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Editorial

Biological Psychiatry: Stage set for radical change

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Historically, psychiatry has been dominated, for many years, by subjective approaches to mental illness. No wonder psychiatrists have been unsettled by the realization that the next major advances in their field are bound to come from genetics and molecular biology.[1] If we put current developments into a historical perspective psychiatry already accommodates a biological approach. This approach became well established in the early part of last century as great advances were made in curing psychiatric disorders caused by readily discernible cellular pathology. At the same time psychoanalysis was invented to deal with problems that were not accompanied by obvious biological abnormalities. Eventually psychoanalysis so captured the imagination of both psychiatrists and the public that the biological approach came to be obscured. Now new developments in biology have set the stage for another change of emphasis.

Causes of mental illness

The border between illness and normality is not well defined. There is also disagreement about whether "normal" means average or ideal. There are patterns of behavior that are very uncomfortable for a person and for those with whom that person interacts. Some patterns are so maladaptive that illness is obviously a proper designation. Mental illness can manifest in different ways. These diverse origins have led people to believe that behavioral abnormalities must have psychological causes. Whereas psychological factors often do play a central role, many forms of psychiatric disorders have been shown to be due to overt brain pathology.

Dementia paralytica (General paresis of insane) is one such brain pathology which, at the beginning of the twentieth century, affected about half the patients in psychiatric hospitals.[2] Clinical features of this pathology include mood symptoms and grandiosity, and the illness progresses to dementia and paralysis. Originally considered to be caused by psychological factors, it is actually a late manifestation of syphilis, with psychotic symptoms appearing only many years after the initial venereal infection. When its etiology was established, antimicrobial agents provided a cure. The eradication of neuro-syphilis is, therefore, a clear illustration of the value of the biological approach in psychiatry. In the years that followed, biological approach led to the elucidation of a number of other disorders with major psychiatric manifestations and with different types of etiologies. Some disorders, such as myxedema, are due to hormonal deficiencies that can be corrected by replacement therapy. Others, like pellagra, are due to dietary deficiency and respond to nutritional treatment. Phenylketo-nuria, a genetic disorder, diagnosable on a simple biochemical test is treated by a dietary regimen based on an understanding of the primary enzymatic abnormality. There are many systemic diseases which may affect the function of many tissues, although their primary manifestations are often behavioral. Because they produce readily detectable gross or microscopic pathology, they could be analyzed by the biomedical technologies that developed in the first half of the twentieth century. These clinical conditions are so well understood still their historical importance for psychiatry is forgotten. We psychiatrists are also confronted with patients suffering from the same types of psychological symptoms- such as depression,

paralysis, and disordered thinking but who do not show any obvious biological pathology. This quandary set the stage for a radical change in psychiatric thought.

Freud changes directions

Despite his training in neurology, Freud abandoned the biological approach because of its limited applicability to his patients and instead applied his psychological imagination to a wide range of human and psychiatric problems. Right from his student days, Freud was interested in neurobiology and he worked with Ernst Brucke, a leading physiologist. Freud studied the histology of the spinal cord and ganglia of eel and published extensively. He also made contributions to neuro-embryology and to the development of techniques for tracing nerve fibers.[3] Subsequently, he turned from basic research to neurology. Jean Martin Charcot, a leading French neurologist kindled Freud's interest in hysterical paralysis and its treatment by hypnosis which probably made Freud consider psychology more seriously. This new interest was further stimulated by his friend Josef Breucr who had successfully treated Anna O., a patient with symptoms of hysterical paralysis, by psychotherapy. This was a turning point in Freud's life. Putting neurology aside he became a psychological investigator to invent psychoanalysis addressing psychiatric problems on the basis of a vision of human development and adaptation which, although unverified, seems plausible. Biology, in contrast, had great difficulty in dealing with behavioral problems other than those caused by systemic illnesses with readily discernible pathologies. However, the development of psychopharmacological treatments greatly increased biology's relevance.

Drug Effect Mechanism

Psychopharmacology originated as an enterprise in which drugs whose actions were not understood were used to treat psychiatric disorders whose causes were obscure. Schizophrenia and the mood disorders in which there are no obvious neuropathological correlates to guide treatment, there seemed to be little else the psychiatrist could do for the patient. With time, several extremely valuable drugs whose usefulness was discovered largely by accident appeared as therapeutic armamentarium. Chlorpromazine was originally developed to induce anesthesia. The antidepressant action of monoamine oxidase inhibitors (MAOI) such as tranylcypromine was discovered by chance observation of the effects of a drug that was developed for treatment of tuberculosis.

Chlorpromazine binds dopamine and other receptors, Imipramine blocks synaptic reuptake of amines, Tranylcypromine blocks monoamine oxidase, Lithium blocks phosphoinositide metabolism, Diazepam binds GABA receptor to infer the physiological cause of the illness from the mechanisms of action of the effective agents.[4-7]

One of the most challenging problems of psychopharmacology is to explain how such alterations of neurotransmitter dynamics influence behavior. It is a complex phenomenon because a given neurotransmitter is often widely distributed in the nervous system and appears to participate in many neuronal circuits. The therapeutic doses of some drugs, such as imipramine and lithium, that reduce pathological behavior, have little or no effect on normal behavior. The palliative behavioral effects frequently are not manifested for days or weeks after administering the drugs at their effective levels, indicating that an adaptive response to these agents. So further developments in psycho-pharmacology will depend, in part, on under-standing how biological regulatory mechanisms in the brain produce sustained reactions to various perturbations of synaptic transmission, which may actually be responsible for the palliative psychological effects.

Focus on genetic factors

Most common psychiatric and drug abuse disorders can be traced to a small number of dimensions of genetic risk and reports show significant associations between specific genomic regions and psychiatric disorders.[8,9] Though, to date only a few genetic lesions have been demonstrated to be responsible for psychiatric conditions.[10,11] In persons diagnosed as schizophrenia and in their relatives with chronic psychiatric illnesses, the gene that encodes phosphodiesterase 4B (PDE4B) is disrupted by a balanced translocation.[12]

Genetic understanding remains limited because the links between genes and mental states defined

as abnormal appear highly complex, involve environmental influences and can be mediated in numerous different ways, for example by personality temperament or life events.[13] Therefore while *twin studies* and other research suggests that personality is heritable to some extent, finding the genetic basis for particular personality or temperament traits, and their links to mental health problems, is at least as hard as the search for genes involved in other complex disorders.[14] Theodore Lidz[15] and Joseph Jay[16,17] argue that bio-psychiatrists use genetic terminology in an unscientific way to reinforce their approach. Joseph maintains that bio-psychiatrists disproportionately focus on understanding the genetics of those individuals with mental health problems at the expense of addressing the problems of the living in the environments of some extremely abusive families or societies.

Role of hereditary factors is evidence from the accumulated research but it is difficult to identify the underlying genetic abnormality directly. The availability of new chromosomal mapping techniques now makes it possible to identify the responsible genes.[18,19] Although the earlier chromosomal localizations reports of genes responsible for manic-depressive disorder[20] and schizophrenia[21] have been questioned.[22,23] The genetic approach is bound to succeed ultimately and it is likely that it will be extended to other conditions such as panic disorder and obsessive compulsive disorder for which a genetic predisposition is also indicated. Genetic analysis may ultimately provide insights into major disorders, as well as reveal factors that predispose particular genotypes to certain temperaments.

Cloning of cDNAs and genomic DNAs that encode neurotransmitter receptors has opened up a new approach to the design of specific drugs that interact with these proteins. One consequence of this development has been the identification of unsuspected receptor subtypes. The discovery in the caudate nucleus of a second molecular form of D is a recent example. Dopamine receptor that contains an insert of amino acid residues in the polypeptide domain is believed to interact with G proteins.[24] And since cloned receptor genes can be expressed after their transfection into cultured cell lines,[25,26] a more precise pharmacological analysis of the receptors can now be carried out than was possible by studying them in whole animals, or even in identified neurons.

