which 177 i.e. 52% were girls. The total number of students fell from 80 in grade 5 to 57 in grade 9. Out of the 341 students enrolled for the study, 50 (14.66%) had a diagnosis of ADHD. The prevalence of ADHD was higher i.e. 20% in fifth and sixth grade (16 out of 80 in each group) and declined as the grade went higher till the ninth grade reaching just 2% (1 out of 57). Out of the 50 children diagnosed with ADHD, 28 (56%) were boys.

According to our analysis of data, combined type of ADHD was the most prevalent accounting for 70% of cases (35 out of 50). Symptoms of pure inattentive type were found to be reported the least, in only 8 percent of symptomatic children, as shown in the following table and chart. We found that almost 40% of children symptomatic for ADHD had at least one comorbid psychiatric disorder. In our study, about 10 percent of ADHD patients were found to be having conduct disorder. We found symptoms of oppositional defiant disorders to be present in 28 percent patients in our study. The prevalence of anxiety-depression symptoms was found to be 6 percent in our study. Nearly 40% percent of students having ADHD had significant aggressive behavior as a symptom. Prevalence of all comorbid disorders were higher in the group having ADHD than a non ADHD population (table 1). Comorbidity was also reported to be greater in boys than girls with ADHD (table 2). It was also noted that prevalence of reported aggressive behaviour in all three domains; namely verbal, towards animals and object as well as physical aggression were significantly higher in students reported to have significant ADHD symptoms. Also these students were reported to have aggression in more than one domain more commonly than those students without reported symptoms of ADHD (table 3).

DISCUSSION

The prevalence estimates of ADHD have varied significantly from study to study despite the latest DSM diagnostic criteria being very popular and comprehensive. The discrepancies arise probably due to the differences in the settings of the studies, the methodology used for screening, varying population structures and other variables [28]. Most studies have reported a prevalence range of 5-10 percent [29-30]. Our study has reported a rather higher prevalence of ADHD compared to most studies. The symptoms on the basis of which the diagnosis of ADHD was given were reported by teachers and parents. Some symptoms may be present due to problems faced by the children in other domains. Also, reporting biases based on their academic performances cannot be ruled out. A clinical assessment of the children who were distinctly reported to be having the symptoms may have decreased the estimated prevalence [31].

The natural course of ADHD follows a declining severity with age [32-33]. This may be ascribed to the natural neurochemical and neurobiological changes occurring in the brain, the effect of environmental learning, personality development, puberty and maturity or a combination of all the factors [34]. Our study too reports a decline with age in the prevalence of ADHD. It has been confirmed time and again that this disorder is commoner in males, owing to genetic factors, neurobiological differences, environmental differences, differences in the pattern of parenting, cultural factors and a combination of these factors [35]. ADHD has been found to be 2 to 9 times commoner in boys [36-37]. In our study, ADHD were reported 1.4 times more commonly in boys. Girl students were in a slightly higher proportion in our study sample. Also, the cultural biases in the reporting of symptoms cannot be ignored. Correcting such factors may give a more accurate idea about sex differences.

There has been a wide controversy in the reports of frequency of subtypes of ADHD. Data of distribution of the subtypes in an older age group, as in our study, are lacking. There have been reports that inattentive type is the commonest followed by combined type in 5-18 years old [38]. Our study however reports the combined type to be more prevalent. Oppositional defiant disorder is the commonest comorbid psychiatric comorbidity reported in our study followed by anxiety and mood disorders. This is in keeping with comorbidity studies worldwide [39-40]. It is also well known that comorbidity of conduct problems and oppositional defiant disorder that complicates ADHD in childhood may lead to substance abuse disorder or antisocial personality disorder in adult life over a longitudinal course [41]. This is a study that has been restricted to a school population rather than a community based population. Hence discrepancies in the findings compared to community based studies may arise [42].

CONCLUSION

Although the observations in the study have been similar to the existing international data in many findings, a large-scale community based study across various centres with better objective and clinical assessment of the children is warranted for more accurate data. The study however adds to the dearth of data as far as prevalence studies on ADHD in the Indian subcontinent are concerned.

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TABLE 1 – PREVALENCE OF COMORBID DISORDERS

DISORDER IN ADHD	PREVALENCE IN NON-ADHD	PREVALENCE IN TOTAL	PREVALENCE
ODD	26%	3%	7%
CONDUCT DISORDER	10%	1%	2.3%
DEPRESSION-ANXIETY	6%	1.7%	2.4%
AGGRESSION	40%	2.7%	8.2%

TABLE 2 : SEX-WISE PREVALENCE OF COMORBID DISORDERS

DISORDER	PREVAELNCE IN BOYS	PREVALENCEIN GIRLS
ODD	7.9%	5.6%
CONDUCT DISORDER	4.2%	0.6%
DEPRESSION-ANXIETY	1.8%	2.8%
AGGRESION	11%	5.65%

TABLE 3 : OVERLAPPING SYMPTOMS IN DOMAINS OF AGGRESSION AND ADHD

NUMBER OF DOMAINS WITH SYMPTOMS	ADHD POPULATION (TOTAL PERCENTAGE)	NON-ADHD POPULATION (TOTAL PERCENTAGE)	TOTAL POPULATION (TOTAL PERCENTAGE)
ONE DOMAIN	9 (18%)	7 (5.4%)	16(4.7%)
2-3 DOMAINS	4 (8%)	1 (0.34%)	5(1.5%)
> 3 DOMAINS	6 (12%)	0(0%)	6(1.8%)

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Correlation between Emotional Intelligence and Cognitive Symptoms in Schizophrenia

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ABSTRACT:

Schizophrenia is characterized by cognitive dysfunction and disturbed inter-personal relationship. Emotional intelligence operates across both the cognitive and emotional systems. The present study examined correlation between cognitive symptoms (i.e. attention/concentration, memory, visual functioning, language and executive functioning) and emotional intelligence (i.e. intra-personal awareness, inter-personal awareness, intra-personal management and inter-personal management) in patients with schizophrenia. Thirty five patients with schizophrenia diagnosed according to the ICD-10 DCR were individually assessed on Cognitive Symptoms Checklist and Mangal Emotional Intelligence Inventory to examine the correlation between cognitive symptoms and emotional intelligence. Results revealed that activity of daily living: money management was significantly correlated with all the areas of emotional intelligence. Internal distractors: emotional, and simultaneous attention were significantly correlated with most of the areas of emotional intelligence. Figure/ground, hearing and processing speed were significantly associated with inter-personal management. Mental flexibility, planning and sequencing were significantly associated with inter-personal awareness.

Key Words: ***cognitive symptoms, emotional intelligence, schizophrenia.***

INTRODUCTION

Scientific findings on emotional intelligence support the notion that emotions are functional when the information they provide is attended to, interpreted accurately, integrated into thinking and behavior, and managed effectively. According to emotional intelligence theory, the cognitive, physiological, and behavioral changes that accompany emotional responses are adaptive – these changes prepare us to respond to the event that caused the emotion to occur.[1] The theory also asserts that emotions serve important social functions, conveying information about other people's thoughts, intentions, and behavior.[2] Indeed, the ability to integrate emotional information into cognitive activities is essential to effective functioning across the life course.[3]

There have been relatively a few researches on the relationship between emotional abilities and performance on cognitive tasks. Theoretical work suggests that exploration of the influence adaptive emotions may have on task performance would enhance our understanding of both task performance and emotion. Singer[4] and Izard[5] pointed out that emotions are an important component of the tapestry of consciousness and cognitive processes. Both Piaget[6] and Damasio[7] argued that emotions may fuel or energize cognitive functioning and learning.

Growing evidence suggests that social cognitive variables such as emotional intelligence mediate rela-tions between neurocognition and social functioning in schizophrenia.[8, 9, 10, 11] Eack et al.[12] used the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) to examine changes in the emotional intelli-gence of persons with schizophrenia resulting from Cognitive Enhancement Therapy. A series of analyses of covariance showed highly significant and large effects favoring Cognitive Enhancement Therapy for improving emotional intelligence, with the most pronounced improvements occurring in patients' ability to understand and manage their own and others' emotions. These findings lend preliminary support to the previously documented benefits of Cognitive Enhancement Therapy on social cognition in schizophrenia, and suggest that such benefits can be extended to patients in the early course of the illness.

Aguirre et al.[13] examined emotional intelligence in persons with schizotypy. Undergraduates identified as high or low in schizotypy based on their responses to the Schizotypal Personality Questionnaire - Brief Version[14] were administered the Mayer-Salovey-Caruso Emotional Intelligence Test[15]. The second aim of their study was to examine relations between the emotional intelligence of persons with high schizotypy and aspects of their social

and neurocognitive functioning. The Social Adjustment Scale - Self Report[16] was used to assess three aspects of social functioning: academic functioning, relations with peers and relations with family. Executive functioning and verbal episodic (secondary) memory were selected as neurocognitive constructs because they are often impaired in schizophrenia spectrum disorders. Assessing with Mayer-Salovey-Caruso Emotional intelligence Test, person high in schizotypy were im-paired in overall emotional intelligence and two aspects of emotional intelligence, namely, the ability to perceive emo-tions and the ability to manage emotions. The finding of impaired emotional intelligence in schizo-types is consistent with the prior studies of social cog-nition in schizotypy that have identified impairments in emotion perception and theory of mind. [17, 18, 19]

Emotional intelligence and its elements were asso-ciated with neurocognition and social functioning in persons with high schizotypy. Overall emotional intel-ligence was associated with aspects of verbal episodic (secondary) memory in the persons with high schizo-typy. The understanding emotions and managing emo-tion branches of emotional intelligence were associated with indicators of verbal episodic (secondary) memory and executive functioning in the persons with high schizotypy.[17]

Neurocognition affects social cognition and that poorer social cognition leads to social discomfort on the job, which in turn leads to poorer rehabilitation outcomes.[20]

Emotional intelligence was found to be associated with working memory capacity, followed by verbal memory, sustained attention/vigilance and negativity. These factors strongly predicted poorer social functioning in first episode schizophrenia, along with poorer quality of life in psychological, social, and health satisfaction facets. [21]

Hence, this study is an effort for better understanding of association between cognitive symptoms and emotional intelligence of the patients with schizophrenia so that, specific cognitive rehabilitation strategies can be made which may help them to improve their emotional intelligence. This will surely help them to adjust in their society in a better way.

METHODOLOGY

This is a cross sectional study designed to assess correlation between cognitive symptoms and emotional intelligence of schizophrenic patients.

Sample:

A sample consisting of thirty five schizophrenic patients was taken using purposive sampling technique. Most of the patients were in the age range of 20-35 years (60%). Most of the patients were educated up to matric (60%). All patients were male and most of them were married (60%) and unemployed (54%). Most of the patients were Hindus (77%), from joint families (60%) and belonging to lower socio-economic status (63%) hailing from rural areas (71%) of Jharkhand and Bihar. Schizophrenic patients with any other neurological disorder/major physical illness were excluded. All subjects were cooperative and gave consent for the study.

Tools:

Socio-demographic Data Sheet: To collect information regarding socio-demographic characteristics and other related information of the sample a socio-demographic data sheet was developed for the present study.

Brief Psychiatric Rating Scale (BPRS): BPRS is 18-items well established scale developed by Overall & Gorham (1962)[22] measuring positive symptoms, general psychopathology and affective symptoms.

Cognitive Symptom Checklist: Cognitive Symptom Checklist is originally developed by Christine O'Hara et al. (1993)[23]. In this study Hindi adaptation (Jahan et al., 2010)[24] of cognitive symptoms checklist was used. It is an important clinical tool, to identify the problems in daily living skills under the heading of attention/concentration, memory, visual functioning, language and execution. This cognitive domains of attention and concentration was further subdivided into the areas of internal distracter (physical, emotional), external distracter (visual, auditory and environmental), sustained attention, divided attention and simultaneous attention. The domain of memory was further subdivided into activities of daily functioning (medication, nutrition/ food preparation sequence, safety, routine, money management, spatial relationship) time and receptive language. The domain of visual process was further divided into vision, visual field/neglect, scanning, discrimination, figure-background, mental imagery and organization. Language was further subdivided into the following headings: hearing, speaking, receptive language (auditory), receptive language (written), expressive language (speaking) and expressive language (writing). Executive functioning was divided into following sub divisions-processing speed/reaction time, initiation/follow-through, self correction, mental flexibility, planning, organization and reasoning. The Cognitive Symptom

Checklist provides a frame work from which clinicians can gather additional information about the nature of specific problems to target to treatment and it prioritizing problems for treatment. Using Cognitive Symptom Checklist, the clinicians can provide both fine tuning of the specific problems areas to be addressed and appropriate situations for the practices of strategies.

Mangal Emotional Intelligence Inventory (MEII): It is 100 items inventory developed by Mangal & Mangal (2004)[25] assesses four areas or aspects of emotional intelligence, namely, intra-personal awareness (knowing about one's own emotions), inter-personal awareness (knowing about other's emotions), intra-personal management (managing one's own emotions), and inter-personal management (managing other's emotions). Each area consists of 25 questions to be answered as YES or NO.

Procedure:

Participants were selected according to inclusion and exclusion criteria. Severity of psychopathology was assessed by Brief Psychiatric Rating Scale. Socio demographic information was collected using the Socio demographic Data Sheet. Information was gathered from reliable sources. Cognitive Symptom Checklist and Mangal Emotional Intelligence Inventory were administered to all participants.

Statistical analysis:

Data obtained was analyzed with respect to the objectives of the study. Frequency, percentage and correlation were applied for the analysis of the data. Statistical Packages for Social Sciences (SPSS) was used for analysis.

RESULTS

Correlation was calculated between variables of cognitive symptoms and emotional intelligence. Negative correlation was found for most of the variables. Higher score on emotional intelligence suggests better emotional intelligence, whereas, higher score on cognitive symptoms suggests poor performance. Hence, negative correlation suggests that better emotional intelligence is related to better cognitive functioning.

Table 1 shows that impairment in internal distracters: emotional and simultaneous attention, were significantly negatively correlated with inter-personal awareness, inter-personal management and total emotional intelligence. It suggests that the higher impairment in internal distracters: emotional and simultaneous attention, were associated with poor inter-personal awareness, inter-personal management and total emotional intelligence. Impairment in external distractors: auditory was associated with poor inter-personal management. Impairment in divided attention was significantly negatively correlated with inter-personal awareness.

Table 2 shows that difficulty in activity of daily living: money management was significantly correlated with all the four areas of emotional intelligence i.e. intra-personal awareness, inter-personal awareness, intra-personal management and inter-personal management. Difficulty in activity of daily living: medication was significantly correlated with poor inter-personal awareness and total emotional intelligence, activity of daily living: nutrition was significantly correlated with poor intra-personal awareness and total emotional intelligence, activity of daily living: safety was significantly correlated with poor inter-personal management and total emotional intelligence, activity of daily living: routine was associated with poor intra-personal management and total emotional intelligence. Deficit in expressive language was associated with poor intra-personal management. Difficulty in other sections of memory was not significantly correlated with any of the area of emotional intelligence.

Table 3 shows that difficulty in figure/ground was associated with poor inter-personal management, but no other section of visual process was significantly correlated with any area of the emotional intelligence.

Table 4 shows that hearing was associated with inter-personal management, but no other section of language significantly correlated with any area of emotional intelligence.

Table 5 shows that impairment in processing speed was associated with poor inter-personal management. Deficit in mental flexibility, planning and sequencing were associated with poor interpersonal awareness. Problem in initiation, problem solving, organization and reasoning were not significantly correlated with any of the area of emotional intelligence.

DISCUSSION

The result suggests that there is significant negative correlation between cognitive symptoms and emotional intelligence in patients with schizophrenia. Emotional intelligence has been suggested to be an important mediating variable in the relationship between neurocognition and functional outcome. There is considerable inconsistency in findings regarding the

relationship between specific cognitive deficits and social impairment in patients with schizophrenia. This inconsistency may relate to variability across studies in how social functioning is measured and preliminary evidence suggests that different indices of social functioning (e.g., laboratory test, community assessment) may have different cognitive correlates.[26]

Result shows that attention was significantly correlated with emotional intelligence. Mainly emotional distractors and simultaneous attention were significantly negatively correlated with inter-personal awareness, inter-personal management and total emotional intelligence. Attention plays a critical role in day-to-day functioning. For instance, attention is important while conversing with others successfully. Hence, association between attention and emotional intelligence is important. It can be helpful to improve the social and occupational functioning of individuals with schizophrenia and thus enhance their quality of life.

Memory efficiency has been shown to play a crucial role in daily living and social outcome in patients with schizophrenia.[27] It is therefore particularly important to determine the factors that are involved in the memory impairment consistently observed in this population, in order to develop more targeted and effective treatment. In sections of memory difficulty in remembering personal things was significantly correlated with intra-personal management, inter-personal management and total emotional intelligence. Difficulty in remembering routine of daily activity and expressive language were significantly correlated with intra-personal management. In a previous study overall emotional intelligence was associated with verbal episodic (secondary) memory, but not executive functioning, in persons with high schizotypy.[13]

In the domain of visual process difficulty in figure/ground perception was significantly negatively correlated with inter-personal management. Visual processing may contribute to deficits on neuropsychological tests of visual cognition, and may also reflect cross-modal disturbances of working memory function.[28]

In the domain of language difficulty in hearing was significantly correlated with inter-personal management. Negative emotion impairs language production, at least in part by increasing physiological arousal.[29] But in previous studies Bommer et al.[30] concluded that patients with pure delusional disorder have difficulties in metaphorical speech comprehension but their basic social cognitive abilities were preserved. However, no such study was found on schizophrenic patients.

In executive functions processing speed and self correction were significantly negatively correlated with inter-personal management. Mental flexibility, planning and sequencing were significantly correlated with inter-personal awareness. These findings are supported by earlier studies reporting that executive functioning is associated with social cognitive deficits.[30] In the other study it was found that emotional intelligence was not associated with executive functioning with person with high schizotypy.[13]

Initial research by Schutte et al.[31] and Schutte and Malouff[32] found a link between emotional intelligence and performance in the cognitive domain. Emotional intelligence predicted student's performance independently of cognitive ability.

Overall, findings of the present study suggest that cognitive symptoms are correlated with emotional intelligence in schizophrenic patients. However, there are few limitations of this study. Only male participants were included and effect of medication could not be controlled. Further research is needed on drug controlled patients of both genders controlling severity of psychopathology. Longitudinal study may help to shed more light on the progress and stability of cognitive symptoms. Such investigations could yield important insights regarding the dimensionality of emotional intelligence deficits in schizophrenia and their correlation with cognitive symptoms.

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Table 1: Showing the correlation between attention/ concentration and emotional intelligence

	Intra-personal Awareness	Inter-personal Awareness	Intra-personal Management	Inter-personal Management	Total
Internal distractors: physical	.103	-.065	-.210	-.216	-.138
Internal distractors: Emotional	-.125	-.406"	-.226	-.387"	-.394"
External distractors: Visual	.369"	-.080	.303	-.146	.206
External distractors: Auditory	.143	-.147	.128	-.348"	-.040
External distractors: environmental	.037	.012	.223	-.051	.101
Sustained concentration	-.009	-.212	-.162	-.236	-.213
Divided attention	-.062	-.344"	-.051	-.139	-.199
Simultaneous attention	-.234	-.616"	-.093	-.377"	-.443"

*significant at 0.05 level, **significant at 0.01 level

Table 2: Showing the correlation between memory and emotional intelligence

	Intra-personal Awareness	Inter-personal Awareness	Intra-personal Management	Inter-personal Management	Total
Activity of daily living: medication	1	.483"	.216	.229	.706"
activity of daily living: nutrition	.483"	1	.180	.262	.668"
activity of daily living: safety	.216	.180	1	.450"	.713"
activity of daily living: routine	.229	.262	.450"	1	.667"
activity of daily living: money management	.706"	.668"	.713"	.867"	1
activity of daily living: spatial relationship	.193	-.214	.053	-.057	.012
Time	.271	-.177	.183	-.006	.125
receptive language	.293	-.112	.017	-.133	.045
expressive language	-.205	-.226	.339"	.012	.000
Personal	-.027	-.107	-.066	-.141	-.116

*significant at 0.05 level, **significant at 0.01 level

Table 3: Showing the correlation between visual processing and emotional intelligence

	Intra-personal Awareness	Inter-personal Awareness	Intra-personal Management	Inter-personal Management	Total
Vision	.120	-.057	-.149	-.116	-.072
Visual field	.032	-.024	-.147	-.158	-.107
Scanning	.170	-.092	.099	-.008	.077
Discrimination	.162	.068	.111	-.014	.129
Figure/ground	.088	-.076	-.030	-.464"	-.141
Mental imagery	.070	-.156	.017	-.051	-.031
Spatial relationship	-.015	-.117	.019	-.111	-.069
Organization	-.120	-.034	.077	-.088	-.050

*significant at 0.05 level, **significant at 0.01 level

Table 4: Showing the correlation between language and emotional intelligence

	Intra-personal Awareness	Inter-personal Awareness	Intra-personal Management	Inter-personal Management	Total
Hearing	.246	-.024	-.279	-.356*	-.140
Speaking	.232	.212	-.012	-.227	.086
receptive language: auditory	.180	.010	-.065	-.287	-.041
receptive language: written	.022	-.117	.056	-.244	-.077
expressive language: speaking	-.053	-.270	-.047	-.110	-.161
expressive language: writing	.234	-.053	.054	-.158	.050

*significant at 0.05 level, **significant at 0.01 level

Table 5: Showing the correlation between executive functioning and emotional intelligence

	Intra-personal Awareness	Inter-personal Awareness	Intra-personal Management	Inter-personal Management	Total
Processing speed	.201	-.132	-.063	-.380*	-.106
Initiation	.088	-.152	-.040	-.221	-.099
self-correction	.252	-.185	.213	.322	.227
Mental flexibility	-.205	-.428*	.056	-.228	-.261
Planning	-.174	-.430*	-.032	-.150	-.266
Sequencing	-.064	-.355*	-.143	-.168	-.248
problem solving	.032	-.264	.219	-.145	.026
Organization	.093	-.236	.232	-.029	.052
Reasoning	.051	-.263	.221	.078	.054

*significant at 0.05 level, **significant at 0.01 level

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PERCIEVED SOCIAL SUPPORT IN FEMALE PATIENTS WITH BIPOLAR AFFECTIVE DISORDER: IMPACT OF PROLONGED HOSPITALIZATION ON MARRIAGE

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ABSTRACT:

Background: *Studies on bipolar disorder have revealed that 90 percent of patients with bipolar disorders end in divorce giving 10 percent chance of survival. The present study was designed to assess clinical, social, cultural, economic and demographic factors in female bipolar patients who are either separated or staying together with their respective spouse despite having a serious psychiatric morbidity.* ***Method:*** *Total sample consisted of two groups of married female patients. Each group consisted of 25 patients diagnosed with bipolar affective disorder according to ICD-10 DCR. Test used to assess support system was Sarson Social Support Questionnaire and Young Mania Rating Scale was used to assess the severity of manic symptoms.* ***Results:*** *The result showed that stable partnerships seem to be achievable when the partner's impairment is perceived as moderate or moderately severe, and when the frequency at which psychotic episodes occur is tolerable.* ***Conclusion:*** *Factors like, economic independence, less number of episodes and those hailing from urban areas are important that keep people in their marriages.*

Key words: ***Bipolar Disorder, Separated, Social Support, Women***

Introduction

Every marriage has challenges even among the most healthy, well-adjusted adults. When you add a mental health condition such as bipolar disorder into the mix, it can really strain a relationship. Being involved in a marriage with a patient who is suffering from bipolar disorder can be one of the toughest challenges for a loving relationship. With the spouse suffering from bipolar disorder experiencing mood swings and the bipolar disorder symptoms of mania or depression at any given time, it can present a tough challenge for both the husband and wife in the relationship. It has been seen that patients with bipolar disorder who had never married or who had been divorced or separated were similar to a group of healthy individuals. Results have shown that these patients have more severe difficulties in their relationships with their husbands than healthy controls matched for age and socioeconomic status. While these problems improve with remission of depressive symptoms, residual difficulties remain (Ruestow et al, 2004). Another study assessed the impact of bipolar disorder on aspects of everyday functioning and partners' attributions for patients' disturbing behaviour. Standardized instruments assessed partners' sexual and marital satisfaction across different affective states. Findings suggested that marital disharmony was greater when patients were ill and worse during manic than depressed phases. Marital disharmony was also more likely when partners believed the patient could control their illness; they had increased domestic responsibilities; or were sexually dissatisfied (Lam et al, 2005). The reason patients with bipolar disorders have extra problems and great risk of divorce is because the spouse suffering from bipolar disorder may experience bouts of depression as well as mania with or without treatment. These mood swings may have nothing to do with their partner or their marriage, yet the partner may feel the impact causing strain on the relationship (Sheets & Miller, 2010).

Increasing number of studies has examined the impact of bipolar disorder on spouse. Recent work on disability associated with psychiatric illness has emphasized the chronic burdensome nature of most psychiatric illness to the individual, their immediate social group and at a worldwide level (Murray and Lopez, 1996). The available data suggest that bipolar disorder may have an important impact on outcome of a marital relationship. In particular, spouse with high expressed emotion and/or negative affective style may be associated with an increased tendency to relapse in bipolar patients (Miklowitz et al, 1988).

Social interventions may be useful in these cases, particularly for those patients who are only partial responders to lithium and live with highly emotional spouses (Priebe et al, 1989). Another group, in New York, examined the gains achieved when a marital intervention was added to a randomly selected sample of married in

patients with bipolar disorder. It was found that additional marital therapy did not differ in symptoms at follow up but patients showed higher overall function and were more adherent to their recommended treatment. The two studies suggest that it is possible to conduct relevant research in these questions and subjective burden of care, difficult behaviours (Clarkin et al, 1990; 1998). However, studies on influence of bipolar disorder in outcome of marriages are scarce, more so in Indian population where strong social support mark an important societal asset for maintenance of relationships.

MATERIAL AND METHOD

The sample was collected from the Central Institute of Psychiatry, Ranchi, India from October 2010 to December 2010. Purposive sampling was used in a cross-sectional design. Patients with bipolar disorder, who were separated, and those who were not, served as participants for this study, respectively. The participants were informed about the intent of the study. The total sample size consisted of 50 married female patients diagnosed with bipolar disorder out of whom 25 were under treatment on outpatient basis and were living with their spouses and other group consisted of 25 patients who were separated from their spouses, convalescing at Inpatient department of CIP. Bipolar Disorder was diagnosed by consensus of two psychiatrists using ICD-10, Diagnostic Criteria for Research. Both group consisted of patients, between ages 18 and 35 years. Clinical groups were assessed on the Sarson Social Support Questionnaire (Short Form) (SSQ) and Young Mania Rating Scale (YMRS). Socio-demographic datasheet included age, education, and habitat, and financial support, number of episodes and duration of illness.

SSQ (Sarson, 1983) was administered on all participants in order to quantify the availability and satisfaction with social support. It is a 6 item self-administered scale. Each item involves two parts: respondents are asked to list the individuals that are available to them for help in specific situational circumstances and how satisfied they are with the support available. Each situational circumstance allows a participant to list up to nine individuals (who are identified through their initials and relationships with the respondent). A six point rating scale (from "very satisfied" to "very dissatisfied") was used to rate the individual's satisfaction with his or her support available. A support score for each item is calculated by the number of individuals the participant listed (number score). The overall support score (SSQN) is calculated by the mean of this scores across the items. The overall satisfaction score is calculated by the means of the 6 satisfaction scores (McDowell & Newell, 1996). For the current study short version (SSQ-SR) (Sarson, 1987) was used. It is popular because of its short administration time. Criterion validity of this test shows a significant negative correlation between the SSQ and a depression scale (ranging from -0.22 to -0.43), and correlations of 0.57 and 0.34 were obtained between an optimism scale and the satisfaction score and the number score, respectively (Sarason, 1983). Cronbach's alpha for internal reliability was 0.97. The inter-item correlations for the satisfaction scores ranged from 0.21 to 0.74, and the coefficient alpha was 0.94. Test-retest correlations of 0.90 for overall number scores and satisfaction scores of 0.83 were obtained (Sarason, 1983).

Young Mania Rating Scale (YMRS) (Young et al, 1978) is an 11-item instrument used to assess the severity of mania. YMRS features operationally-defined anchor points and the normal expected score is $\geq$20. Ratings are based on patients self-reporting, combined with clinician observation. Descriptive statistics, independent sample t-test and Pearson's correlation wherever applicable, were used using SPSS, version 13.

RESULTS

In socio-demographic variables (Table 1), significant difference was observed in occupation ($p<.05$) and education ($p<.01$) of the selected samples. It was observed that, in the non-separated group, most of the respondents of were employed, were hailing from urban areas, and also had educational background of intermediate to graduation. In the separated group, however, most of them were illiterate, unemployed and belonged to lower socio-economic status. [Insert Table 1 here]

Statistical significance was found between separated and non-separated female patients of bipolar disorder with respect to scores of age, number of episodes, duration of illness (years) and SSQ. It was found that scores of SSQ was significantly higher in non-separated patients as compared to separated patients, representing better perceived social support. The scores were significantly higher with respect to age, number of episodes, and duration of illness and YMRS representing poor illness profile in separated patients with bipolar disorder (Insert Table 2 here).

No correlation was found between scores of SSQ and YMRS with various clinical variables in the non-separated group (table 3a), whereas, significant negative correlation was found between number of episodes and SSQ ($p<0.01$) and between Duration of illness (Years) and SSQ ($p< .05$). (Table 3b) It can be understood that more is the duration of illness and number of episodes, poorer will be the perceived social support in female patients with bipolar disorder who have been separated from their respective spouses. [Insert table 3a and 3b here]

DISCUSSION

This is one of the introductory attempts in order to find out perceived social support and its association with illness variables in separated female patients with bipolar disorder. In this study we used SSQ, YMRS and clinical, social, cultural, economic and demographic details in order to see what factors are responsible for patients having poor social support (both separated and non separated with their spouses) despite having serious psychiatry morbidity and to determine the impact of bipolar disorder on marriage.

We found significant difference in the scores of SSQ between two groups clearly defining lack of social support secondary to social isolation due to factors like divorce, deliberate isolation etc, which could be aggravated due to lower education level and increased unemployment in the separated group. Studies have shown that divorce is associated with a wide variety of quality of life indicators, including low economic well-being, physical illness, and low overall life satisfaction (Gove, 1972; Kessler & Mcrae, 1984), also making it an important outcome factor.