Gene regulation study opens up the possibility of fathoming the mechanisms of tolerance and addiction to drugs, which are other important causes of mental illness. The molecular biology of receptors will also permit many other types of advances. In situ hybridization studies with cDNAs encoding receptors, peptide neurotransmitters and enzymes involved in neurotransmitter biosynthesis are leading to the development of new types of maps of the brain. Such molecular maps will ultimately be correlated with the neuronal networks that control certain behaviors, such as the reward systems that are stimulated by certain drugs.

There is no denying the fact that the ongoing research is bringing newer insights into the understanding of cause of abnormal behaviour there is a long way to go. Moreover, it is difficult to envision drugs that will undo the effects of maladaptive behaviour, emotional deprivation, and child abuse. To cope with the resultant behavioral problems we must, therefore, continue to develop psychological techniques designed to reorient, clarify, and reeducate. And there is no substitute for the preventive measures that can brought about by social and psychological intervention. But contemporary social and behavioral sciences are as limited in addressing psychotherapy and psychoprophylaxis as the biology of Freud's time was in approaching the molecular genetics of mental illness. So the next revolution in psychiatry must await new ways of approaching behavior. Meanwhile, the psychiatrists and biologists who are committed to a molecular approach to mental illness can confidently look forward to some very productive years.

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Review Article

Gonadal Hormones and Schizophrenia : A Clinical Review

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Introduction

There are clear gender differences which have been elucidated in most neurological and psychiatric disorders. The incidence of anxiety, depression, eating disorders and Alzheimer's dementia is more in women whereas men on the other hand are more likely to be afflicted with alcohol and drug abuse problems, antisocial personality disorder, attention deficit disorder and Tourettes syndrome.[1] A number of these gender differences have been attributed to differences in the mechanisms involving sex hormones.[2] Studies have revealed that the same neuropeptides and steroids underlying reproduction are also involved in other brain processes like cognition, memory and emotions that are non reproductive in nature.

It is important to note is that however that not every hormone behaviour relation shows gender differences. This is often the case with neuropeptides having similar location and function in the brains of males and females. Even with the sex hormones, there is notable overlap in the distribution of oestrogen and androgen receptors in the two genders in the non reproductive brain regions.[3-4]

Neuroactive Steroids and Neurosteroids

Neuro-endocrinologists have given the concept of neuroactive steroids and neurosteroids.[5-6] Neuroactive steroids are synthesized in the periphery and carried by the blood stream to the brain tissues with the steroid receptors. These include testosterone, estrogen and corticosteroids. Neuroactive steroids affect multiple brain functions via intracellular receptors that regulate transcriptionally directed changes in protein synthesis. These physiological actions occur within hours or days.[7] Neurosteroids are synthesized exclusively by the brain and for use by the brain. Examples of neurosteroids include allopregnenolone, pregnenolone, dehydroepiandrosterone and their corresponding sulphate esters.[8-9] Neurosteroids influence neuron excitability by non genomic means by acting as allosteric modulation of GABA-A, NMDA and opioid receptors.[10] Neurosteroids rapidly alter excitability of central nervous system through binding to neurotransmitter gated ion channels. These actions occur within seconds or milliseconds.

Hormones and the Developing Brain

Sexual hormones help organise the foetal brain as masculine or feminine. A critical concept in review of hormone–psychopathology literature is that the current level of hormones in adult need not be the crucial factor .It may be that fetal hormones have already induced brain pathology long before symptoms appear in adulthood. Current levels may or may not be responsible for symptomatic expression. After the fetal organisation and establishment of a masculine or feminine brain circuit, the second activation of this circuit is brought about by pubertal hormones resulting in gender typical adult social behaviour, an array of non-reproductive behaviours that can be influenced by the level of hormones currently in circulation in adult.[7] Besides this our own neural morphology also exhibits plasticity to current hormonal titres. Example noted would be of the hippocampal dendritic spines increasing and decreasing rapidly to fluctuations in endogenous sex hormones in adult

female rats.[12-13] Sex hormones also influence neural transmission by innervating the neuron directly or coexisting with the neurotransmitter within the neuron or acting upon the local circuitry to indirectly impact the transmitter system.[14]

Sexual Hormones and the Neuropathology of Schizophrenia

Speculations for mechanisms for pathogenesis of schizophrenia have been driven largely by the influence of drugs on behaviour of schizophrenics and mentally healthy individuals. It is the result of anti-psychotic (neuroleptic) medications for schizophrenic patients[15-16] that has led to the development of the neurotransmitter hypothesis and neurodevelopmental model for aetiology of schizophrenia. Although the evidence of schizophrenia is similar between the two genders, epidemiology studies have revealed subtle sex differences. Men develop the disease earlier in life, experience more severe symptoms and respond less well to pharmaceutical therapies than do women.[17-18]

Sex differences in the effectiveness of typical and atypical drug therapies suggest sex hormones play a role in both neurotransmitter function and structural development. One prominent example is the capacity of estrogen to influence the release of dopamine and serotonin[19] which may offer some protection to the female brain. Women appear to derive neuroprotection from estrogen because women's first episodes of schizophrenia are years later than in male schizophrenics, and women's responses to drug therapies are better, but only during their reproductive years.[19]

Similarly, sex differences in language ability of non patients and patients suggest men and women have different structural changes with the disease.[20] Similarly, the verbal ability in schizophrenic women is similar to healthy women, whereas schizophrenic men show clear deficits. The implication is that these data point to sex differences in morphology of temporo-parietal and frontal brain regions associated with phonological processing, most likely occurring during fetal development and this may be a reflection of the greater hemispheric functional asymmetry of men relative to women. The suggestion is of complex androgen/estrogen interplay during fetal life underlying abnormal hemispheric dominance in schizophrenic males.[21]

The development of schizophrenia during the reproductive period in a majority of those affected suggests that this disorder is related to a disturbance in the balance between one or more inhibitory and excitatory factors in response to the flood of reproductive hormones to the brain and consequent compensatory remodelling of synapses in specific brain areas.[21] Receptors for and neurons containing reproductive hormones are strongly expressed in the hypothalamus, and receptors for these hormones are strongly expressed in the extrahypothalamic nuclei of the basal forebrain that receive afferents from the amygdala and hippocampus and project via the thalamus to the cerebral cortex. The forebrain nuclei that express reproductive hormone receptors are regulated by glutamatergic and cholinergic and by dopaminergic, serotonergic, and GABA-ergic inhibition. Although no single anatomic site or disturbance in physiology that is pathognomonic or essential for development of schizophrenia has been identified, recordings from the basal forebrain nuclei in schizophrenic patients demonstrated abnormal electrical activity in these areas and pathologic examination demonstrated a higher than normal level of dopamine receptors in this region in some individuals with this disorder.[7]

Amelioration of symptoms of schizophrenia with antagonists of inhibitory receptors or by convulsive therapy could indicate that the underlying pathophysiology is a loss of the physiologic equilibrium between brain excitatory and inhibitory systems in this critical brain area in genetically susceptible individuals. The maximum occurrence of schizophrenia during the reproductive period and the range of responses to different antipsychotic agents by different individuals suggest that this imbalance is associated with pathologic extension of physiologic inhibition by one or more inhibitory factors beyond the basal forebrain in response to the flood of excitatory hormones to the brain during the reproductive period.[3]