Higher YMRS scores show increased disease burden in separated group which could be attributed primarily to lack of social support or the reverse causality in terms of higher affective symptoms leading to lack of social support. Similar findings were seen in other studies though both separated and non-separated groups were not compared simultaneously (Kessler & Mcrae, 1984; Ruestow et al, 2004). Dorz et al, 2005 found the presence of psychopathology in association with interpersonal sensitivity; hostility and perceived social support aspects, and not the severity of affective symptoms being most important factors affecting social adjustment in women with bipolar disorder.

The significant correlation between lower SSQ scores, number of episodes and duration of illness in separated group in comparison to non-separated group, shows that affective disorder can cause interpersonal difficulties which can lead to divorce, also shown by Kessler et al, who found that 48.2% of the respondents had at least one psychiatric disorders either before or during the first marriage subsequently divorced, compared to 35.9% of the respondents who had no disorder before or during the first marriage (Kessler et al, 1998). It is possible that unmeasured variables, such as childhood adversity or stressful living conditions, could have led both to psychiatric disorders and to subsequent adverse marital outcomes.

The findings of the current study could not be generalized due to representation of female gender and small sample size. Also cross-sectional examination makes the result more difficult to interpret as social support changes with time and improvement in illness. Other factors like attitudes, expressed emotions and marital adjustment may also provide with important additional information. Future effectiveness trials are needed to adjudicate between these contending causal interpretations to determine whether divorce can be prevented through treatment of psychiatric problems.

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Table 1: Comparison Of socio-demographic characteristics between separated and non-separated patients of Bipolar Disorder (N=50)

Variable		Non-Separated patients, (N=25) n/(%)	Separated Patients (N=25) n/(%)	X^2	df	p
Religion	Hindu	20(80)	20(80)	5.43	2	.516
	Muslim	2(8)	4(16)			
	Christian	3(12)	1(4)			
Occupation	Employed	17(68.0)	8(32.0)	6.48	1	.023*
	Unemployed	8(32.0)	17(68.0)			
Habitat	Rural	9(36.0)	14 (60.9)	2.97	1	.148
	Urban	16(64.0)	9(39.1)			
Education	Illiterate	5(20.0)	13(56.5)	6.82	1	.016**
	Literate	20(80.0)	10(43.5)			
Socio-economic status	LSES	6(24)	15(60)	7.21	2	.022
	MSES	14(56)	9(36)			
	HSES	5(20)	1(4)			

Significant at *p<.05, **p<0.01

Table no. 2: Group Difference in Social Support Questionnaire, YMRS, Duration of illness (years) and number of episodes (N=50)

Variable	Non-Separated patients (N=25) Mean±SD	Separated Patients (N=25) Mean±SD	t	df	P
Age	28.04±2.82	31.61±2.95	4.71	46	.001**
Number of episodes	3.16±.987	5.52±1.71	5.975	46	.001**
Dur of illness (yrs)	3.64±.907	6.52±1.782	7.200	46	.001**
SSQ3.66±.877	2.55±.890	4.450	48	.001**	
YMRS35.80±8.078	47.12±9.144	.756	48	.001**	

**p is significant at <0.01

SSQ= Social Support Questionnaire, YMRS= Young Mania Rating Scale

Table no. 3a: Correlation between scores of SSQ and YMRS with number of episodes, duration of illness (years) and education in Non-Separated patients of Bipolar Disorder (N=25)

Variable	SSQ r	YMRS r
Number of episodes	.234	-.205
Duration of illness (Years)	.212	-.181
Education	.151	-.240

P=NS

Table no.3b: Correlation between scores of SSQ and YMRS with number of episodes, duration of illness (years) and education in Separated patients of Bipolar Disorder (N=25)

Variable	SSQ r	YMRS r
Number of episodes	-.572**	.278
Duration of illness (Years)	-.150*	.469
Education	.050	-.048

SSQ= Social Support Questionnaire, YMRS= Young Mania Rating Scale

Correlation is significant at*p<.05, **p<0.01 (2-tailed)

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Original Articles :

Identification of bipolar spectrum disorder in patients with unipolar depression using bipolar spectrum diagnostic scale- A Pilot Study from Eastern India

Varnun S Mehta & Basudeb Das

ABSTRACT:

Background: *It has been suggested that soft bipolarity could account for 4% to 5% of the general population. The concept of bipolar spectrum disorder (BSD) has been reconstructed to describe patients who do not meet the strict DSM-IV criteria for bipolar I and II disorders, but who were otherwise bipolar at the soft end of the spectrum.*

Objectives: *To identify the presence of bipolar spectrum disorder in patients suffering from unipolar depression using the bipolar spectrum diagnostic scale (BSDS).*

Methodology: *Fifty three such patients of either sex satisfying ICD-10 DCR criteria for mild/moderate/ severe depression without psychotic symptoms in the age group of 18-60 years were selected for the study.The patients were rated on Montgomery-Åsberg Depression Rating Scale (MADRAS) to assess the severity of depression and the Bipolar Spectrum Diagnostic Scale (BSDS) to assess the presence of bipolar spectrum disorder.*

Results& Conclusion: *The prevalence of Bipolar Spectrum Disorder was found to be 22.6%. There was no relation of the group scores with the number of episodes and family history of affective illness. Though the bipolar spectrum diagnostic scale is a sensitive tool to recognize the individuals with depressive episode having underlying bipolarity, its use is more valuable as a supplement to other clinical characteristics.*

KEY WORDS: ***Unipolar Depression, Bipolar Spectrum Disorder***

INTRODUCTION

The concept of bipolar spectrum arises from the work of Kraepelinand Kretschmer, who wrote about affective states ranging from the severest to the mildest that pass without sharp boundary into the domain of personal predisposition or temperament. They described individuals with affective temperaments in whom low-grade affective manifestations of a subdepressive or hypomanic nature—without necessarily reaching a clinical or pathologic level—oscillated over long periods of the lifespan. Akiskal (1983) proposed the concept of a soft bipolar spectrum, with bipolar I at the severe end, bipolar II in the middle range, and BP III (pseudo-unipolar depression) at the softest end.This concept was further widened to include those individuals having depressions with hypomanic episodes, both protracted and brief in duration, cyclothymic and hyperthymic traits, and those with familial bipolarity. Thus, the prevalence rate of 1% commonly cited in the literature rose to 5 to 8 % with the inclusion of these categories under its rubric (Angst, 1998; Judd & Akiskal, 2003). Although individuals within the bipolar II spectrum represent the most common bipolar phenotype (Simpson et al, 1993) they are often unrecognized, poorly researched, and typically mismanaged. These individuals do not seek clinical consultation for hypomania but for their depressive states and are treated with antidepressants giving rise to potential consequences as mood switching, rapid cycling and treatment resistance (Akiskal &Mallya, 1987).More recently,Ghaemi et al (2002) reconstructed the concept of bipolar spectrum disorder (BSD) to describe patients who do not meet the strict DSM-IV criteria for bipolar I and II disorders, but who were otherwise bipolar at the soft end of the spectrum as described by (Akiskal & Mallya, 1987).

Much research has been conducted on the clinical prevalence of bipolar II disorder among patients who present with major depressive disorder to various clinical settings worldwide.It is seen that from 27% to 62% of all major depressions conform to the features of bipolar II or

its variants (Akiskal et al, 2000). The French EPIDEP study (Hantouche et al, 1998) based on a representative national clinical sample provides the most compelling data on the high prevalence of bipolar II among major depressive patients. The main finding was that at index interview, 22% of major depressive patients could be diagnosed as bipolar II based on history of hypomania; a month later, upon reinterview, 40% of patients could be diagnosed as bipolar II on the basis of more in depth evaluation. The proportion of depressive patients who can be classified as bipolar II further increases if the 4-day threshold for hypomania proposed by the DSM-IV is reconsidered. As the diagnosis of bipolarity in patients with unipolar depression would have treatment implications and prognostic significance, its identification becomes very crucial. There are many features which predict a bipolar outcome in these patients. Major depressive disorder (MDD) with early onset, hypersomnic-retarded features, rapid onset and offset of depression, pharmacological hypomania, postpartum episodes, psychotic depression, and bipolar family history are some among them(Strober & Carlson, 1982).

The current diagnostic gold standard tool, the structured Clinical Interview for DSM- IV (SCID) is not sufficiently sensitive to the diagnosis of hypomania or subthreshold manic states (Akiskal& Benazzi,2003b). An alternative method for the diagnosis of bipolar spectrum is to measure the number of hypomanic symptoms reported by subjects. Angst et al (2003) have developed the hypomanic symptoms checklist (HCL), which has been tested in the French EPIDEP study (Hantouche et al, 2003; Akiskal et al, 2003). Hirschfeld et al (2000) have developed a self-report scale for bipolar disorder, the Mood Disorder Questionnaire (MDQ) which was shown to have 0.73 sensitivity and 0.90 specificity. However, when a study was conducted to verify the sensitivity of the MDQ in a population of bipolar spectrum patients, it was found that the MDQ's sensitivity was good for bipolar type I (0.70) but less impressive for bipolar type II or NOS (0.30) (Miller et al, 2002). Recently, another scale has been developed by Ronald Pies to target bipolar II and NOS conditions: the Bipolar Spectrum Diagnostic Scale (BSDS). It is a self-rating scale for the entire bipolar spectrum and is a valuable supplement to the clinician's semi-structured interview. It was used by Ghaemi et al(2005) with the scale having equal sensitivity to diagnose bipolar I and bipolar type II or NOS.The current study is the first in India to use it as validation tool for the assessment of bipolar spectrum disorder in young adults with unipolar depression.

METHODOLOGY

The study was carried out at the Central Institute of Psychiatry, Ranchi which is a tertiary care centre catering to patients from Eastern India. The study was approved by the institutional review board. It was a cross sectional design and patients visiting the outpatient department as well as the inpatients were selected for the study.Fifty three patients of either sex between 18 and 60 years of age fulfilling ICD-10-DCR (WHO, 1993)criteria for mild/moderate/severe episode, single or recurrent without psychotic symptoms at the first contact to the institute and giving informed consent were selected.Those having severe medical illness, mental retardation or any co-morbid psychiatric disorder were excluded.The socio-demographic and clinical characteristics of all patients were noted. They were then rated on the Montgomery-Åsberg Depression Rating Scale (MADRAS)to assess the severity of depressionand only those individuals with a score ≥15 were selected. This scale consisting of 10 item checklist is used in patients with major depressive disorder, as a sensitive measure of change in symptom severity during the treatment of depression (Montgomery &Asberg,1979). The Bipolar Spectrum Diagnostic Scale (BSDS) was subsequently applied to assess the mood symptoms in them. It is a self rating scale which is composed of two parts. The first part is a paragraph containing 19 positively valenced sentences describing many of the symptoms of bipolar disorder. A checkmark to each sentence is worth one point. The second part is one simple multiple-choice question, asking them to rate how well the story describes them overall. The final scores of≥13 represent positive screens for bipolar disorder on the BSDS.

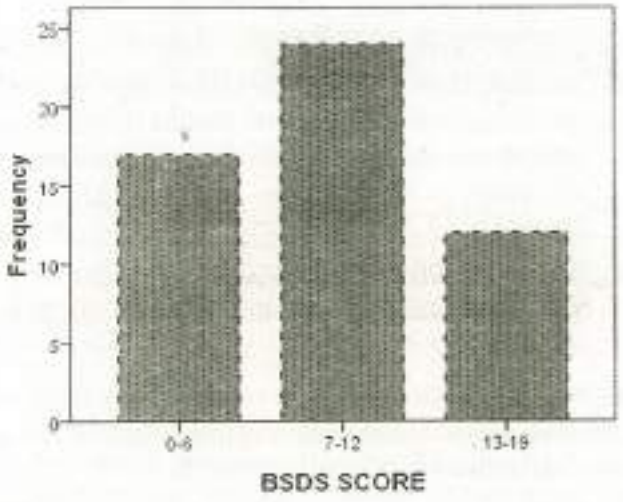
RESULTS

The data obtained was analyzed with Statistical Package for Social Sciences-version 16.0 for Windows® (SPSS Inc., Chicago, IL, USA). Normality of data was assessed using histogram and Shapiro-Wilk test.The socio demographic and the clinical characteristics of the group have been summarized in Table1. It was seen that the mean age of the patients was 37.49 years having a mean educational background of 10 years. Two third of the patients suffering from depression were males (67.9%). The mean duration of the index episode was 5.51 months.Most of the patients were suffering from a depressive episode of moderate severity with a mean score of 26.64.The mean BSDS score was 9.07 which were far below the threshold for a positive diagnosis of bipolar spectrum disorder. The representative group had approximately equal number of employed and unemployed

individuals. Majority of the patients were married (71.7%) and only a few belonged to higher socioeconomic status (5.7%). Seventy three percent of the patients came from the rural habitat. There was no previous history of depressive illness in sixty two percent of individuals with 28% patients reporting less than three episodes in the past and very few of them (9.4%) having more than three episodes. Approximately seventy two percent of individuals did not report presence of any psychiatric illness in the family. Only eleven percent of patients had a family history of depressive illness and only 3.8% patients had relatives suffering from non affective illnesses.

There was no relation between the groups with bipolar spectrum disorder and the past psychiatric illness ($p<0.05$) as seen in Table 2. Also, Table 3 shows that there was no significant difference seen in the group with respect to the family history of psychiatric illness ($p = 0.236$). The prevalence of the bipolar spectrum disorder was 22.6% as shown in Figure 1.

Figure 1: Prevalence of Bipolar Spectrum Disorder



DISCUSSION

The high percentage of males suffering from depression is in contrast to most of the epidemiological studies which point towards the female preponderance in depression. Studies concerning the gender differences in the symptomology of depression in non-clinical samples have found women to have a higher number of symptoms or a more severe type of depression (Angst & Dobler, 1984; Dion & Giordano, 1990). So, the nature of the study design which excluded patients with psychotic symptoms in the presence of a severe depressive episode could explain the difference in the findings. However, one study in Mumbai among young adults attending college, men were found to be moredepressed (25%) than women (18%) (Parikh et al, 2001). The average age of onset for recurrent unipolar major depressive episode falls between 30 and 35 years, whereas single episode major depression begins few years later. A similar finding was observed in our study with the average age of onset being 37.49 years. Mirza and Jenkins (2004) have found depressive disorders to be associated with middle age, low level of education, financial constraints and relationship problems. Studies have shown that economic hardship is a significant cause of depression. The Chennai Urban Rural Epidemiology Study (CURES)showed that there was an inverse relationship in prevalence of depression with income and education (Poongothai et al, 2009). However, no difference was found in the employment status of the patients in our study and they had a mean education of 10 years. Western studies report people in the lower economic status to be more depressed compared to those in the middle and high income status (Kessler et al, 1994; Isometsa et al, 1997). It has also been shown that illiterate people have higher prevalence of depression compared to their more educated counterparts (Pallson et al, 2001). Our study reflects similar findings with most of the people hailing from the rural background (71.7%) and only a few of them belonging to higher socio- economic status (5.7%). No significant difference was found in the bipolar spectrum disorder scores in patients with respect to the family history. However, the presence of family history of bipolar disorder has been the most important predictor of bipolarity in patients with unipolar depression. In fact, these patients with positive family history are considered as suffering from unipolar depression(Akiskal, 2002). Also, the presence of recurrent depressive episodes is also a predictor of bipolarity. Data from the National Institutes of Mental Health Collaborative Depression Study on "unipolar" patients who switched to bipolar II during11 years of follow-up found high rates of recurrent depression in such patients(Akiskal et al, 1995). Similar results couldn't be replicated in our study probably due to the low sample size.

Benazzi (2002) found that about 45% of 107 unselected outpatients with mooddisorders showed evidence of bipolar spectrum illness using the MDQ (Mood Disorder Questionnaire). Hirschfeld et al (2005) found that of 649 patients taking antidepressants for depression diagnosed by a primary care practitioner, 21% screened positive for bipolar disorder on the MDQ. When the

criteria proposed by Ghaemi et al (2002) was used to diagnose bipolar spectrum, the rate of bipolar I, II, and BSD was reported to be 61% in psychiatric outpatients who had at least 1 major depressive episode in a study conducted in Poland (Rybakowski et al, 2005). Daniel et al (2005) have used both the criteria proposed for BSD and the Hypomanic Symptom Checklist to diagnose bipolar spectrum Disorder. Between 47.1% and 77% of the individuals with major depression were diagnosed as having bipolar spectrum, depending on the diagnostic criteria used. In our study, the prevalence of the bipolar spectrum disorder was 22.6%. Our findings are in the range of prevalence of bipolar spectrum disorders across various studies (Akiskal et al, 2000). There could be several reasons for the comparatively lower prevalence. One of the factors could be the sole reliance on the self report measures by the patient to diagnose the disorder based on the probability criteria. The lack of inclusion of family history of bipolar illness, age of onset of depression, atypicality of symptoms and treatment response to antidepressants would lead to exclusion of patients having underlying bipolarity. Also, patients with severe major psychotic depression were not included in the study which could have led to low prevalence rates. But this could not be the likely factor as BSDS is a self report scale and patients with low insight into their illness may often underreport their symptoms (Ghaemi et al, 2005). The Bipolar Disorder is difficult to detect using self report measures (Laje et al,2002). One of the reasons could be the difficulty in recognizing the hypomanic or sub-hypomanic features by the patient as they do not cause substantial impairment. The BSDS scale has its advantage in that it focuses on change in the energy and drive during hypomanic episodes rather than emphasis on mood symptoms. We conclude that though the bipolar spectrum diagnostic scale is a sensitive tool to recognize the individuals with depressive episode having underlying bipolarity, its use is more valuable as a supplement to other clinical characteristics.

LIMITATIONS OF THE STUDY

The small size of the population was one of the limitations of the study. Also, there is a need for comparison of this scale with other self report scales.

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TABLES

Table 1: Sociodemographic and clinical characteristics of the group

Variables		Mean (SD)
Age		37.49(1.30)
Education in years		10 (5.07)
Duration of index episode in months		5.51 (6.32)
MADRAS total score		26.64 (8.18)
BSDS Score		9.07 (4.02)
		N (%)
Sex	Male	36 (67.9)
	Female	17 (32.1)
Occupation	Employed	22 (41.5)
	Unemployed	31 (58.5)
Marital status	Married	38 (71.7)
	Unmarried	15 (28.3)
SES	Lower	27 (50.9)
	Middle	23 (43.4)
	Higher	3 (5.7)
Habitat	Rural	39 (73.6)
	Urban	14 (26.4)
Past Psychiatric history	≤ 3 episodes	15 (28.3)
	>3 episodes	5 (9.4)
	Absent	33 (62.3)
Family Psychiatric History	Manic illness	7 (13.2)
	Depressive illness	6 (11.3)
	Non-affective illness	2 (3.8)
	Absent	38 (71.7)

Table 2: Comparison of the BSDS scores with the past psychiatric illness

BSDS Scores Illness	Past psychiatric V	N(%)	X2	df	P	Cramer's
0-6	< 3 episodes	4 (26.7)	8.89	4	0.058	0.289
	> 3 episodes	1 (20)				
	Absent	12 (36.4)				
7-12	< 3 episodes	4 (26.7)				
	> 3 episodes	4 (80)				
	Absent	16 48.5)				
13-19	< 3 episodes	7 (46.7)				
	> 3 episodes	0 (.0)				
	Absent	5 (15.2)				

Table 3: Comparison of the BSDS scores with the family psychiatric illness

BSDS Scores	Family psychiatric illness	N(%)	X2	df	P
0-6	Manic	42(28.6)	8.00	6	0.236
	Depressive	0(0)			
	Non-Affective	0 (0)			
	Absent	15 (39.5)			
7-12	Manic	2 (28.6)			
	Depressive	4 (66.7)			
	Non-Affective	2 (100)			
	Absent	16 (42.1)			
13-19	Manic	3 (42.9)			
	Depressive	2 (33.3)			
	Non-Affective	0 (0)			
	Absent	7 (18.4)			

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The cost of the opioid dependence syndrome.

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ABSTRACT:

The study was conducted in the peripheral area of Delhi where the de-addiction centre, AIIMS New Delhi was running. Majority of patients were within the radius of 60km. Their substances of abuse were heroin (Smack), prescribed opioids, and raw opium. The patients with lower educational level represented a major proportion of the sample and there was no effect of educational level on the expenditure. In India, the expenditure of the opioid dependent patients is increasing. The age group of 31-40 years represented the major proportion of the sample and the expenditure was decreasing progressively with the age of the patients. Most of the patients were transport operators especially auto rickshaw drivers. There was definite decrease in the productivity in the form of decreased wages and decreased earning. Most of patients spent more than 3-4 times their percapita income which suggests that the more than 50% of burden was passed to his family members. The patients with more percapita income spent more. The patients who were not on treatment had two times more expenditure than the patients undergoing treatment. Among the untreated patients the maximum expenditure (70% of total expenditure) was on procuring opioids, whereas among the patients, who were on treatment, the expenditure on procuring opioid is only 33% and the maximum loss was due to loss of productivity. The difference between the mean expenditure of the patients undergoing treatment and the patients not on treatment is 2 times.

Key words: ***Pain Suffering , Value, Non-Health, Raw Opium, Smack***

Review of literature

Patterns of substance use keep changing all the time. Changes may occur in the socio-demographic profile of opiate users, the type of drug use, the route of the administration and adverse consequences like economic, health related, and social problems **(8, 9, 14 and 35)**. Heroin use among the young adults has increased during 1988-1992 (SAM SHA 1995). It has been suggested that a decline which was reported after 1992 may be because of underestimation or under reporting **(31, 31 and 32).**

The use of illicit or licit drugs causes health, social and economical problems within the society. Sickness, death, injury, pain and suffering associated with illicit drug use are all burdensome to the society directly or indirectly. Thus, the drug abuse is a major drain on society's resources. Overall the societies as well as individuals, who are addicted, have to pay the costs of such addiction. Broadly the costs incurred are in the forms of

(i) Values of goods and services (Health and non-health).

(ii) Value of the lost productivity (Health and non-health).

(iii) Some non-quantifiable costs (Heath and non-health) i.e., pain, suffering bereavement etc. **(23).**

Most of the earlier studies tried to calculate the costs of first two mentioned areas (Cruze et al., 1981; Harwood et al., 1984; and Rice et al., 1990, 1991, 1999). They have used top-down approach in their cost evaluation for calculating the cost of treatment. This approach involves examining all the costs of a treatment centre, or hospital for instance over 1 year, and allocating the resource use to the activity levels of the centre for the year. This method ensures all known costs attributable to the service are allocated to an activity. For many services, only broad totals may be available and therefore this crude approach would be needed. Another approach is bottom-up approach. It gives more accurate estimate than the top-down approach. It involves identifying and measuring each individual activity and directly measuring the relevant resource use. Detailed resource tracing will ensure that a proportion of the capital cost and overheads are allocated to each unit of activity. With good resource management systems this approach can give very accurate costs for each individual event. However, it gives accurate estimate; it is likely that this methodology will not always results in

a total cost figure for the unit's activity equal to total expenditure over the period being examined **(7, 12, 27,28 and 29).**

Using the Cost of Illness approach, the cost were estimated in four broad areas; medical care, cost productivity, crime and social welfare. They found that the cost of heroin addiction in United States was US$21.9million in 1996. Of these costs productivity loss accounted for approximately 53%, criminal activities 24%, medical care 22.5% and social welfare 0.5% **(29).**

In 1992 in US it was calculated the cost per physician visit was $166 and the number of outpatients' visit were 10.5 million. With this value the cost of outpatient care was $1.7430 billion **(15 and 22).**

The misuse of alcohol, tobacco and illicit drugs cost more than $18.4 billion in Canada in 1992($649). Alcohol accounted for $1.3 billion in direct health care **(34).**

The US, substance abuse related care accounted 20% of total Medicaid general hospital days in 1992, that was $4billion. It was $8billion in 1994 **(8).**

Alcohol and drug abuse cost society an estimated $176.4 billion during 1992 in US as a result of lost productivity from premature death and illness among alcohol and drug abusers , associated crime related costs of alcohol and drug abusers and time spent by alcohol and drug abusers in residential treatment . An estimated $ 107 billion in overall productivity losses attributed to alcohol abuse and $ 69.4 billion to drug abuse **(23).**

Short falls in productivity and employment among individuals with alcohol or drug abuse disorders accounted for estimated losses of $ 80.9 billion in lost productivity. Of these, it is estimated that $66.7billion resulted from alcohol problems and $ 14.2billion resulted from drugs problems **(11).**

Buck et al (2001) found that the medical health and substance abuse services users were 7-13% of Medicaid enrollers. Across the 10 states, the expenditure on mental health and substance abuse services represented 11% of total Medicaid expenditures. When their expenditures for non-medical health and substance services were also considered, they account for 28% of total Medicaid expenditures **(4).**

In India , the cost of illness studies related to other illness have been done but alcohol and drug abuse related studies have been very few. The expenditure on health in India in 1990 was 6% of GDP (1.3% in public sectors + 4.7% in private sectors)(Ray, R., 1998). Some studies in India reflect, on an average drug abuser spends about Rs. 500 per week. Drug dependence also has an impact on addicts 'employment, and losses due to missing work. In Delhi, it was seen that an abuser spends around 35-95 per day on drugs **(24 and 25).**

Sharma et al (1995), a heroin addict in Ngaland spends about Rs. 1500/- per month and opium addict spends about Rs. 100-500 per month; and inject able drug abuser spends spends between Rs. 60-120 daily. In this study, expenditure was mainly on opioid procuring and loss of income due to reduced productivity **(33).**

In India, such studies are lacking. Therefore it was planned to estimate the cost attributable to opioid dependence syndrome. Such study will be beneficial for policy making regarding the treatment programmes as well as for researchers who would be interested in the economic evaluation for opioid dependence syndrome.

Aim: To estimate an average monthly expenditure over a period of three months by opioid dependent patients attending a De –addiction Centre.

Materials and Method

The study was carried out at De-Addiction Centre, AIIMS, and New Delhi during 1999 to2001. It is a centre where pharmacological as well as non-pharmacological treatments are given. The study sample comprised of 2 groups. Group I: consisted of the opioid dependent male patients who were aged between 15-45 years and registered at the centre for the first time. Group II: consisted of the opioid dependent male patients who were aged between 15-45 years and were on treatment for more than preceding 3 months from the centre. Two groups were chosen because the patients from group I did not have the cost of treatment. As per ICD-10 DCR Opioid Dependent Patients registered in the OPD were assessed for inclusion in either of the two groups. The male patients aged 15-45 years who came first time to the centre were included in group I and who were on treatment from the centre for at least past three months were included in group II. The patients dependent on substance other than opioids except nicotine and the patients suffering from any chronic psychotic and/or physical illness were excluded from the study. Those fulfilling the inclusion and exclusion criteria were assessed with the help of *a semi structured Performa(*which was specially prepared by investigators for the purpose of this study based on the assumptions made by the researchers*)* for detail expenditure incurred in association with opioid dependence

after taking written informed consent. All information given by the participants in the study was corroborated by the guardians. The corroborators were adults who had stayed with the patients and they themselves did not have any psychotic illness. A purposive sample of one hundred and fifty six patients in the group I and fifty three in the group II was assessed. First of all, the information regarding demographic variables was collected and then the cost incurred in following areas by the patients was assessed.

a. The cost of treatment

i. The cost of drug treatment (detoxification and maintenance)

The every drug which the group II patients were on for past 3 months were enquired about and their total amount in milligrams, and it was multiplied by the market price price of the each drug (in Rs. / mg) to get the cost of the treatment for the period of 3 months.

ii. The infrastructure cost.

For the group II patients, the cost per visit to OPD per day was used in the study, which was obtained from the Central Govt. Health Services, Ministry of Health and Family Welfare, New Delhi (It was Rs. 40/- per first visit to an OPD, and Rs. 30/- per subsequent visit to the OPD during 1999-2001)

b. The cost incurred in procuring opioids.

i. The cost of buying opioids: According to self-structured performa, the amount of opioids and other substance of abuse along with opioids were calculated in the gram, milligram, puria, capsules or ampoules for past 3 months. The amount of opioids or other substance in gram, milligram, puria, capsules or ampoules was multiplied by the mean price in Rs. per gm, mg, puria, capsules, or ampoules which was paid by each patient of both groups..

ii. The cost of its transportation from the patient's houses to the trafficking place and vice-versa. It was calculated by summing the rupees spent by the patients separately for group I and II as bus or auto-rickshaw fairs while visiting the places of trafficking.

c. Loss of productivity due to average loss of working days

The number of days of absence was enquired and it was multiplied by the patients' daily earning during past 3 months. The product was the lost productivity in rupees due to average loss of working days.

Data analysis.

For each patient, all the costs were summed up to get the Grand Total cost. The mean, median and standard deviation was obtained for each type of cost and the grand total cost against various categories of marital status, occupation, age, percapita income, and education for the patients of group I and group II separately.

The Kruskal- Wallis one way analysis of variance was used to see the significant differences within the different categories of age, marital status, occupation, per capita income and education for the patients of group I and group II separately.

Results

Total number of patients diagnosed as opioid dependence syndrome who attended De – addiction Centre OPD, AIIMS, New Delhi for the first time during the period of study (6 months) was 450. Out of them only two were women. Most of the patients (80%) were from Delhi. Most of the patients were fulfilling the inclusion & exclusion criteria but only one hundred fifty six patents were included under group I and fifty three in group II.

In group I, patients aged 15-20 years were least common (5.1%) and 31-40 years comprised the largest group (48.7%) (Table 1). This age group (52.8%) dominated in group II also. There were no patients in the age range 15-20 years in this group (Table 6).

Among the patients of group I, the majority of patients (51.9%) were educated upto primary and middle school level and only 7% were graduates or postgraduates (Table 2). Similarly among the patients of group II, the maximum number of patients (50.9%) fell in the category of primary and middle school level education and only 9.2% were graduates or postgraduates (Table 7).

Among the patients of group I, 60.5% were married and lowest number of patients (10.2%) fell in the category of widower, divorced or separated (Table 3). Similarly in group II, the maximum number of patients (60.3%) was married while 18.8% of patients were either widower, divorced, or separated (Table 8).

In both the groups, the maximum number of patients (41.09% and 45.4%) was transport operators, mainly the

auto-rickshaw drivers operating in Delhi. Professional, Technical and allied jobs categories in both groups were 2.6% and 3.7% respectively (Table 4 & 9).

In group I, most of the patients were with the percapita income between Rs. 501-1000 and Rs. 1001-2000 who constituted 73.3% (35.5 + 37.8%) of total number of patients (Table 5) and in group II also the patients with same percapita income constituted the 79.3% (35.9% + 43.4%) of total number of the patients. In both the groups were minimum numbers of patients having percapita income more than Rs. 4000/- (Table 10).