Oestrogen and Schizophrenia

Early clinicians such as Kraepelin and Kretschmer described signs of chronic 'hypo-estrogenism' in women with schizophrenia. Von Kraft-Ebing was among the first to describe women becoming psychotic before or during menstruation,

i.e. when blood levels of estrogen are relatively low. Kraepelin even created a separate diagnostic category, labelled 'menstrual psychosis'. Kretschmer reported cases where the outbreak of schizo-phrenia and related psychoses had a temporal relationship with 'surgery of ovaries, pregnancy, delivery, and puerperium'. Finally, Manfred Bleuler noted that late onset schizophrenia with onset after age of 40 years was much more frequent in women than in men, a finding he attributed to the 'loss of ovarian function' starting at around that age.[22]

Oestrogen receptors can be found in abundance in many extra-hypothalamic regions throughout the brain. The limbic system in particular, including the amygdala and hippocampus, is rich in oestrogen receptors, as are the basal ganglia and many areas of the cerebral cortex.[23] There are at least two subtypes of estrogen receptors, namely estrogen receptors-alpha and estrogen receptors-beta, which are transcribed from two distinct genes.[24] Recently authors have reported a variation in the endogen receptor-alpha (ESR1) gene to be associated with schizophrenia and speculated that the mechanism of this association may involve alternative gene regulation and transcript processing. Through classical genomic and rapid nongenomic interactions with these receptors, oestrogen functions as a 'neuroactive steroid', influencing signalling pathways and neurodegenerative process within the CNS.[25]

Oestrogen has neuromodulatory and neuroprotective properties. It has been found to affect dopamine and serotonin at multiple levels. Oestradiol decreases the activity of monoamine oxidase, increases the activity of tryptophan hydroxylase, manipulates expression of the serotonin transporter, down regulates $5\text{-}HT2_A$ receptors. Hypoglutamatergic neurotransmission in the hippocampus and frontal cortex has also been implicated in the pathogenesis of schizophrenia, given the observation that glutamate N-methyl-D-aspartate (NMDA) receptor antagonists such as phencyclidine produce a psychomimetic state in animals and humans.[26] Oestradiol is known to up regulate NMDA receptors, change their submit configuration and increase in NMDA agonist binding in the rat brain,[27] which could presumably help reverse hypoactive glutamatergic functioning in schizophrenia.

Oestrogen is known to have diverse neuroprotective properties that could be of particular relevance to its ability to mediate the onset and course of brain disorder in schizophrenia. Recent in-vitro and in-vivo research has confirmed that oestrogenic compounds can protect brain cells against injury from excitotoxicity, oxidative stress, inflammation and apoptosis.[28-30] They can also enhance neurogenesis, angiogenesis, synaptic density, plasticity and connectivity, axonal sprouting and remyelination and expression of neurotrophic factors.[31-33] It is believed that these neuroprotective processes are mediated predominantly through action of neuronal oestrogen receptor-alpha.[34] Recent findings also suggest that the psychoprotective properties of oestrogens might stem from their preservation and enhancement of neuronal mitochondrial function during injurious circumstances, as mitochondria are responsible for regulating the viability and death of neurons[35] and may be dysfunctional in the brains of individuals with schizophrenia.[36]

Testosterone, Androgens and Schizophrenia

Although most studies have stated details of role of oestrogen in schizophrenia, a basic feature is that oestrogen is a metabolite of testosterone.[7] Testosterone may directly activate steroid sensitive tissue or be metabolised to oestrogen through enzyme aromatase or to dihydrotestesterone through 5 alpha reductase.[37] In the brain tissues possessing aromatase and that includes most of the subcortex, testosterone is likely functioning as a prohormone. Thus its effects on function are only after it is metabolised to oestrogen which then subsequently binds to oestrogen receptors.[38] Various studies on role of testosterone showed that testosterone levels were no different in schizophrenic men compared to healthy men.[7]

DHEA serves as a prohormone for oestrogen and testosterone. Attempts to co relate levels of DHEA and DHEA-S (Dehydroepiandrosterone sulphate) have yielded inconsistent results.[7] In various studies the DHEA levels in schizophrenic patients was found to be lower than controls.[39-40] In a more recent study in male Schizophrenic patients, the serum levels of DHEA were increased but that of DHEA-S were decreased.[41] Another study noted that morning serum DHEA levels and/or DHEA to

cortisol ratio were directly related to aspects of memory performance and were inversely co related with ratings of psychosis and parkinsonian movements in chronic, medicated, institutionalised schizophrenics.[42] These findings raise the possibility that low DHEA levels or low DSHEA to cortisol ratio identify a particularly impaired subgroup of chronic schizophrenic patients.

Pregnenolone and Schizophrenia

Pregnenolone is a neurosteroid with pleotropic actions in rodents that includes enhancement of learning and memory, neuritic outgrowth and myelination. Further pregnenolone administration also results in increase in allopregnenolone which also has neuroprotective effects and increases neurogenesis, decreases apoptosis and inflammation, modulates the hypothalamic pituitary adrenal axis and markedly increases GABA-A receptor responses, which appear to be dysregulated in schizophrenia.[43-44] Allopregnenolone potentiates GABA-A responses more potently than benzodiazepines or barbiturates.[45] In addition, pregnenolone elevates pregnenolone sulphate, a neurosteroid that positively modulates NMDA receptors and potentially contribute to the amelioration of NMDA receptor hypofunction in schizophrenia.[46-47]

Serum pregnenolone levels were found to be low compared to control subjects in one study[48] while conversely in another study[49] the pregnenolone levels were found to be higher in postmortem brain tissues of schizophrenic patients. It has been hypothesised that these elevations could be antipsychotic induced mainly clozapine.[49]

Role of Hormones in the Treatment

Most recent studies as discussed above support the oestrogen protection hypothesis of schizophrenia and have thus had important implications for role of oestrogen as therapeutic agent for schizophrenia. Women with a history of deterioration in mental state during menstrual cycle or puerperium seem to benefit most from oestrogen augmentation therapy, especially considering the additional benefits of oestrogen replacement during menopause.[50] Although oestrogen has proven neuroprotective and with antipsychotic effects, its long term safety for use as an adjunctive treatment in schizophrenia is unclear given its stimulating effects on peripheral tissues such as breast and endometrium.[51] Hence any long term administration must be in conjugation with a progesterone which can attenuate the beneficial effects of oestrogen.[23] Recently SERMs (Selective Estrogen Receptor Modulators) have become popular in this regard that they share the neuroprotective and neuroregulatory effect of oestrogen in the CNS[28] but have tissue specific effects on peripheral oestrogen receptors.[52] Raloxifene, with agonist action in the brain but antagonist action in breast and endometrium is a suitable option.[51] Also, women are more susceptible to hyperprolactinemia associated with long term, high dose antipsychotic use, which inturn can have serious consequences like early menopause, osteoporosis and even breast cancer.[53-54] Raloxifene thus becomes all the more a suitable option considering it actually preserves bone density and has anticancer properties in the breast.

Role of oestrogen supplementation in men with schizophrenia is controversial. This is due to the feminising effects such as gynaecomastia and decreased libido. However these are not reported in studies that use less than 2.5 mg of oestrogen daily for the duration of less than 4 weeks.[55] In fact oestrogen has been used effectively to prevent bone loss and enhance cardiovascular function in men with prostrate cancer.[55] Oestrogen has shown in multiple studies to significantly improve general psychopathology symptoms such as depression, anxiety, insight and cognition is of particular relevance to treatment of schizophrenia and must not be underestimated.[50] Another hormone recently reviewed in three pilot studies[56-58] is pregnenolone where results suggest that pharmacological intervention neurosteroid pregnenolone may have therapeutic benefits in schizophrenia. Clinical studies in larger cohorts will however be required further.

Conclusions

Studies involving hormonal therapies in schizophrenia are still in a nascent stage. It is only time that will reveal the success of failure of hormonal therapy in schizophrenia. Yet this seems to be a novel area for both treatment and clinical research in schizophrenia.