In groups I (n=156), the number of patients with heroin dependence syndrome was 136 (87.1%). Within this group seven patients were also using oral benzodiazepines; four were using oral benzodiazepine and inj-buprenorphine; and three were using inj-buprenorphine also in addition to heroin in intermittent manner. In group I, 12 patients were using Affim or Doda, as the primary drug of abuse. One of them was also using oral benzodiazepine in addition. In 8 patients buprenorphine (injectable) was the primary drug and three of them were also using Avil(Pheniramine).

In group II, *heroin* was the primary drug in forty nine patients (92%), buprenorphene (injectable) in three, and *poxta* in one. They were also taking the prescribed drugs (buprenorphine or dextopropoxypoxyphene)

In group I, the maximum mean expenditure per month was in age group (15-20 years) and progressively declined with age and reduced to a minimum in the 41-45 years age group. However, across the different categories within the group, the expenditures per month was not significant (p=0.20). Same trend was found in the expenditure per month for buying opioids and again there was an insignificant difference across different categories of age within the same group of patients was insignificant (p=0.08).

Among the patients of group I, the main expenditure per month was on procuring opioids for all the variables (age, marital status, per capita income, occupation and education) (Table 1-5) and in group II, the main loss was because of average loss of working days for all above variables (Table 6-10). There was apparent trend or increasing expenditure due to lost productivity with age and the maximum expenditure were in age group between 31-40 years.

In patients of group I, the maximum mean expenditure per month (Rs. 8970) was among the patients who were either widower, divorced, or separated (Table 3). In group II, maximum mean expenditure per month was among married patients (Rs. 3899) (Table 8). However, the differences across the categories within both groups of patients were non significant.

In the patients of group I, difference of mean expenditure per month across the patients with different educational level was less (range = 5891-7648) (Table 2). In the patients of group II such range was Rs. 2094-4422. The maximum mean expenditure per month was among the patients who were high school students (8th to 10th class). The difference was again non-significant (p=0.76) within the patients with different educational levels in this group (Table 7).

In the patients of group I, the mean expenditure per month ranged from Rs. 5963-9328 within the categories of occupation. The monthly mean expenditure was more than Rs. 9000 among those who were professional, technical and related workers, administrative executive and managerial workers; and workers not classified by occupations. The difference across the different occupations was insignificant (p=0.63) (Table 4). In patients of group II, maximum mean expenditure per month was among sales workers (Rs. 7433). However the range of expenditure per month across the patients with different occupations was between Rs.461 to 7433 and it was still insignificant (p=0.049) (Table 9).

In the group I, the patients with highest percaptia income (Rs. >4000/month) had highest mean expenditure per month (Rs. 8118). The mean expenditure per month showed increasing trend with increase in per capita income but the difference across the patients with different percapita income was insignificant (p=0.94) (Table 5). In group II, the patients with percapita income between Rs. 501-1000 per month had highest mean expenditure per month (Rs. 4384). The difference across the different patients with different income group was non-significant (p=0.265) (Table 10). In both groups, almost in each category the mean expenditure was 3-4 times more than that of their percapita income.

The grand total cost (including all type of cost) incurred by the group I patients was Rs. 1102611 (mean=Rs. 7063/month) (Table 11) and for the patients of group II, it was estimated Rs. 162045(mean=Rs. 3057/month) (Table 12). In group I, the maximum expenditure was on procuring opioids and in group II, it was due o lost productivity.

There difference between the mean expenditure of patients of group I and group II were 2 times in almost all variables considered.

Table 1: for the patient of group 1

Cost of opioid dependence for each category of age.

Table 1	Age (Years)	15-20	21-30	31-40	41-45	P value
	N = 156	8 (5.1%)	41 (26.2%)	74 (46.7%)	33 (21%)	
Mean ± S.D.	A	7035±3939	8006±5085	6226±4311	4203±2978	0.1366
	B	106±178	184±279	202±408	141±262	0.8766
	C	1262±1530	1083±1646	1848±2657	1670±2850	0.54
	E(7245)	8404±4226	7274±5543	7276±5394	6021±5641	0.26

*Significant (Krushkal-Wallis one way analysis of variance)

A = The cost in Rs /month of buying opioids

B = The cost in Rs/month of transportation of opioids by the patients from the patients houses to the trafficking place or vice-versa.

C = Loss of productivity due to average loss in Rs/ monthof working days.

D = The cost in Rs / month of treatment including the cost of drug treatment (Detoxification & maintenance) and the infrastructure cost.

E = The total cost in Rs / month.

Table 2 for Group I Patients

Cost of opioid dependence for each category of education.

Table 2	Education	Illiterate	Primary & idle School Educated	High School Educated	Graduate & post Graduate	P Value
	N = 156	38 (24.3%)	81 (51.9%)	28 (17.9%)	11 (7%)	
Mean ± S.D.	A	4819±3964	588±5204	4419±4011	4897±3206	0.496212
	B	177±230	179±447	199±308	146243	0.553
	C	895±1597	1580±2445	2090±2986	2522±2820	P = 0.18
	E	5891	7048	6708	7566	0.58

*Significant (Krushkal-Wallis one way analysis of variance)

Table 3 for Group I Patients

Cost of opioid dependence for each category of education.

Table3	Marital Status	Never married	Married	Widower, divorced or separated	P Value
	N = 156	33 (21.1%)	107 (68.5%)	16 (10.2%)	
Mean ± S.D.	A	5496±4048	5116±4600	5201±4507	0.3145
	B	177±261	174±262	348±808	0.228
	C	1493±2381	1481±2439	2421±2474	0.15
	E	7107±5311	6771±5446	8870±5400	0.17

*Significant (Krushkal-Wallis one way analysis of variance)

Table 4 : For the patients of Group I

Cost of opioid dependence for each category of occupation.

Table 4	Occupation	Professional, technical & related workers; administrative executive and managerial workers; and clerical & related workers	Sales workers	Service workers; farmer, fisherman, hunter, loggers and related workers; and production and related workers	Transport operators	Labourers	Workers not classified by occupation	P Value
	N = 156	4 (2.6%)	19 (12.2%)	19 (12.2%)	64 (41.03%)	26 (16.5%)	24 (15.3%)	
Mean ± S.D.	A	7949±3100	4860±3954	3931±3011	6102±3972	4860±3836	7555±6788	0.122
	B	149±217	109±148	101±173	29±40	207±438	91±...	0.85
	D	1202±1865	1613±2538	3941±8808	1714±2737	1966±1731	11185±2230	0.41
	E	9936±6096	6621±4734	8593±4981	7107±5058	6371±4685	9046±7826	0.83

*Significant (Krushkal-Wallis one way analysis of variance)

Table 5 : For the patient of Group I

Cost of opioid dependence for each category of percapita income.

Table 5	Percapita income	<500/month	501-1000 /month	1001-2000 /month	2001-3000 /month	>4000 /month	P Value
	N = 156	10 (6.4%)	55 (35.5%)	59 (37.8%)	22 (14.1%)	(6.4%)	
Mean ± S.D.	A	5441±5704	5084±4174	5409±4182	4548±3111	7477±7906	0.5341
	B	115±242	138±235	206±467	228±434	193±257	0.78
	C	843±733	1633±2059	1696±2589	2023±3548	4486±1040	0.35
	E	6200	6876	7312	6810	8118	0.94

*Significant (Krushkal-Wallis one way analysis of variance)

Table 6 : For the patients of Group II

Cost of opioid dependence for each category of the age.

Table 6	Age (Years)	15-20	21-30	31-40	41-45	P value
	N = 53	0	13 (24.5%)	28 (52.8%)	12 (22.6%)	
Mean ± S.D.	A	0	630±1078	1323±1972	583±1145	0.48
	B	0	81±225	39±75	0	0.136
	C	0	350±1261	1749±4522	1500±3118	0.35
	D	0	476±255	738±1113	768±500	0.15
	E	0	1536±4042	3850±4530	2851±4067	0.80

*Significant (Krushkal-Wallis one way analysis of variance)

Table 7 : For Group II patients

Cost of opioid dependence for each category of education.

Table 7	Education	Illiterate	Primary & idle School Educated	High School Educated	Graduate & post Graduate	P Value
Mean ± S.D.	A	498±1014	872±1401	1556±2564	1068±888	0.46
	B	13±37	50±163	8±25	142±99	0.04*
	C	333±1000	1378±3869	2333±4942	827±1455	0.80
	D	1349±1896	514±310	524±246	965±683	0.58
	E	2094±1880	2715±4048	4422±5509	3002±2064	

*Significant (Krushkal-Wallis one way analysis of variance)

Table 8 : For the patients of Group II

Cost of opioid dependence for each category of marital status.

Table 8	Marital Status	Never married	Married	Widower, divorced or separated	P Value
Mean ± S.D.	A	506±989	1251±1916	573±1067	0.25
	B	80±240	18±50	68±111	0.57
	C	413±1371	1994±4527	315±474944	0.38
	D	1073±1584	634±556	423±263	0.16
	E	2133±2378	3899±4750	1379±1414	0.138

*Significant (Krushkal-Wallis one way analysis of variance)

Table 9 : For the patients of Group II

Cost of opioid dependence for each category of occupation.

Table 9	Occupation	Professional, technical & related workers; administrative executive and managerial workers; and clerical & related workers	Sales workers	Service workers; farmer, fishermen, hunter, loggers and related workers; and production and related workers	Transport operators	Labourers	Workers not classified by occupation	P Value
	N = 53	2 (3.7%)	7 (13.2%)	4 (7.5%)	23 (43.4%)	8 (15.1%)	9 (17%)	
Mean ± S.D.	A	0	2006±2380	766±974	811±1072	949±1012	640±851	0.33
	B	101±142	47±82	57±75	44±75	50±146	27±80	0.56
	C	0	4000±8080	0	701±1685	2468±6380	850±1708	0.48
	D	340±0	1286±2030	607±416	804±588	442±197	516±261	0.98
	E	481±540	7430±5485	1711±1867	2098±2167	3877±6400	2849±2010	0.049*

*Significant (Krushkal-Wallis one way analysis of variance)

######Table 10 : For the patient of Group I

Cost of opioid dependence for each category of percapita income.

Table 10	Percapita income	<500/month	501-1000 /month	1001-2000 /month	2001-3000 /month	>4000 /month	P Value
	N = 53	3 (3.6%)	19 (35.9%)	23 (43.4%)	8 (15.9%)	0	
Mean	A	386±521	5000±1600	1351±1931	264±718	0	0.22
± S.D.	B	0	23±59	59±175	44±82	0	0.79
	C	1000	2557	867	0	0	0.42
	D	311±126	903±1326	520±348	787±439	0	0.121
	E	1887±1749	4384±5323	2798±3294	1085±1040	0	0.266

*Significant (Krushkal-Wallis one way analysis of variance)

Table 11 : All type of the cost for Group I

Table 11/Group I (n=156)	Mean (Rs.)	Grand total (Rs.)
A	5308	828083 (70%)
B	180	28094 (1.4%)
C	1580	246494 (28.5%)
E	7068	1102671 (100%)

Table 12 : All type of the cost for Group II

Table 12 /Group II (n=53)	Mean (Rs.)	Grand total (Rs.)
A	981	52000 (33%)
B	40	2163 (1.4%)
C	1349	71527 (51%)
D	685	36305 (14.6%)
E	3057	162095 (100%)

Table 13 : All type of the cost attributable to raw abuse for group I (n=12)

Table 13	Mean (Rs.)	Grand total (Rs.)
A	1841	22090
B	52	625
C	586	7009
D	2494	29924

Table 14 : Sociodemographic variables

Table 14	Group I	Group II
Age (N=156)		
15-20	8(5.1%)	0
21-30	41(26.2%)	13(24.5%)
31-40	74(48.7%)	28(52.8%)
41-45	33(21%)	12(22.6%)
Education		
Illiterate	38(24.3%)	9(17%)
Primary & middle school	81(51.9%)	27(50.9%)
High school	28(17.9%	12(22.6%)
Graduate	11(7%)	5(9.2%)
Marital status		
Never married	33(21%)	11(20.9%)
Married	107(68.5%)	32(60.3%)
Widower, divorced or separated	16(10.2%)	10(18.8%)
Percapita income(Rs)		
< 500/month	10(6.4%)	3(5.6%)
501-1000	55(35.5%)	16(30.3%)
1001-2000	59(37.8%)	23(43.4%)
2001-4000	22(14.1)	8(15.9%)
>4000	10(6.4%)	3(5.6%)
Occupation		
Sales workers	19(12.8%)	7(13.2%)
Transport operators	64(16.5%)	23(43.3%)
Laborers	26(16.5%)	8(15.1%)
Professional , technical, and related workers; Administrators , executive and managerial workers; and clerical and related workers.	4(2.6%)	2(3.7%)
Farmers, fishermen ,hunters, loggers. And related workers;And production and related workers	19(12.8%)	4(7.5%)
Workers not classified by occupation	24(15.3%)	9(17%)

Discussion

In Myanmar, the member of drug abusers registered with government hospitals in 1997 was 58,728 of which 60.8% were opium abusers. 30% were heroin users and polydrug users (WHO report, 2001). In present study in group I (n=156), the number of patients with heroin dependence syndrome was 136 (87.1%). Within this group seven patients were also using oral benzodiazepines; four were using oral benzodiazepine and inj-buprenorphine; and three were using inj-buprenorphine also in addition to heroin in intermittent manner. In group I, 12 patients were using Affim or Doda, as the primary drug of abuse. One of them was also using oral benzodiazepine in addition. In 8 patients buprenorphine (injectable) was the primary drug and three of them were also using Avil (Pheniramine).In group II, the heroin was the primary drug in forty nine patients, buprenorphene (injectable) in three and posta in one Illicit substance use was reported by this group over and above the prescribed drugs (buprenorphene or detropropoxyphene) they were getting from the centre..

In India, the prevalence is increasing in the younger age group **(5 and 33).** The current heroin use in general population among males has increased from 0.3% to 1.1% in some parts of India (Channavasabana et al., 1990, Mohan et al., 1992, 1993, 1994, 1998, 1999). In present study the patients aged 31-40 years comprised the largest group (>50%)(Table 1and 6). Rice et al. (1999) also fond that 80% of male patients alcohol and drug abuse were aged between 20-49 years **(27).**

In India, a study reported the monthly expenditure of a heroin dependent patient to be Rs. 1,500/month. The expenditure per month per opium addict was Rs. 100-500/ month. It was estimated Rs. 1800-3600 per month for an injecting drug user in Nagaland. In the study, the data on the separate cost due to procuring heroin is not available **(33).** In the present study, the cost incurred in procuring opioids was considered separately which constituted around 70.1% of total expenditure for the patients of group I and which 33% was for the patients of group II. The mean monthly expenditure per patient was for 2495 for an opium (Affim, doda) abuser and Rs. 4575 for a heroin dependent (Table 12&13) which is four times that of the cost reported earlier **(33).**

In this study among the patients of both the groups , the maximum number of patients (>50%) reported primary and middle school level education and only 7% in group I and 9.2% in group II were graduates or postgraduates (Table 2 and 7). The reason was not investigated but could be a reflection of the educational status of patients coming to our centre and not a function of opioid abuse per se. Mullahy and Sindelar (1989) found that the alcohol abuse at young ages was associated with a 1.5 year reduction in education attainment **(21).**

In this study, among the patients of group I, 60.5% were married and minimum number of patients (10.2%) fell in the category of widower, divorced or separated (Table 3). In group II also, the maximum number of patients (60.3%) were married and 18.8% of patients were either widower, divorced or separated (Table 8).

In this study, in both group I and II the maximum number of patients (41.89% and 45.4%) were transport operators mainly the auto rickshaw drivers (Table 4 & 9).

This study found that the monthly expenditure of an opioid dependent patient undergoing treatment was Rs. 3057/- and who were not on treatment had 7068/-. In India , the cost of illness studies related to other illness have been done but alcohol and drug abuse related studies have been very few. The expenditure on health in India in 1990 was 6% of GDP (1.3% in public sectors + 4.7% in private sectors) **(26).** In India, on an average drug abusers spend about Rs. 500 per week. In Delhi, it was seen that an abuser spends around 35-95 per day on drugs. (Prasant , 1993; Purohit ,1994) Sharma et al (1995), a heroin addict in Ngaland spends about Rs. 1500/- per month and opium addict spends about Rs. 100-500 per month; and injectable drug abuser spends between Rs. 60-120 daily **(33).**

In group I, the maximum mean expenditure per month was in age group (15-20 years) and lowest in age group (41-45). The expenditure per month progressively decreased with age and reduced to a minimum in the 41-45 age group, although the difference in the expenditure per month were not significant (p=0.20) (Table 1). Same trend was found in the expenditure per month due to buying opioids and again there were insignificant differences within the different age group. There was an opposite trend that the cost increased progressively with the age in group II (Table 6). In a previous Cost of Illness study, the core cost of alcohol and drug abuse and mental illness increased progressively upto age of 44 years then it decreased in both the samples of male and female separately **(28).**

In this study, among the patients of group I, the main expenditure per month was on procuring opioid in all the considered variables whereas in group II it was because of the lost productivity. However, we could take

into account only the cost due to average loss of working days (Table 12). In the previous studies main costs was due to lost productivity which included loss due to morbidity as well as mortality (Rice et al., 1991; Single et al., 1998; Xie et al., 1998). The patients who were on treatment had more number of days of absence from duty because of weakness and the patients who were not on treatment and were active abusers had to work to earn money to arrange the opioids and hence did not have much absence from duty. There has been definite reduction in the wage or earnings of the patients reported previously (Rice et al., 1990, 1999; Kraestmer 1994b, Buchmueller & Zuvekas 1994; 1996 Grant et al., 1994).

In the group I, the maximum mean expenditure per month (Rs. 8970/-) was among the patients who were either widowers, divorced or separated (Table 3). In the patients of group II, maximum expenditure was among married patients (Rs. 3899/-) (Table 8). In the group I the patients with highest per capita income (Rs. > 4000/month) has highest mean expenditure per month (Rs. 8118) and the mean expenditure per month showed increasing trend with increase in the percapita income (Table 5). In group II, the patients with percapita income of Rs. 500-1000 per month had highest mean expenditure per month (Rs. 4384/-) (Table 1). In both the groups, almost in each category the mean expenditure was 3-4 times greater than their percapita income. In this study the differences across different categories of marital status and per capita income within the both groups of patients were insignificant. NIDA with NIAAA (1998) and Rice et al., (1990, 1999) also found no clear relationship between the expenditure by drug abusers and their income status or marital status. It had also been reported that there was worksite productivity effects in terms of lost earnings of drug and alcohol abusers. The loss of earning attributable to alcohol and drug problems affects everyone in a household whether earnings are reduced through lower wage rates or reduced days of work. This loss would directly affect the wellbeing of any additional members, particularly those who do not work, or do not have an independent source of income. The same was also with present study, which was reflected in the form of mean expenditure 3-4 times greater than per capita income.

Limitations

1. This study could include only limited aspects of opioid use which are attributed as the causes of economic loss.
2. Number of the patients was too small to provide a broader picture of loss of productivity and cost of opioid use.
3. The cost was not correlated with severity of the illness.
4. The amount of opioids was estimated in different units i.e. mg, gram, puria, or capsules, hence we could not estimate the price range of these substances prevailing in illicit drug market.
5. The study was confined to the patients who sought treatment at a treatment centre, which is only the tip of iceberg so it would be difficult to generalize the estimated cost for the whole population of opioid users at a city level.

For future work in this field

1. To include the cost incurred for many other aspects of substance abuse.
2. To correlate the cost with severity of illness.
3. To evaluate the cost-effectiveness of the any treatment program of treatment centre.
4. To estimate the cost of population samples of substance abusers, so that the estimated cost to can be generalized.

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EXECUTIVE FUNCTIONS IN PATIENTS WITH SINGLE AND MULTIPLE EPISODES OF MANIA ON CTMT

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ABSTRACT:

Background: Neuropsychological studies on Bipolar Disorders (BD) documented dysfunction in executive functioning and it has been reported that some dysfunction persists even after manic symptoms disappear. There is sufficient literature suggesting executive dysfunction in multiple episodes manic patients but there is lack of studies related to single episode manic patients. The present study was conceptualized to assess the neuropsychological deficits in the cases with Bipolar Affective Disorder (mania with the history of single and multiple episodes). Methods: Sample of the study consists of 60 subjects; thirty inpatients were with the history of multiple episodes of manic illness and 30 inpatients with single episode of manic illness. Each group received Comprehensive Trail Making Test (CTMT) and Executive Functioning Scale of Cognitive Symptoms Checklist, and the performances of both groups were compared on trail making Test and Executive functioning Scale. Results: At baseline, multiple episodes manic patients shown greater deficits relative to single episode manic patients on executive functioning measures. Deficits were in terms of psychomotor speed, visual search and sequencing, attention and impairment in set shifting. Though, the executive functioning deficits were found in single episode manic patients too in some extent. Conclusion: The results of the present study demonstrate that executive dysfunction remained in bipolar disorder cases even in remitted state but the degree of impairment differ in multiple episodes manic group and single episode manic group. The cognitive deficits are having detrimental effect on day to day functioning, such as daily routine work, taking care of personal hygiene and making decision in day to day life.

Key words: ***Bipolar Disorder; Multiple episodes manic; Single episode manic; Executive functions.***

The term *Executive functioning*, has encompassed number of meanings. Definitions have included those controls and regulatory processes that (i) Integrate information perceived in the external world and transform perception into higher order symbols, (ii) Compare incoming information with what knowledge stored in memory and (iii) Combine the incoming perceptions with information about the person's internal physiological state and biological drives. According to this terminology, executive functioning is arguably the most complex aspect of one's cognitive capacities, due to variety of functions required to select, plan, organize and implement a behavioural response appropriate to a constantly changing world. Bipolar disorder (BD) is a recurrent, cyclical disorder that is characterized by alternating episodes of depression and mania, interspersed with periods of apparent recovery, or eutymia (Goodwin, F. K., Jantison K. R., 1990). However, there is accumulating evidence that recovery in BD is incomplete (Ferrier, I. N, Thompson J. M., 2002). Patients with Bipolar disorder show persistent cognitive impairment during remission (Bearden C. E. et al, 2001; Clark L., Iversen S. D., Goodwin G. M., 2002; Thompson J. M., Gallagher P, 2005). Deficits have been observed on several tests of executive or frontal lobe function (Zubieta J. K. et al, 2001; Thompson J. M., Gray J. M., et al., 2003)

The CTMT is developed by Reynolds in 2002 (Reynolds C. R, 2002). The CTMT assess problems with psychomotor speed, visual search and sequencing, and attention and impairment in set shifting, also appear appropriate.

Some important studies have compared the performance of controls to remitted Bipolar Disorder patients on Trail Making Test (TMT).The results are consistent with that Bipolar Disorder patients' performance was worse in all studies; this difference did not always reach statistical significance (Jones B.P.et al, 1994; Tham A., Engelbrektson K et al, 1995; Hawkins K.A et al, 1997). Illness severity may be an important contributor to impaired TMT performance. Several studies have compared the

TMT performance of Bipolar Disorder patients to that of Unipolar disorder patients and schizophrenics. Remitted Bipolar Disorder patients performed worse than Unipolar Disorder (Paradiso S., 1997; Ferrier I.N. et al, 1999; Mojtabai R. et al , 2000). In some studies the performance of unipolar disorder was better than bipolar disorder cases (Jones, B.P., D et al, 1994). While two other studies found no differences between the two patient groups (Goldberg T.E.et al, 1993; Mojtabai R.et al, 2000). Chronic Bipolar Disorder and schizophrenic patients were compared twice, once when both groups were in acute relapse and then again after 4 weeks of treatment. BD patients performed better than schizophrenics during the acute phase. Despite significant symptomatic improvement, the performance of BD patients on the TMT was similar in the acute and recovery phases. So their advantage over schizophrenics disappeared after 4 weeks of treatment (McGrath J., Scheidt, S., Welham J. and Clair, A., 1997).

Material and Method

Sample:

The sample consists of 60 patients with Bipolar Affective Disorder (30 manic patients with the history of single episode and 30 manic patients with the history of multiple episodes) in the age range of 20-40 years. All participants were male and right handed. All the subjects were educated up to matric level. All were married, Hindus by religion and employed and most of them belongs to rural areas of Jharkhand and Bihar. Subjects with any other co-morbid neurological / psychological disorder or with major physical illness were excluded. All subjects participating in the study were co-operative. Informed consent was taken for the study.

The following tools were used in the present study:

Socio-demographic and Clinical Data Sheet: It is semi structured Proforma developed for the purpose of present study. It contains information about socio-demographic variables like age, sex, religion, education, marital status, domicile and occupation and clinical details like diagnosis, age of onset, total duration of illness, history of alcohol or substance abuse, family history of mental illness, any history of significant head injury, seizures, mental retardation and any other significant physical, organic or psychiatric illness.

Young Mania Rating Scale (YMRS): This scale has been developed and standardized by Young et al, 1978). It has been used for the assessment of severity of the manic symptoms in the patients. This scale included 11 symptoms constructs. Each item is rated on 5 point rating scale (0-4). Score '0' indicates "absence of symptoms" and '4' indicates "extremely severe symptoms".

Hand Preference Battery: This is a six item scale by Annett (1970) in which subjects is asked to show some everyday activities. Depending on the hand he uses for all six items he is assigned to that particular preference. Subjects were asked to "show me how you": Write letter legibly, Throw a ball to hit a target, Hold a tennis racket, Hammer a nail into wood, Hold a match while strike, Hold a toothbrush while cleaning your teeth.

Comprehensive Trail Making Test (CTMT): The CTMT is developed by Reynolds. The CTMT comprises a standardized set of five visual search and sequencing tasks that are heavily influenced by attention, concentration, resistance to distraction and cognitive flexibility (or set shifting), in addition to more obvious visual search and sequencing demands of the task. The basic task of trail making, and thus of CTMT, is to connect a series of stimuli (numbers, expressed as numerals or in word form, and letters) in a specified order as rapidly as possible.

Executive Functioning Scale of Cognitive Symptoms Checklist:

The original Cognitive Symptoms Checklist was developed by O'Hara et al (1993) which was translated into Hindi to facilitate local Indian population for the identification and treatment of problems in five basic cognitive areas: attention and concentration, memory, visual processes, language and executive functions. Executive functioning was divided into following sub divisions-processing speed/ reaction time, initiation/follow- through, self correction, mental flexibility, planning, organization and reasoning It can be either self-administered or administered by clinicians, with further inquiry or interpretation performed by appropriately trained clinicians.

Procedure:

Patients were selected as per ICD-10 DCR criteria. All the subjects who were included in the present study were assessed with the help of semi structured clinical data sheet. Detail about history of co-morbidity, substance abuse, family history of mental illness, history of any neurological problem, mental retardation, etc. were noted. Each subject was assessed through clinical history. After applying Young Mania Rating Scale clinical population was selected. Each subject was assessed with Hand Preference Battery and only right handed patient were included in the sample. After initial screening of the patients, Comprehensive Trail Making Test was administered and subsequently Executive Functioning Scale of Cognitive Symptoms Checklist was also administered on all patients.

Results and Discussion:

Table 1: Showing Socio-Demographic Profile of Sample

Variables	Educational Level	Single Episode Mania M ± SD/N	Multiple Episode Mania M ± SD/N	X^2
Age		29.07 ± 5.93	30.16 ± 5.48	741
Education	Up to Matric	24 (80.0%)	16 (53.3%)	7.20
	Up to Intermediate	6 (20.0%)	9 (30.0%)	
	Up to Graduation	-	2 (6.7%)	
	Up to PG	-	3 (10.0%)	
Religion	Hindu	25 (83.3%)	21 (70.0%)	2.35
	Muslim	2 (6.7%)	6 (20.0%)	
	Christian	-	-	
	Sama	3 (10.0%)	3 (10.0%)	
Marital Status	Single	18 (60.0%)	11 (36.7%)	3.27
	Married	12 (40.0%)	19 (63.7%)	
Domicile	Rural	16 (53.3%)	16 (53.3%)	7.64
	Urban	14 (46.7%)	8 (26.7%)	
	Semi-urban	-	6 (20.0%)	
Occupation	Employed	11 (36.7%)	11 (36.7%)	7.33
	Unemployed	2 (6.7%)	7 (23.3%)	
	Student	7 (23.3%)	1 (3.3%)	
	Others	10 (33.3%)	11 (36.7%)	
Family type	Nuclear	20(66.7%)	24 (80.0%)	1.36
	Joint	10 (33.3%)	6 (20.0%)	

The data have been analyzed and presented in table 2 and table 3.Table 2 shows the performance of the (Single Episode Manic) SEM and (Multiple Episode Manic) MEM groups on the Comprehensive Trail Making Test. The groups differed significantly in their performance, in term of time taken on all five trails of the Test. Considering performances in terms of errors made, the groups differed significantly in Trail 1, Trail 2, Trail 3, Trail 5 and not significantly in Trail 4 of the test in terms of error. The analysis further reveals that the MEM group took greater time than SEM groups and also committed more number of errors on all five trails of the test.

Table 2: Showing the performances of both groups on Comprehensive Trail-Making Test.

Variables	Groups	Mean Rank	Sum of Ranks	Z- Score
TRAIL 1 (Time)	SEM	22.67	680.00	3.48**
	MEM	38.33	1150.00	
TRAIL 1 (Error)	SEM	26.23	787.00	2.45*
	MEM	34.77	1043.00	
TRAIL 2 (Time)	SEM	23.70	711.00	3.02**
	MEM	37.30	1119.00	
TRAIL 2 (Error)	SEM	25.00	750.00	2.67**
	MEM	36.00	1080.00	
TRAIL 3 (Time)	SEM	23.22	696.50	3.23**
	MEM	37.87	1133.50	
TRAIL 3 (Error)	SEM	27.40	822.00	1.97*
	MEM	33.60	1008.00	
TRAIL 4 (Time)	SEM	25.33	760.00	2.29*
	MEM	35.67	1070.00	
TRAIL 4 (Error)	SEM	27.32	819.50	1.72
	MEM	33.68	1010.50	
TRAIL 5 (Time)	SEM	21.27	638.00	4.10**
	MEM	39.43	1182.00	
TRAIL 5 (Error)	SEM	22.03	661.00	3.99**
	MEM	38.73	1169.00	

**p< 0.01 level of confidence
*p < 0.05 level of confidence

In the area of time taken in Trail1, Trail 2, Trail3 and Trail 5 both the group differs significantly at 0.01 level whereas on Trail4, Trail 2 the difference was found at 0.05 level. Similarly, in the area of error on Trail 2 and Trail 5 the difference was found significant at 0.01 level and Trail 1 and Trail 3 both the groups differ significantly at 0.05 level, where as in the area of error on Trail 4 the difference was apparently existing as mean value (33.68) for multiple episode manic group is higher in comparison to mean value (27.32) of single episode manic group but the difference is not significant. Findings of the study further suggest that poor performance in Comprehensive Trail Making Test is indicator of impairment in maintaining; shifting mental set is significantly higher in multiple episodes manic group than single episode manic group. Though,

the performance of any neuropsychological test implies sum degree of attention engagement but the Trails making test have large attentional component although we cannot eliminate the possibility that some medication effect might have caused greater impairment and probably that would have only hindered more the cognitive performance of multiple episodes manic group as they are on pharmacotherapy since longer time.