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Review Article

Prescription Errors – Need to Detect and Report

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The prescription errors and adverse drug events continues to be an important problem in clinical practice. Barker and McConnell first drew attention towards the fact that medication errors occur more frequently than suspected and that at a rate of 16 errors per 100 doses.[1] As the awareness about 'medication errors' grew, a multidisciplinary group of 27 national organiza-tions formed the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP).[2]

In 2007, the IOM report[3] on medication safety emphasized the importance of severely reducing medication errors, improving communication with patients, continually monitoring for errors, providing clinicians with decision-support and information tools, and improving and standardizing medication labeling and drug-related information.

Definition

The National Coordinating Council for Medication Error Reporting and Prevention defines a medication error as any pre-ventable event that may cause or lead to inappropriate medication use or patient harm, while the medication is in the control of the health-care professional, patient, or consumer.[2] Adverse drug events (ADEs) are defined as injuries that result from medication use, although the causality of this relationship may not be proven.[4] An adverse drug reaction is defined as "an undesirable response associated with use of a drug that either compromises therapeutic efficacy, enhances toxicity, or both."[5]

Black Box Warnings and High-Alert Medications

The FDA, in 1995, established the black box warning (BBW) system to alert prescribers to drugs with increased risks for patients. These warnings are intended to be the strongest labeling requirement for drugs or drug products that can have serious adverse reactions or potential safety hazards, especially those that may result in death or serious injury.[6] According to the Institute for Safe Medication Practices (ISMP),[7] "High-alert medications are those likely to cause significant harm when used in error."

Epidemiology

Beso et al[8] identified one or more dispensing errors at the final check stage in 2.1% of 4849 dispensed items, and outside of the pharmacy department in 0.02% of 194,584 items. Another study found the incidence and type of medication errors in UK pediatric hospital in 0.15% of admissions (195 errors; one per 662 admissions) and the highest rate occurred in neonatal intensive care (0.98%). Errors involving the intravenous route were commonest (56%), with antibiotics being the most frequent drug involved (44%).[9]

In an Indian study by Pote et al[10], the medication errors were analyzed prospectively in 3 medical wards of a teaching hospital. The drug-drug interactions errors were the most frequent (68.2%) followed by incorrect dosing interval (12%) and dosing errors (9.5%). The medication classes most frequently involved were antimicrobials (29.4%) followed by cardiovascular drugs (15.4%), GI drugs (8.6%) and CNS agents (8.2%). The results showed that the number of errors increases with age and number of medicines prescribed.

In a systematic literature review of 16 studies, eleven reported dosing errors as the most common type of medication error, three studies found it to be the second most common type.[11]

The economic burden for all areas of healthcare from drug misadventures exceeds $100 billion annually in the United States[12]. The data regarding the incidence and economic impact of medication errors is lacking in developing world.

Classification

Medication errors can be classified in many ways. Some of the methods of classifying medication errors are listed below.

1. Based on onset[13]

Medication errors can be classified as active or latent based on the onset. Active errors have an immediate effect. Latent errors have delayed effects, are easily identifiable and thus can be corrected before it recurs.

2. Based on underlying cause[14]

Based on their cause medication errors can be classified as below:

Omission error: This error takes place when a patient has not received his or her medication by the time the next dose is due.

Wrong dose error: This type of error occurs when the patient receives an amount of medicine that is greater than or less than the amount ordered.

An unordered error: This error occurs when a patient receives a medication for which the physician did not write an order.

Wrong dosage form error: It involves the administration of a drug in a dosage form different from the one that was ordered.

Wrong time error: It occurs when the patient does not receive his/her medication within a predefined interval.

Wrong route error: They occur when the correct dosage form is administered, but in the incorrect site on the patient's body.

Deteriorated drug error: It is reported when the physical or chemical integrity of a medication dosage form has been compromised, as with expired drugs or intravenous medications requiring refrigeration that are stored at room temperature.

Wrong rate of administration errors: These errors can occur with infusions of intravenous fluids or liquid enteral fluids.

Wrong administration technique errors: It involves the use of an inappropriate procedure during administration of a drug.

Wrong dose preparation error: It occurs when a product is incorrectly made or manipulated before administration.

Extra dose error: It occurs when the patient receives one or more dosage units in addition to those authorized, such as the dose administered after the dose was cancelled.

3. Based on medication error index[15]

Medication errors may also be classified based on their error index (NCERP) as shown in table 1.

Table-1. Medication error categorization index

Error Category	Result
Category A	Circumstances or events that have the capacity to cause error.
Category B	An error occurred, but the medication did not reach the patient.
Category C	An error occurred that reached the patient but did not cause patient harm.
Category D	An error occurred that resulted in the need for increased patient monitoring but no patient harm.
Category E	An error occurred that resulted in the need for treatment or intervention and caused temporary patient harm.
Category F	An error occurred that resulted in initial or prolonged haspitalization and caused temporary patient harm.
Category G	An error occurred that resulted in permanent patient harm.
Category H	An error occurred that resulted in near-death event
Category I	An error occurred that resulted in patient death.

4. Based on severity[16]

Based on their severity medication errors may be classified as A, B and C.(Table 2)

Aetiology

The medication errors can occur at one or more of the following five stages: (a) ordering/ prescribing, (b) transcribing and verifying, (c) dispensing and delivering, (d) administering, and (e) monitoring and reporting. The top 10 causes of medication errors identified by the United States Pharmacopoeia (USP) are performance deficit, procedure or protocol not followed, miscommunication, inaccurate or omitted transcription, improper

Table-2. Classification of medication errors based on the severity

Degree of Severity	Definition	Examples
A	Potentially serious error that can cause permanent harm to patient may increase hospitalization or need of additional treatment	Overdose of potassium chloride in total parenteral nutrition, order of doxorubicin instead of daunorubicin
B	Clinically significant error can increase need for patient monitoring	Tazobactam 4 gm twice daily to an obese septic patient
C	Clinically non-significant error that does not harm the patient	Pantoprazole IV to a patient who can swallow

documentation, drug distribution system error, knowledge deficit, calculation error, computer entry error and lack of system safeguards.[17] The Institute of Safe Medicine Practices (ISMP) identifies the following areas as potential causes of medication error.[18] Failed communication: Hand writing and oral communication, drugs with similar names, missing or misplaced zero and decimal points, use of non-standard abbreviations, poor drug distribution practices, complex or poorly designed technology, access to drugs by non-pharmacy personnel, work place environmental problem that lead to increased job stress, dose miscalculations, lack of patient information, lack of patient understanding of their therapy.

Methods for Detection

To prevent the further occurrence of medication errors, it is essential to detect them. Many methods are employed to detect the occurrence of medication errors. Some of them are described below.

- *Anonymous self reports*: The person committing the error (or witnessing one) reports the mistake without being associated with it.
- *Incident reports:* This involves the official written legal report of a medication error as documented by hospital staff.
- *Critical incident technique:* This event-sampling technique involves in-depth analysis of a large number of individual errors to identify common causal factors.
- *Disguised-observation technique:* An observer accompanies the person giving the medications, witnesses the administration of each dose, writes down exactly what the subject does while administering drugs and notes consumption of the medication by the patient.
- *Dispensing error detection techniques:* To study the errors that occurred before the medication is prepared for administration to the patient, such as pharmacy dispensing errors, various techniques like participant observer technique, critical incident method are employed.

Prevention

In order to prevent, the system needs to provide resources to monitor and evaluate errors and to implement methods to reduce them. This process is referred to as a ***system approach*** to medication error reduction.[13] A system is defined as "an interdependent group of items, people, or process with a common purpose[19]. The ISMP suggest a number of error prevention tools ranging from forcing functions to independent double check systems.[14] These include software programs with forcing functions that require the entry of additional pertinent patient information before the order is completed and the medication is dispensed. These programs also trigger other alerts such as look alike and sound alike medications. A number of agencies like United States Food and Drug Administration (US FDA), ISMP and USP keep track of medication errors and publish guidelines to avoid medication errors. In India, there are around thirty Pharmaco-vigilance centers operating as regional and peripheral centers situated at medical colleges in several states and are scanning instances of adverse

drug reaction since January 2005.

Conclusion

Prescription errors are a source of consider-able mortality, morbidity, and health-care costs in the world today but the important thing is that they can be prevented. A combined approach of regulatory, managerial and educational interventions may be an ideal way to minimize the occurrence of prescription errors. Prospective observational studies of are needed to more accurately determine the frequency of prescription errors in psychiatry. The healthcare providers using electronic system to write prescriptions (e-prescribing) were seven times less likely to make errors than those writing their prescriptions by hand.[20]

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Review Article

A Review of Neurobiology of ADHD

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Introduction

ADHD is one of the most common childhood neuropsychiatric disorders, affecting 3-7% of school-age children[1]. It has the distinction of being one of the most researched disorders in medicine[2]. It is characterized by the symptoms of inattention, hyperactivity or increased motor activity and Impulsivity or poor impulse control.[3] Described for the first time at around the turn of 20th century, ADHD has come a long way from Still's explanation of symptoms due to a defect in 'moral control'[4] and Goldstein's conclusion of the symptoms having CNS etiology or due to brain Injury.[5] In contemporary thinking, ADHD is not a single patho-physiological entity and appears to have a multi-factorial etiology. Multiple genetic and environmental factors are hypothesized to act together to create a spectrum of clinical and neuropsycholoical symptomatology. Current theories emphasise the central role of attentional and executive dysfunctions in the pathophysiology of ADHD[6,7] and implicate impaired functioning of Pre-Frontal Cortex (PFC) in its functioning. A lot of research has taken place in the field of genetics, animal studies, neurobiology, structural and functional imaging in the past 20 to 30 years which have led to the greater understanding of the etiology and management of ADHD. Recently FDA has approved the first brain wave test for aiding in the diagnosis of ADHD in children and adolescents between the age group of 6 to 17 years[8]. This test is based on electroencephalogram technology. It computes the ratio of theta and beta brain waves in 15 to 20 minutes. Children and adolescents with ADHD have a higher theta-beta ratio than those who do not have the disorder. Thus, a highly integrated story is emerging regarding the etiology and pathophysiology of ADHD which in turn informs its management. The current review aims to highlight the gains made so far in the understanding of the neurobiology of ADHD. The current understanding in the area of neuropsychology, genetics, imaging (both structural and functional) and neuronal (neuro-anatomical and neuro-chemical) mechanisms will be highlighted.

Neuropsychological Functioning in ADHD

The clinical presentation of ADHD suggests that neuropsychological dysfunction is one of the cardinal features of ADHD and many of the behavioral, cognitive and affective features of this disorder are explained by neuropsychological dysfunctions. As mentioned above, the central role of executive and attention dysfunction is emphasized in the etiopathogenesis of ADHD. Although there is lack of consensus as to what exactly constitutes executive processes, there is some agreement that these processes include attention and inhibition, task management, planning, monitoring, and decoding.[9] One specific executive process, namely inhibition, has been suggested to be the core deficit in ADHD.[9,10] As per this model, deficient inhibitory control impairs the ability of patients with ADHD to engage other executive control strategies like disruption of working memory, planning and organized behavior. These studies indicate that children with ADHD exhibit sub-average or relatively weak performance on various tasks of vigilance, verbal learning (particularly encoding), working memory, and

executive functions such as set-shifting, planning and organization, complex problem solving, and response inhibition.[10,11-16] Deficits on the Stroop color–word test appear to be among the most significant neuropsychological impairments.[12] These dysfunctions are also present in adolescents[15] and young adults.[17,18] These deficits are significantly associated with ADHD even after statistically controlling for psychiatric co-morbidities,[14,16,19–22] learning disabilities,[15] gender[23–30] and other socio-demographic variables. The tests that are most often used for neuropsychological assessments in patients suffering from ADHD are: versions of the Continuous Performance Test (CPT), the Stroop task, Trail Making, Verbal Fluency (FAS), and the Wechsler Adult Intelligence Scale (WAIS).[31]

Genetics of ADHD

Genetic studies (family, twin and adoption studies) implicate a robust genetic contribution to ADHD with heritability estimates ranging from 60-90% among studies.[32, 33] Despite robust heritability, genome-wide association studies have failed to come up with any associations that are significant after correction for multiple testing[34] though multiple candidate genes have been identified. A plausible genetic hypothesis for ADHD, as is there for other psychiatric symptomatology, is that it is a mixture of dominant and recessive major genes which act with complex polygenic transmission patterns.[32]

Many studies report alterations in the genes encoding for molecules involved in catecholamine signaling, e.g., the dopamine (DA) receptors (D1 and D5 receptors,[35–38] D4 receptor),[36,37,39] Nor-Epinephrine (NE) receptors (the alpha 2A receptor),[40-42] the DA and NE transporters[35,38,43,44] and dopamine beta hydroxylase (the enzyme needed for the synthesis of NE).[35,42,45] There are also associations with the catabolic enzyme, monoamine oxidase, and some serotonergic genes.[46] Expression of ADHD like symptoms in individuals with established neurogenetic syndromes with well defined genetic mutations like Tuberous Sclerosis Complex, Fragile X syndrome and Turner Syndrome to name a few, presents a unique opportunity to study the effect of genetic mutations on biological pathways or neural circuits resulting in ADHD symptoms.[47]

Structural Imaging Studies

Patients with right hemispheric lesions show features similar to ADHD. In right hemisphere, right Pre-Frontal Cortex (PFC) is the area that has been most implicated.[48-51] Studies have shown that the size of the right PFC is reduced in patients with ADHD.[52-57] Diffusion Tensor Imaging studies have also reported disruptions in white matter tracts emanating from the PFC in patients with ADHD, which is consistent with weaker prefrontal connectivity.[58,59] Other brain regions like caudate, corpus callosum and cerebellum, have been reported to be smaller in some studies of children with ADHD.[60] There is also evidence of slower prefrontal maturation in some patients with ADHD.[61] Many studies have shown that children with ADHD through age 19, the cerebrum, particularly the right hemisphere, is smaller by about 3% to 5%[62-67] and have reduced white matter volumes.[65]

Functional Imaging Studies

Correlating with Structural Imaging Studies, Functional Brain Imaging studies have found reduced functional activity of the right PFC in patients with ADHD.[52-57] Neuroreceptor imaging studies have supported the hypothesis of weakened catecholamine transmission in ADHD.[68] Studies of the DA transporter have been mixed, with many studies showing increased levels in the striatum,[69-71] but other studies have found no effect[72] or reported decreases.[73] This possibly reflects genetic heterogeneity in the DA transporter gene. Recent imaging studies have assessed DA release in the striatum and found evidence of decreased DA release in adult patients with ADHD.[74] Positron emission Tomography (PET) studies have shown that stimulant medicines like methylphenidate blocks Dopamine Transporters and increases extracellular Dopamine levels which in turn normalizes PFC fuctioning.[75]

Neuronal Mechanisms of ADHD
Neuro-Anatomical Correlates of ADHD – The Central Role of Pre-Frontal Cortex (PFC)

Much of the research points to the central role of PFC dysfunction in ADHD. PFC is the most highly evolved association cortex in the human and is the last to mature (late adolescence) and probably is the region responsible for differentiating human

beings from other mammals. Various regions of PFC have various specialized functions. In majority of the individuals the portion of the left PFC is involved with language and speech production (i.e. Broca's Area) while the right PFC is important for the regulation of attention, behavior and emotion.[76] While the Dorso-Lateral PFC is important for regulation behavior and attention, Ventro-Medial PFC is important for regulating emotions.[76,77] Through its extensive connections with rest of the brain it orchestrate thoughts and responses[78] and provides intelligent decision making, insight, and judgment.[79,80] It is also essential for so called executive functions[77] and able to keep firing its network even in the absence of an external stimuli which provides for the neuro-anatomical basis of working memory.