In most of the previous studies sample the subjects included who were much older and who had long term exposure to psychotropic medication. Present study has tried to find out the difference in Neurocognitive functions during the medication between their repeated episodes and the short term exposure to medication having only the first episode. The cognitive deficits in multiple episodes group could be the endophenotype of mood disorder (Nehra R., Chakrabarti, S, Pradhan, B.K. Khera, N, 2006). It has been shown that neuropsychological deficit in Bipolar Disorders correlate with both the number of affective episode and overall duration of illness. The result of present study evidenced for the indication of greater impairment with larger time spent in affective episodes. It is possible that the progression of illness and greater correlation between neuropsychological deficits and severity of illness are often considered to be indicator of progressive disease process.

Illness severity could be an important contribution to impaired TMT (Trail Making Test) performance, has been reported by some previous studies. Poor performance on CTMT by multiple episodes manic group can be attributed to psychomotor slowness and deficits in visual scanning as the comparison of single episode manic group. This could be due to impairment in the ability to focus, sustained attention, and execution of the task (Mirsky A. F. et al, 1995). The difference was most evident for the "time-taken" criteria in all Five Trails, wherein multiple episode patients performed poorly than single episode patients. The multiple episode patients did not differ from single episode patients in terms of errors made, on Trail 4. Patients with multiple episodes were more impaired on TMT when compared the groups only on "Time Taken" and "Errors Made" were not considered.

Table 3 shows the problems that reported by SEM and MEM groups on the Cognitive Symptoms Checklist: Executive Functioning Area. The groups differed significantly in Processing Speed/Reaction Time, Initiation/ Follow-Through, Self Correction, Mental flexibility, Planning and Problem Solving. The groups did not differ significantly in Sequencing, Organization and Reasoning. The analysis reveals that the MEM group experiencing problem more than SEM group.

Table 3: Showing the Executive Functions Score on Cognitive Symptom Checklist on Both Groups.

Variables	Groups Rank	Mean Ranks	Sum of	Z- Score
Processing speed / Reaction Time	SEM	20.92	627.50	4.48**
	MEM	40.08	1202.50	
Initiation/Follow-Through	SEM	25.03	751.00	2.78**
	MEM	35.97	1079.00	
Self-Correction	SEM	24.35	730.50	3.04**
	MEM	36.65	1099.50	
Mental Flexibility	SEM	27.80	834.00	1.37*
	MEM	33.20	996.00	
Planning	SEM	24.27	728.00	3.04**
	MEM	36.73	1102.00	
Sequencing	SEM	29.70	891.00	0.497
	MEM	31.30	939.00	
Problem Solving	SEM	23.42	702.50	3.36**
	MEM	37.58	1127.50	
Organization	SEM	27.33	820.00	1.79
	MEM	33.67	1010.00	
Reasoning	SEM	26.72	801.50	1.78

** $p < 0.01$ level of confidence
* $p < 0.05$ level of confidence

In the sub area of executive functioning, processing of speed/reaction time, initiation/follow through, self correction, planning and in problem solving sub area both the group differ significantly on at 0.01 level, whereas on mental flexibility sub area the difference was found significant at 0.05 level. The difference on mean value of sequencing, organization and reasoning sub area was apparently existing as mean value (31.30), (33.67) and (34.28) for multiple episodes group was higher in comparison to mean value (29.70), (27.33) and (26.72) of single episode group respectively. Though it was not significant but the findings suggest that multiple episode patients report more impairment than single episode patients. This indicates that multiple episode patients have more problems in Executive Functioning Area. Particular significance has been attached to these deficits because they have been linked to the intensity of the disease process and are persistent despite the psychiatric symptoms

reduction and have been linked to psychosocial and competitive employment[1]. The result of the present study clearly indicates that multiple episode group has executive deficits in the form of slower information processing than the single episode group.

Cognitive impairment in bipolar illness may be a stable characteristic of the illness, although discrepancies have emerged with regard to what dysfunctions remain during remission periods (Martinez-Aran. A et al, 2004). Although the traditional view of bipolar affective disorder is that the majority of patients have full remission between episodes. Recent evidence suggests that residual cognitive deficits are still present (Kessing L V, 1998; Cavanagh J.T.et al, 2002; Tham A., 1995). The nature of the cognitive deficits in bipolar illness in general is shown by impaired performance in tests of executive function, attention and memory (Bearden C. E.et.al, 2006; Quraishi, S. Frangou, S, 2002; Martinez-Aran 2000). Findings are consistent with the findings of the Mishra et. al, 2009). However, the groups differ significantly in Sequencing, Organization and Reasoning. Neuropsychological deficits are possibly trait-related. The deficits in the long run can cause considerable impairment in psychosocial and occupational functioning (Martinez-Aran et al, 2004b & a, Thompson J. M.et al, 2005. Cognitive deficits have detrimental effect on day to day functioning related to cognitive areas which have been found significantly more in multiple episode patients as compared to single episode patients in present study.

Conclusion:

The findings of the study suggest that subject suffering with mania having multiple episodes shown more impairment than single episode manic group in the area of executive functioning. It has been found that neuropsychological deficit in bipolar disorders positively correlated with both the number of affective episodes and overall duration of illness. In present study manic patients group with multiple episodes have been found poor in Attention, Concentration, Abstract Reasoning, Set Shifting, Mental Flexibility, Abstract Thinking, Processing Speed/ Reaction Time, Initiation/Follow-Through, Self Correction, Mental Flexibility, Planning And Problem Solving task. This cognitive impairment in bipolar illness may be stable characteristics of the illness and in the long run can cause considerable impairment in psychosocial and occupational functioning. The cognitive deficits of this nature have detrimental effect on day to day functioning such as daily routine work, taking care of personal hygiene and making decision in day to day life, delivering / bearing occupational and professional responsibilities.

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Case Report :

Supersensitivity psychosis: A case report

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ABSTRACT:

A 30 yrs old male patient diagnosed as a case of paranoid schizophrenia was treated initially, with various antipsychotics, both typical and atypical, for a long period, without any significant improvement and having marked extrapyramidal symptoms. Subsequently clozapine was administered and patient had shown significant improvement to that but afterward patient had worsened again with appearance of involuntary dyskinetic movements. Clozapine was substituted with quetiapine with which patient responded but relapsed again after sometime. Sodium valproate was added and patient had sustained improvement after that. The concept of supersensitivity psychosis alongwith its treatment implications was reviewed from the relevant literature.

Key words: *supersensitivity psychosis, antipsychotics, clozapine*

Introduction

Since the introduction of neuroleptics in psychiatry, the behavioural toxicity of these drugs has been increasingly recognized. Over 30 years ago, Chouinard and colleagues described worsening of psychotic symptoms in association with long-term neuroleptic therapy (Chouinard et al, 1978). It had been observed that psychotic relapse in a number of patients on neuroleptics did not follow the usual course of schizophrenic illness. For example, certain patients relapsed immediately upon a reduction in dosage and showed new schizophrenic symptoms or worsening of previous psychopathology. Prior to these observations, Ungerstedt and Ljungberg (1977) had predicted limbic dopaminergic supersensitivity on the basis of animal experiments. The clinical syndrome, termed supersensitivity psychosis (SSP), is hypothesized to result from post-synaptic dopamine (DA) receptor supersensitivity in mesolimbic pathways in the same way that tardive dyskinesia (TD) is thought to develop in the neostriatum (Chouinard & Jones, 1980).

The phenomenon of SSP is still under investigation - at least three psychiatric presentations during the past twenty years have dealt with its documentation (Borison, 1987; Sramek et al, 1989; Green et al, 1989). Specific diagnostic criteria have been developed to distinguish SSP from pre-existing psychopathology (Table 1).

Table 1

Chouinard's Diagnostic Criteria for Supersensitivity Psychosis

(A) The patient must have a 3 month history of receiving antipsychotics.

(B) At least one of the following major criteria must be present:

1) Reappearance of psychotic symptoms upon decrease or discontinuation of medication during the last 5 years - within 6 weeks for oral medication, 3 months for I.M. depot medication.

2) Greater frequency of relapse (acute psychotic exacerbation) during continuous treatment with neuroleptics.

3) Tolerance to the anti-psychotic effect of the neuroleptic (overall increase in dose by 20% or more).

4) Extreme tolerance: worsening of psychosis whenever dosages are increased without presence of significant parkinsonian symptoms.

5) Psychotic symptoms upon decrease of medication are new schizophrenic symptoms (not previously seen) OR are of greater severity.

6) Psychotic relapse occurs upon sudden decrease (20%) of medication but not if same decrease is gradual.

7) Presence of drug tolerance in the past but presently treated with high doses of neuroleptics on at least a bid regimen.

(C) At least one of the following minor criteria must be present if only one major criterion is present:

1) Tardive dyskinesia.

2) Rapid improvement in psychotic symptoms when the neuroleptic dose is increased after a decrease or discontinuation.

3) Clear exacerbation of psychotic symptoms by stress.

4) Appearance of psychotic symptoms at the end of the injection interval (for patients on long-acting intramuscular medication).

5) High levels of prolactin or neuroleptic activity (twice normal).

(D) Exclusion criteria:

1) Patients in the first acute phase of illness.

2) Patients with continuous severe psychosis unresponsive to neuroleptics.

(E) Subtypes:

Stage I: Withdrawal type: reversible when only major criteria #1 and/or #6 are present.

Stage II: Tardive type:

IIA - masked and mostly reversible when major criterion #3 is present.

IIB - masked and mostly irreversible when major criterion #7 is present.

IIC - overt and mostly irreversible when major criterion #1 is present with any other major criteria (other than #6).

Stage III: Severe type: when major criterion #4 is present.

Case Report

A 30 yrs old male patient diagnosed as a case of paranoid schizophrenia was treated initially, with various antipsychotics, both typical and atypical, for a long period, without any significant improvement and having marked extrapyramidal symptoms. Subsequently clozapine was administered and patient had shown significant improvement to that but afterward patient had worsened again with appearance of involuntary dyskinetic movements. Clozapine was substituted with quetiapine with which patient responded but relapsed again after sometime. Sodium valproate was added and patient had sustained improvement after that.

Discussion

The considerable improvement witnessed in the patient suggests that anticonvulsants may have a role in the treatment of SSP. The dose used in the patient was low and serum level was below the conventional therapeutic range.

Antiepileptic drugs are not known to be effective in previously untreated psychosis, although their use is well recognized in bipolar affective disorder. A report has appeared documenting the successful use of these drugs in three patients treated with neuroleptics (Wassef et al, 1989). Our rationale for prescribing antiepileptics in SSP is based on the hypothesis that neuroleptics facilitate a kindling-like effect in the limbic system, thereby aggravating psychotic symptoms. Limbic kindling in animals has been studied as a model for human psychopathology (Stevens & Livermore, 1978).

Kindling represents a model of epilepsy and neuronal plasticity in animals. The term "kindling effect" was coined by Goddard in his classic paper off the subject (Goddard et al, 1969). Intermittent application of an initially subconvulsive electrical stimulus leads to progressive intensification of seizure activity culminating in the production of a generalized motor convulsion from the same stimulus. Seizures in the early stages resemble the manifestations of human complex partial epilepsy (McNamara, 1986). Important parameters in the induction of kindling include the nature of the stimulus and its ability to induce an after discharge. The interval between successive stimuli is particularly important - continuous stimulation does not lead to development of kindling. Once kindled, the animal remains susceptible to seizure provocation upon reintroduction of the stimulus at a later date. In other words, the effect is long-lasting, if not permanent. If spaced repetition of the stimulus is continued after completion of kindling, the animal will eventually develop spontaneous seizures. Thus, the kindling phenomenon is one of several experimental models of epilepsy.

Kindling can be elicited from many sites in the brain where a hierarchy of susceptibility exists. The limbic system, particularly the amygdala, is generally held to be the most susceptible. Kindling has been described in many

species and may contribute to human epileptogenesis as suggested by several lines of indirect evidence (McNamara, 1986). Diverse modes of stimulation can elicit kindling. For example, systemically administered metrazol, lidocaine, or cocaine can induce pharmacological kindling (Majkowski, 1986).

Neuroleptic drugs are known to lower the seizure threshold to varying extents. Clinically, this effect is quite minimal and seizures are infrequently observed in patients taking neuroleptics, even those with a past history of epilepsy. However, if the concept of a repeated, subthreshold, seizurogenic chemical stimulus is applied to neuroleptic therapy it is easy to see how kindling may be possible. Continuous treatment invariably involves a fluctuation in blood levels from peak values to trough levels. In contrast, erratic or discontinuous drug exposure may alter the "inter-stimulus" interval sufficiently to ensure that the changes necessary for kindling never take place.

Neuroleptic drugs exert powerful antidopaminergic effects in the brain, which are felt to be the basis of their antipsychotic action. Although the effects of DA on kindling are far from clear, an intact dopaminergic system appears to protect against the progress of amygdala-kindled seizures to generalized convulsions (Sato et al, 1979). In the study haloperidol was found to decrease the latency for appearance of kindling in rats. Furthermore, there is evidence of a link between aberrant limbic electrical activity and a subsequent increase in DA sensitivity (Csernansky et al, 1985; Csernansky et al, 1988). Thus, limbic kindling as a result of repeated administration of a seizure threshold-lowering drug with antidopaminergic properties could be expected to result in increased psychotic symptomatology. At the same time, though, the treatment for such a condition would be neuroleptic drugs. This fits with clinical observations of SSP in which worsening psychosis follows prolonged treatment, and is masked in the early stages by increasing the dose of the offending agent. The model predicts that DA depletion states predispose patients to SSP whereas functional DA overactivity protects against the development of SSP. Once SSP is established, however, dopaminergic supersensitivity will worsen psychotic symptoms. In severe cases of SSP increasing the dose of neuroleptic leads to a worsening of symptoms, as though reintroduction of the causative stimulus were triggering the psychosis.

One might expect antipsychotic drugs with more potent effects on the seizure threshold to be more associated with the development of SSP. Clinically, such a correlation has not been reported so far. This is understandable since these drugs have a variety of effects on other neurotransmitter systems. Any correlation is further confounded by the concomitant use of anticholinergic medication. Kindling is retarded by muscarinic blockers and facilitated by a decrease in noradrenaline, serotonin, or DA (Majkowski, 1986). Although other drugs such as tricyclic antidepressants also lower the seizure threshold, they tend to enhance the noradrenergic system which inhibits kindling (McIntyre & Edson, 1982). Nonetheless, tricyclic antidepressant drugs have been reported to induce rapid-cycling illness in some bipolar patients (Wehr & Goodwin, 1987).