The PFC mediates TOP-DOWN attention, thus regulating our attention so that we devote our resources to that which is relevant to our goals and plans.[81-85] It also helps us to focus and sustain our attention on boring tasks[86] and tasks which are not inherently salient.[87-91] This is accomplished by its extensive connections to sensory cortices namely temporal (visual) and parietal (auditory).[85,92]

PFC is also essential for regulation of behavior, for planning future course of action and inhibition of inappropriate behavior.[68] This is achieved by its extensive connections to motor and pre-motor cortex, to sub-cortical structures such as the caudate and sub-thalamic nucleus and through its connections to cerebellum via pons.[93,94]

The ventro-medial portion of PFC, also known as orbital cortex monitors and inhibits emotions and emotional habits through its extensive connections to Amygdala, Hypothalamus, nucleus acumbens and through its connections to brain-stem nuclei (like raphe nuclei and locus coeruleus) which mediates stress response.[95-98]

The Neuro-Chemical Correlates of ADHD – The Central Role of Catecholamines Norepinephrine (NE) and Dopamine (DA)

The PFC is also very sensitive to its neurochemical environment. Too little (drowsy or fatigued) or too much (stress) can hinder with its normal functioning and can produce symptoms of ADHD.[99] Thus it needs the right balance of neurochemicals for its optimal functioning. The catecholamines constitute the mainstay of its neurochemical environment. In- fact disruption of optimal catecholamine concentration in PFC have similar effects as the ablation of PFC itself.[100] Thus, this brain region is extremely sensitive to genetic and environmental insults. While NE stimulation of alpha-2A receptors enhances PFC function by strengthening appropriate network connections (increasing "signals"), DA stimulation of D1 receptors exerts its beneficial effects by weakening inappropriate connections (decreasing "noise").[99] Medications effective in ADHD normalize catecholamine transmission in their therapeutic doses thus optimizing the neuro-chemical environment of PFC in patients with genetic abnormalities of these pathways.

Conclusion

Converging data from studies in the fields of genetics, neuropsychology, neuro-radiology, neuro-anatomy and neuro-chemistry in the past 30-40 years have enhanced our understanding of this complex neuropsychiatric disorder. These advances will hopefully contribute to the development of more rational, targeted and specific pharmacotherapies and management plan for ADHD and its associated co-morbidities.

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Original Article

Quality of Life in Gastrointestinal Disorders

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Abstract

Background: - *Gastrointestinal disorders are so prevalent; there has been an increasing need to assess the burden of these conditions by using symptom and Health Related Quality of Life (HRQL) assessments, especially in the clinical setting. Society is changing rapidly, and new aspects need to be considered when evaluating treatment of disease. Health-related quality of life (HRQL) is a relatively new addition to the tools clinicians use to gain a better understanding of the impact of disease and its treatment. Health-related quality of life assessments have been made in many areas of gastroenterology, such as reflux disease, inflammatory bowel disease and irritable bowel syndrome, to describe the burden of illness and the impact of treatment. Keeping this Health-related quality of life as a prediction of treatment response is another interesting option. Its ability in the context of surgical intervention and outcomes is also emerging even though more work must be done in this area, Health-related quality of life evaluations, as an additional tool in the management of patients. In mind a study was planned with following aim.* ***Objectives:*** *To compare the quality of life in functional gastrointestinal disorders, organic gastrointestinal disorders and normal healthy controls.* ***Method:*** *Three groups of patient (50 cases of organic gastrointestinal disorder [OGID], 50 cases of functional gastrointestinal disorder [FGID] and 50 normal controls) were selected for study from out patients department of GI medicine, Sardar Patel Medical College & AG Hospital Bikaner Rajasthan during 1st January 2010 to 31st December 2011. Inter group comparison of various domain of Quality of Life e.g. Physical Fitness, Daily Activities, Pain, Social Activity etc. was done by Coop's Chart for adult primary care practice and other socio-demographic data on a self designed Performa. Statistical analysis was done by using appropriate statistical methods.* ***Results & Conclusion****: Quality of life of FGID group was significantly more compromised in almost all domains in comparison to OGID group and normal control.*

Keywords: *GI disorders, Quality of Life.*

Introduction

Gastrointestinal disorders are one of the commonest digestive diseases worldwide and leads to significant morbidity and burden on healthcare resource.[1.]Functional gastrointestinal disorders (FGIDs) are common disorders that are characterized by persistent and recurring GI symptoms. These occur as a result of abnormal functioning of the GI tract, they can affect any part of the GI tract, including the esophagus, stomach, bile duct and/or intestines. The most common and best researched FGID is Irritable Bowel Syndrome (IBS) – abdominal pain associated with altered bowel habits of diarrhea, constipation or alternating between both. Other common FGIDs include functional dyspepsia (pain or discomfort in the upper abdominal area, feeling of fullness, bloating or nausea), functional vomiting, functional abdominal pain, and functional constipation or diarrhea.

It is important to understand that these are not psychiatric disorders, although stress and psychological difficulties can make FGID worse. It has been reported that IBS is the second leading

cause, after the common cold, for missing work or school. In the past, FGID was merely considered an "umbrella" for many clinical pictures where the term functional reflected an unknown etiology and/ or pathogenesis and their existence was even denied by some physicians.[2] In the last years, the fast-growing insight into the pathogenesis of intestinal diseases has been narrowing the field of disturbances "not explained by structural or biochemical abnormalities", in parallel with the progress of diagnostic tools and the development of novel technologies.

Quality of life [QoL] as a concept has been increasingly accepted as an important outcome measure in patients and caregivers of chronic illnesses. QoL include the conditions of life resulting from the combination of the effect of complete range of the factors such as those determining health, happiness and a satisfying occupation, education, social and intellectual attainments, freedom of actions and freedom of expression[3]. The concept is further understood as an individuals' perception of their position in life in context of the culture and value systems in relation to their goals, expectations, standards and concerns. Health- related quality of life is by definition subjective and multidimensional. The purpose of focusing on HRQL is to go beyond the presence and severity of symptoms of disease and side-effects of treatment, examining how patients perceive and experience these manifestations in their daily lives. Key and core domains reflecting HRQL are represented by physical, metal and social functioning.[4]

We are living in a rapidly changing environment marked by economic and social instability. The changes in society are thus likely to influence the working life, quality of life and disease pattern among groups in society over time.[5,6] Medical practitioners have traditionally focused on organic diseases and their treatment, "however" Patients, are concerned with their symptoms, regardless of the presence of organic or non-organic findings. To the patients, the symptoms are indicators of disease, while clinicians have traditionally concentrated on histopathological or serological findings. The wider concept of HRQL encompasses not only the condition for which the patients is treated, but also correlated morbidity and other aspects of treatment; such as side-effects that make one treatment preferable over another.[7] Keeping this view in mind a study was planned with following aim.

Objectives

To compare the quality of life in functional gastrointestinal disorders, organic gastrointestinal disorders and normal healthy controls.

Material and Methods

Study Design:

The present study was an instrument rated cross sectional study conducted in the department of psychiatry in collaboration with department of gastroenterology including 50 patients of functional gastrointestinal disorder and 50 patients of organic gastrointestinal disorder patients who fulfill ROME 111 criteria and other test such as x-rays, CT scans, blood tests with positive results, and compared with same number of healthy controls matched for age, sex and socioeconomic status written consent was taken to participate in the study.

Inclusion criteria:

1. Aged 18-50 years.
2. Patients Ability to co-operate and participate in the study as evidenced by the signed consent.

Exclusion Criteria:

1. Any alarm symptoms of underlying physical pathology.
2. Any unexplained weight loss.
3. Any uninvestigated rectal bleeding.
4. Unable to follow the language and complete the questionnaire.

Tools:

1. Semi-structure self designed Performa constituting socio- demographic details.
2. ICD-10 criteria for psychiatric diagnosis.[8]
3. The Coop's chart for adult primary care practice.[9]

Observation

Table-1. Socio-Demographic Variables of Study Groups

S. No.	FGID (N = 50)	OGID (N = 50)	Normal Control (N = 50)	
Age (in years)				
20-30	17(34%)	12(24%)	15(30%)	
30-40	13(26%)	20(40%)	17(34%)	$x^2 = 7.588$
40-50	17(34%)	15(30%)	13(26%)	p – 0.269
50-60	03(6%)	0 3(6%)	05(10%)	
Sex				
Male	35(70%)	30(60%)	28(56%)	$x^2 = 2.207$
Female	15(30%)	20(40%)	22(44%)	p- - 0.331
Marital Status				
Unmarried	8(16%)	05(10%)	06(12%)	
Married	40(80%)	44(88%)	42(84%)	$x^2 = 1.927$
Divorcee	01(2%)	0	01(2%)	p – 0.926
Widow	01(2%)	01(2%)	01(2%)	
Religion				
Hindu	38(76%)	32(64%)	35(70%)	$x^2 = 1.714$
Muslim	12(24%)	18(36%)	15(30%)	p – 0.424
Family Type				
Nuclear	24(48%)	28(56%)	26(52%)	$x^2 = 0.663$
Extended Nuclear	16(32%)	14(28%)	15(30%)	p – 0.955
Joint	10(20%)	8(16%)	09(18%)	
Education				
Illiterate	14(28%)	22(44%)	18(36%)	
Primary	13(26%)	12(24%)	14(28%)	$x^2 = 7.128$
Secondary	15(30%)	6(12%)	7(14%)	p – 0.522
Post Graduate	3(6%)	4(8%)	3(6%)	
Professional	2(4%)	02(4%)	2(4%)	
Occupation				
Employed	24(48%)	26(52%)	25(50%)	
Unemployed	9(18%)	6(12%)	6(12%)	$x^2 = 4.91$
Housewife	10(20%)	14(28%)	15(30%)	p – 0.848
Student	6(12%)	03(6%)	04(8%)	
Retired	01(2%)	01(2%)	0	
Income				
0-1000	06(12%)	6(12%)	8(16%)	
1001-2000	08(16%)	11(22%)	10(20%)	
2001-3000	15(30%)	06(12%)	08(16%)	$x^2 = 9.248$
30001-4000	09(18%)	08(16%)	10(20%)	p – 0.508
4001-5000	08(16%)	12(24%)	06(12%)	
>5000	04(18%)	07(14%)	08(16%)	

Table-2. Mean Score on Nine Domains of Coops QoL

	Mean Score			p value		
Domain	**FGID [A]**	**OGID [B]**	**Normal Control [C]**	**AB**	**BC**	**CA**
Domain 1 Quality of life	3.6	2.46	1	< 0.0001	< 0.001	< 0.001
Domain 2 Physical Fitness	3.6	2.92	1.22	< 0.0001	< 0.0001	< 0.0001
Domain 3 Feeling	2.96	2.12	1	< 0.0001	< 0.001	< 0.0001
Domain 4 Daily Activities	2.82	2.46	1	< 0.003	< 0.001	< 0.0001
Domain 5 Pain	2.1	2	1.2	< 0.4007	< 0.0001	< 0.0001
Domain 6 Social Activity	1.2	1.2	1	—	< 0.0001	< 0.0001
Domain 7 Change in Health	3.6	2.1	1	< 0.0001	< 0.001	< 0.001
Domain 8 Overall Health	2.96	1.76	1	< 0.0001	< 0.0001	< 0.0001
Domain 9 Social Support	2.46	1	1	< 0.0001	—	< 0.0001

Table-3. Shows Overall Comparison of Quality of Life Between Study Group and Control Group

Post HOC Table

	Mean Score	SD	Comparison	t	p
FGID	29.7	7.79	AB	3.849	0.0002
OGID	24.3	6.14	BC	13.321	<0.0001
Normal Control	10.2	4.28	AC	15.513	<0.0001

Result

Socio-demographically matched 50 patients of FGID, 50 patients of OGID and 50 Normal Control (total 150 study subjects) were studied. Above 60% of the subjects in these were between age group of 20-40 years of age. Hindus, married subjects and males outnumbered these groups. Most of the participant of the study were educated, employed and were from middle socio-economic strata (Table-1).

Table-2 shows the mean score among the functional gastrointestinal disorders, organic gastrointestinal and normal healthy group on the nine domains of the COOPS quality of life. It was found that the quality of life in FGID was more compromised on all domains except for domain of pain and social activity. The perception of pain and social activity was equally compromised in both groups [OGID & FGID] in comparison to normal control.

When overall quality of life was compared it was found that quality of life was compromised in both organic & functional gastrointestinal disorder in comparison to normal subjects but it was most hampered in functional gastrointestinal disorder patients. [Table-3]

Discussion

In the present study it has been found that patients with functional gastrointestinal disorders showed a significant impairment of quality of life as compared to the organic gastrointestinal disorder and normal healthy controls groups. The mean score on all the domains suggest that quality of life of patients is functional gastrointestinal disorder was found to be globally affected with all the domains including the physical, psychological, social, and environmental.

The domain 'physical well-being' [physical fitness] contains questions about physical health, sleep, pain and coping with every-day life and impairments in socio-adaptive functioning. In the present study also, it has been found that FGID have more impaired functioning in physical domain of quality of life in comparison of patients with OGI disorders and healthy normal controls. Similar findings have been reported in various studies and they have reported that patients with FGID have been found to be poor physical or mental health in comparison of OGID.[10,11]

The domain of psychological well-being [feeling] is associated with negative feelings of mood, sadness, anxiety, and dissatisfaction with oneself. Patients with functional gastrointestinal disorders had highly significant impaired quality of life in this domain. Because these FGID disorders are often associated with anxiety about future of oneself and family, sadness about the condition of oneself along with feelings of self-blames guilt and social shame. A study recently carried out in France by Coffin et al[12] on a sample of 858 IBS patients (Rome II criteria) attending gastro-enterology consultations, showed similar results between FGID and OGID whose QOL was measured with a specific instrument, the Gastrointestinal Quality of Life Index (GIQLI).[13]

The domain of 'health' includes questions about physical safety and security, home environment, health and social care and other questions about one's daily life. Because patients with FGID often experience feelings of anxiety, danger, and constant worry towards the physical security this could have attributed to their lower scores on this domain. Overall, HRQL evaluations reflect the burden of illness from the patient's point of view. According to Maslow, the patient has basic needs, such as physiological requirements, security, social relationships, self-confidence and self-actualization. If these are fulfilled, well-being is promoted. If these needs are not satisfied, anxiety, tension and stress are created. This means that all patients will have to be treated individually to meet

their needs, which may include specific treatment, explanations and understanding. For the patient, his/her symptoms are generally the major concern, regardless of whether or not the condition is medically serious.[14,15]

The domain of 'social activity and social support', which especially contains questions about satisfaction with personal relationships and with support by friends, in our study the domain of social activity has been found highly impaired in FGID and OGID in comparison to normal healthy control, but in the domain of social support only FGID shows significant impairment because of long term care and futures concerns. Many times they consider themselves responsible for the condition and this feeling of guilt causing problems in personal relationship and they avoid social gathering.