Earlier reports of SSP found a relationship between this condition and the presence of TD in affected patients (Chouinard et al, 1978). However, later studies in different patient populations have not replicated this finding (Chouinard et al, 1986; Csernansky et al, 1986), supporting the idea that different susceptibilities exist among patients. Clinically, "poor prognosis" schizophrenia is associated with a tendency to develop TD, whereas "good prognosis" patients are more likely to develop SSP (Chouinard et al, 1986). The correlation of TD and SSP in a population of patients was reported with poor prognosis schizophrenia. Subsequent studies included both good and poor prognosis patients. Thus, any study looking at the relationship between TD and SSP should examine patients according to their prognosis.

There are important implications for continuing to escalate the dose of neuroleptic in the face of SSP. TD, originally thought to be its homologue in a different neuronal pathway, appears to reach a plateau of severity beyond which it does not worsen. For this reason, neuroleptics are prescribed in treatment-resistant cases to mask the movement disorder. In SSP, however, there should be no limit to the expected severity of the condition if kindling is indeed contributing to its pathogenesis.

Conclusion

The authors have presented evidence that antiepileptic therapy is beneficial in some drug-resistant schizophrenics who have SSP. Further understanding of the pathophysiology of SSP would enable clinicians to take prophylactic measures when prescribing neuroleptics, and to administer specific treatments for the condition once it developed.

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Case Report :

Neuro-Psychological Profile of Velocardiofacial Syndrome - A Case Report

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ABSTRACT:

Velocardifacial (VCFS) is congenital problem with the physical and psychological anomalies having significant positive correlation with various psychiatric/neuropsychological problems. Most commonly reported is schizophrenia 25% followed by ADHD 20%. Apart from these psychiatric co morbidities, number of cognitive impairments is also common in the cases of Velocardiofacial syndrome.

The objective of this case history presentation is to discuss neurocognitive functions of the cases with such rare entity. To find out the neuropsychological profile and cognitive impairment detail psychological evaluation was done. On psychological evaluations patient was cooperative and participated actively in testing. Results support the view that such patients are having significant difficulty in the area of cognition and suspected anomalies in the functioning / lesion in the multiple area of the brain. Results further reveals the deficits in the area of memory, attention, visuospatial ability, intelligence, social skills and overall in personality. VCFS is complex problem related to physical, congenital cardiac anomalies and multiple psychiatric symptoms need multimodal intervention approach including behavioural, cognitive and neuropsychological rehabilitation for the management of the syndrome.

Key words: ***Velocardiofacial Syndrome, Schizophrenia, Neurocognitive, Congenital, ADHD***

Introduction:

Velocardiofacial Syndrome (VCFS) was described first clinically by Kirkpatrick and DiGeorge in the 1960s and later on by Shprintzen and colleagues in the 1970s. The physical phenotype of VCFS is highly heterogeneous, with 180 possible clinical manifestations. It has significant cognitive / physical involvement as it was defined as a constellation of immunologic deficiencies secondary to thymus, hypoplasis and hypocalcaemia, secondary to hypoparathyrodism. The most common ones are-congenital anomalies present in about 75% of patients who have VCFS. The most prevalent are tetralogy of Fallot, ventricular septal defect with pulmonary atresia, persistent truncus arteriosus, and interrupted aortic arch. On screening of patients with cardiac anomalies, 3% to 15% had the chromosomal deletion indicative of VCFS (Marino, Mileto and Digilio, 2005). ***VCFS understand by palate anomalies (velo) congenital cardiovascular defects (cardio) and mild facial dysmorphism (facial).*** Abnormal facies are common in VCFS and are characterized by hypoplastic alae nasi, prominent nasal root, long narrow face with flat cheeks, narrow eye opening, small mouth and retruded chin, and small-cupped ears. Palatal abnormalities are present in up to 75% of patients. Most affected patients have insufficiency of the palate, with cleft palate being less common and cleft lip being rare. Clinically, the cleft anomalies in VCFS cause hypernasal speech, (Kirscher, 2005). Other physical features of VCFS include tortuous retinal vessels, growth retardation, juvenile rheumatoid arthritis, and urinary system anomalies. Since its inception in early 1960s researchers discovered that VCFS is extremely wide and includes more than 180 possible congenital anomalies.

Though the reported prevalence of VCFS is around 1 in 10000 but the magnitude of the problem may be severe as the actual prevalence of the VCFS is difficult to ascertain because the diagnosis of VCFS is only possible through cytogenetic test and high cost of FISH *(Flurscence in Situ Hybridization)* test is not allowing the people and clinicians as well for easy excess of such testing. It is proved that the VCFS is caused by chromosome 22 at band 22q 11.2. Therefore some clinicians are in favor of renaming the syndrome as 22q11.2 deletion syndrome.

The VCFS and psychiatric problems have been found positively correlated. Especially VCFS and schizophrenia are highly associated as 25% persons suffering from VCFS develop schizophrenia. Overall 79 % cases of VCFS reported for having psychiatric

disorders mainly ADHD, Anxiety disorder and also Mood disorder. They also share common problem like social isolation / withdrawals, social rejection, low self esteem, and deficits in social skills (Basset A S, Chow EW, Abdel Malik et al, 2003).

The embryonic origin of physical disease associated with VCFS is impaired migration of the neural crest cells which give rise to mesenchyme of the third and forth pharyngeal arches which further differentiate into face, cleft, thymus, parathyroid glands and cardiovascular system. The region containing the smaller 1.5 million base deletions in VCFS contains 24 genes. It is likely that a haploinsufficiency (missing part) of one or combination of these genes predisposes the individual who has VCFS to the accompanying physical and psychological symptoms. TBX_1 gene have been found responsible for developmental anomalies, common features include thymus and parathyroid glands, hypoplasia, cardiac outflow abnormalities, abnormal facial structure, vertebrae and cleft palate. It also plays significant role in development of arteries. TBX_1 protein potentially contribute in neuropsychiatric and cognitive deficits in VCFS (Mc Darmid H E, Marrow BE, 2002 & Paylor R, Glaser B, Mupo A, et. al., 2006)

Case History:

A case report is presented of Mr. U., 22 years old, male, unmarried, no family history of psychiatric illness, but having past history of two psychotic episodes from since 6 years. The Patient was born out of full term normal delivery at hospital; there is history of delayed milestone development, he took lot of time in learning essential life skills like speaking, taking food, self care, etc. The patient was restless and hyperactive from the childhood but his problem was increased since last 6 years. Most of the time, he keeps on moving here and there and had roaming around tendency. Once he goes outside, never come back by his own. He is over talkative and making big claims, he has the behavioural oddities like teasing the girls of village, his sleep was decreased, and he hardly sleeps 2-3 hours out of 24 hours. He takes his personal care properly but did not bear his responsibilities properly. His pervasive and persistent mood was cheerful. On mental status examination (positive findings), he was kempt and tidy, eye contact was maintained, rapport was established, cooperative attitude, decreased reaction time with increased productivity of speech, restlessness, affect cheerful, appropriate and communicable, delusion of grandiosity, impaired judgment, grade one insight was present. No H/o Tics, mannerism, stereotypy was reported.

Mr U was assessed for his multiple functioning on following tests:

- PGI –Battery of brain dysfunction (PGI-BBD)
- Wechsler Adult Performance Intelligence Scale (WAIS)
- Stanford Binet Intelligence Scale,
- Vineland-Social Maturity Scale (VSMS)
- Luria-Nebraska Neuropsychological Battery (LNNB)
- Rorschach Inkblot Test
- Human Figure Drawing Test (HFDT)
- Indian Disability Evaluation and Assessment Scale (IDEAS)
- Conner's Rating Scale,
- Young-Mania Rating Scale (Y-MRS)

Results: The following tests findings of assessment has been drawn and are being presented -

Attention Patient has poor level of attention and unable to focus attention n task (concentration) and on PGI-BBD; significant level of cognitive dysfunctions was elicited.

I Q His intellectual and social adaptive functioning was on the border line level. Performance IQ is poor than Verbal IQ

Human Figure Drawing
- Moderate level of cognitive impairment.
- Poor self concept, low energy, high aspiration
- Hostility,
- Regression and organicity

On Rorschach
- Poor Productivity
- Quick reaction time
- Conservative processing approach
- Uses the fantasy for reality in stressful situation
- Serious meditational impairment.
- Highly vulnerable to loss of control and unable to cope with the stress.
- Has an avoidant extratensive style.
- Tendency to economize and avoid complexity.
- Prone to use his feelings more directly in decision making by merging them with his thought.

- Poor human empathy and
- Reserved interest level

Neuropsychological deficits on LNNB
- Impaired Visuo-spatial skills
- Deficits in expressive speech
- Intact writing ability on written material but inability to write on auditory commands/stimulus.
- Disruption on reading ability
- Mild dysfunctions on arithmetic
- Dysfunction in short term memory and intermediate memory.

- **Findings on Young Mania Rating Scale, Corner's Rating Scale and IDEAS** suggests:
  - Manic like symptoms,
  - ADHD like symptoms and
  - Moderate level of disability on social functioning.

Discussion:

The VCFS is complex congenital anomalies / problem caused by physiological and genetic abnormality, commonly associated with multiple psychiatric conditions. Studies of school aged children shows that already in childhood, individual who had VCFS had high psychiatric morbidity with multiple behavioural and cognitive abnormalities more commonly ADHD, anxiety disorder, mood disorder and schizophrenia the findings of the present study are in similar track where it is apparent that this case has shown borderline level of social and daily living skills and social adaptive functioning. The individual suffering from VCFS most often share the common risk factor such as social isolation and rejection by family members and otherwise too may also be contributing factor for impairment in social isolation, persistent low self evaluation, and poor interaction with environment. The findings of present case study on LNNB suggests lesion in left hemisphere and the possible involvement of left temporal lobe, might be responsible for poor attention process, and difficulty in organizing the things in proper useful manner. The findings are consistent with Bish JP et al. (2005). The MRI findings of the children having VCFS is in favor of abnormal activation of the parietal cortex and the researchers proposed that a parietal dysfunctions in individual who have VCFS may impair their ability to orient visual cues and contribute to an overall executive dysfunctions (Gothelp D, Hoeft F, HinardC, et al, 2007). The result of the present study shows the evidence of poor intellectual functioning of the case, discrepancy in verbal and performance IQ as the verbal IQ is more than performance IQ. The full scale IQ of present case is on borderline category. These findings are further consistent with the study of Swillen, Devriendt and Legius (1997). The average full-scale IQ score in individuals with VCFS is in the mid- 70s, within the borderline-intelligence range, in 25% to 40% of subjects intelligence is in the mental retardation range. Cross-sectional studies in children who had VCFS indicated an 8 - to 10-point higher verbal IQ (VIQ) than performance IQ (PIQ) (Campbell and Swillen, 2005) whereas in adults, VIQ was 3.6 points lower than PIQ, (Henry, Amelsvoort and Morris, 2002). The evidence of decline of VIQ scores in adults is confirmed by longitudinal study (Gothelf D, Elliez S, Thompson T et al, 2005).

The cognitive profile of subjects who have VCFS is characterized by relative strength in the area of reading, spelling and weakness in visuospatial memory and arithmetic. The cognitive level task requires the shift of attention cognitive flexibility and working memory functions mainly dealt by frontal cortex and caudate nucleus and task related to visuospatial numerical ability by posterior parietal cortex is found impaired as the findings of LNNB clearly indicate the possible lesion in the posterior area of temporal lobe and adjacent area of the parietal lobe as well. The findings are consistent with the findings of Eliez S, Barnea-Goraly N, Schmitt J E et al (2002) and Simon T J, Beardon C E, Mc- Ginn DM et al, (2005). The individual having VCFS also manifest deficient skills in various area, poor self concept, poor decision making, presence of hostility/ aggression might be considered as resultant of lesion/deficits / involvement of various significant areas of the brain which platys very significant role either independently or conjointly with other areas on above neurocognitive / sociocognitive functions. The findings of the study also reveal the manic like symptoms and ADHD like symptoms. VCFS have increased rate of affective disorders. Mood swings are common. About two third children and adolescents reported the problem of bipolar disorder (Poplas D F, Feadda G L, Veit S et al, 1996, Fenstien C, Eliez S Blacy C et al 2002).

Since the VCFS is not simple entity rather it's a complex set of physical, psychological, neurological and physiological problems. In individuals with VCFS physical, psychiatric and neurocognitive deficits vary widely in scope and severity. Because of the complexity of the problems the management is another challenging task for clinicians/ psychiatrist as antipsychotic medicines most

often produce multiple side effects. Because schizophrenia and ADHD is most common psychiatric co-morbidities with VCFS, the question arises whether to provide stimulants medication. There are multiple concerns regarding the use of stimulants/antidepressants/ antipsychotics in subjects having VCFS because of their congenital cardiac anomalies and the use of such medicines can increase the risk of hypertension and tachycardia. In such condition apart from pharmacological (psychotropic or otherwise) multimodal treatment approach is required, including behavioural intervention, cognitive rehabilitation, social skill training and parental guidance in cases of children to be considered inevitable part of management of VCFS syndrome.

Conclusion: Velocardiofacial Syndrome (VCFS) was described in 1960s with multiple physical, psychological and congenital cardiac anomalies. Further researches supported the view of common co morbidities of psychiatric disorders and multiple cognitive deficits and neurological involvement as well. Such complex conditions produce the difficulty on diagnostic clarification and challenge for clinician in management process of such syndrome. It needs the sharp skills of clinician to identify the problem symptoms for arrival of specific diagnosis and use of multimodal approach of intervention for the management of multiple physical, cognitive, psychiatric, behavioural and social problems. Sometimes in case of children parental counseling and family counseling in case of adulthood onset of problem may also become essential to deal with problem successfully in totality.

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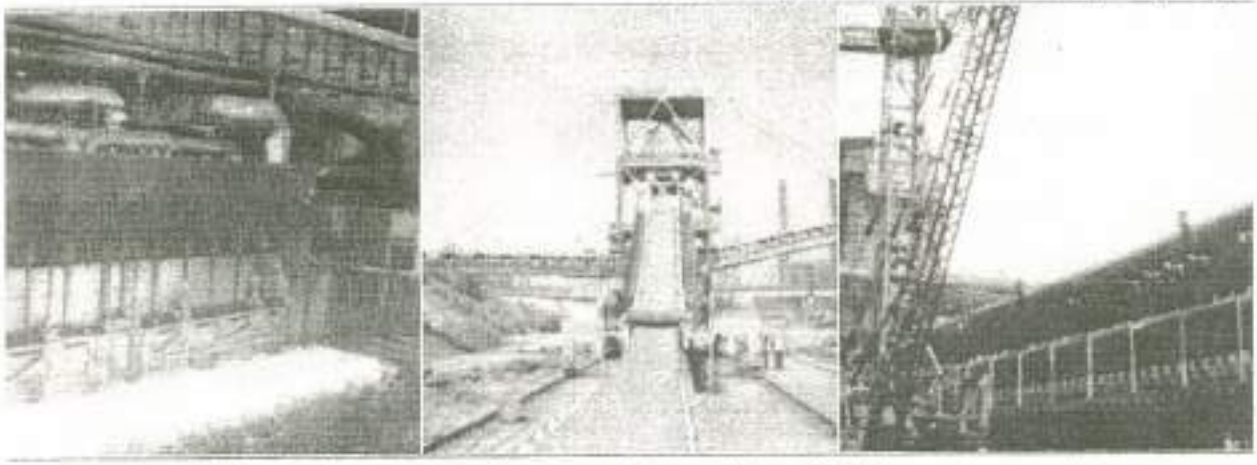

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