Coffin et al[12] also demonstrated a significant correlation between symptom intensity and deterioration of QoL. In a study conducted in the United States among 126 IBS patients. Hahn et al[16] also found a strong relation between the severity of patient perceived disorders and the degradation of QoL. Similar results have also been found in a study where except for the mental health domain, all of the QoL scores were significantly higher for individuals who reported mild to moderate pain or abdominal discomfort during the four weeks preceding the investigation compared with those reporting severe or very severe pain or discomfort. it is very clear from the study that the overall quality of life is compromised in both FGID and OGID patients.

Stewart AL et al[17] found that quality of life was significantly more impaired in gastrointestinal disorders than those with other conditions such as arthritis, hypertension and myocardial infarction. This can partly be ascribed to the fact that gastrointestinal conditions affect several of the domains measured. Lack of vitality, emotional distress, pain, limitations in physical and social activities have been found in efflux patients. Sleep disturbance has also been found in patients with heartburn and regurgitation.[18] The difference between symptomatic GERD and reflux esophagitis is seen on endoscopy. In symptomatic terms no differences can generally be found. Nor have the effects on quality of life been correlated to esophagites.[19] The level of anxiety and pain in heartburn patients has been found to be a factor in predicting effect of treatment.[20]

Interactions between patients and health-care professionals are becoming increasingly complicated. Technical, development allows a more rigorous assessment of possible disease signs with serological tests and imaging. On the other hand, time pressure seldom allows comprehensive capture of psychological, social and other aspects of disease, which is increasingly important with the rapidly changing environment. The quality of life results provide a basis for a holistic view of the patients and supplement the traditional outcomes.[21] The treating health professional took seriously to all the symptoms and concerns of the patients whether they have any organic pathology or not.

Further suggestion

In the future, quality of life evaluations are most likely to be also used for assessing possible outcomes of various medical treatments and surgical interventions. The effects and psychotherapeutic intervention on the quality of life should also be assessed.

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Original Article

Oxidative Stress Status in Depressive Patients having Suicidal Behaviour

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Abstract

Background: *Suicidal behaviour has been associated with major depressive disorders and so is oxidative stress. However no information is available regarding the oxidative stress status in patients suffering from suicidal behaviour.* ***Methods:*** *One hundred and five (105) patients having suicidal behaviour, 50 depressive patients, and 60 healthy controls were recruited. The patients were screened by Structured Clinical Interview of Diagnostic and Statistical Manual of Mental Disorders (DSM) IV TR criteria, Hamilton Rating Scale for Depression (HRSD), Suicide Intent Questionnaire (SIQ), and California Risk Estimator for Suicide (CRES). Oxidative stress parameters namely malonyldialdehyde (MDA), protein carbonyl (PC), reduced glutathione (GSH) and nitric oxide (NO) were estimated from the plasma /venous blood as applicable.* ***Results:*** *Plasma MDA and PC levels were significantly increased and GSH and NO levels were significantly reduced in patients with suicidal behaviour as compared to depressive patients without suicidal behaviour and healthy controls. MDA and PC were positively correlated and whereas GSH was negatively correlated with suicidal behaviour and the relationship were significant.* ***Conclusion:*** *Our study showed for the first time that oxidative stress is enhanced significantly in patients having suicidal behaviour.*

Keywords: *Depression, oxidative stress, suicide ideators, suicide attempters.*

Introduction

Major depressive disorders (MDD) are often associated with suicidal behaviour.[1] More than half of the patients having depression express suicidal ideas and one third of patients with suicidal ideas progress to commit a suicidal act.[2] Biochemical alterations have been studied extensively in patients having depression and studies have shown alterations in oxidative stress.[3-8] Reactive oxygen species and reactive nitrogen species generated in various metabolic pathways when off-limits the antioxidant capacity, the state is called as oxidative stress. Recent studies have shown that several oxidative stress markers are altered in patients with major depressive disorders (MDD).[3,4] Increased levels of blood MDA (a marker for lipid peroxidation), has been reported in patients having depression.[5–7] Glutathione (GSH) is an important antioxidant, which protects cells against damage caused by free radicals. Significant decreased level of GSH in blood has been reported in patients having depression.[8] Protein carbonyl (PC) is the marker for damage to proteins because of the oxidative stress. Alterations in the plasma levels of PC have been reported in psychiatric disorders. Non significant alterations in the PC levels have been reported in the early and late stage patients of Bipolar disorders in comparison to controls.[9] Nitric

oxide is known to be both a reactive oxygen species (ROS) and a neurotransmitter in the central nervous system and the peripheral nervous system.[10] However, the findings for NO levels in patients having depression are mixed. Significant increase in NO levels has been detected in patients with depression.[11,12] On the contrary, a decrease of 73% in nitrite content has been reported in patients with depression as compared to normal controls.[13]

Since suicidal behaviour is closely linked with MDD, it may be possible that oxidative stress may also have some association in the development of suicidal behaviour in depressive patients. No report, however, is available on the oxidative stress profile in suicidal behaviour excepting a report by Kim et al,[14] who observed increased levels of nitric oxide metabolites in suicidal depressives. The objective of the present study was to find out any relationship between oxidative stress parameters in depressed patients with suicidal behaviour.

Methods

Samples

One hundred and five (105) patients having suicidal behaviour and 50 depressive (MDD) patients were recruited from psychiatry outpatient department of University College of Medical Sciences and Guru Teg Bahadur Hospital, a tertiary care hospital in the capital city of India during one year period (2010-2011). Sixty healthy controls (60) were also enrolled in the study by voluntary participation. The controls were departmental staff members, community participants, or un-related attendants of the patients. All the enrolled subjects (patients and controls) were drug naive. They were not taking any dietary supplements, or any substance known to affect the analysis of our study. The patients with suicidal behaviour were divided into two groups (i) Suicide ideaters (SI) who had developed suicidal ideas during depressive phase but had never attempted suicide and (ii) suicide attempters (SA), who had attempted suicide during stressful conditions. The study was approved by the Institutional Ethical Committee for Human Research. All patients and controls provided written informed consent before taking part in the study. Sociodemographic data were collected in a semi structural performa approved by the Ethical Committee. In case of participants below the age of 18, consent was taken from the guardian /parents. Subjects with age > 60 years, or < 16 years were excluded from the study. The patients with prolonged substance abuse, alcoholism or taking psychotropic medication for more than 3 months were also excluded from the study.

Assessment Instruments

The patients who were included in the study were screened for the presence of MDD by using Structured Clinical Interview of Diagnostic and Statistical Manual of Mental Disorders (DSM) IV TR criteria. The enrolled subjects were further categorised for the severity of depression with the help of Hamilton Rating Scale for Depression (HRSD), which is a 21 question structured interview for the assessment of severity of depression.[15] Suicidal behaviour was assessed and categorised on the basis of Suicide Intent Questionnaire (SIQ), which has been constructed and standardised specially on Indian Population.[16] It is a ten questions based questionnaire which provides the severity and intensity of the suicidal intent. California Risk Estimator for Suicide (CRES) was also applied on all the patients except in patients < 18 years of age. It provides the degree of risk of committing suicide in Depressive patients.[17]

Blood Processing and storage

Venous blood (5 ml) was collected from the study subjects. In case of inpatients who had attempted suicide, blood was collected within 24 hours of attempt. Desirable aliquots of whole blood and plasma were prepared and the aliquots were stored at -80°C. The aliquots were then assayed within a week.

Oxidative Stress Parameters

MDA estimation in plasma: MDA was measured using thiobarbituric acid method as described by Girroti et al 1991.[18] The MDA concentration was calculated using extinction coefficient $1.56 \times 10^5\ M^{-1}\ cm^{-1}$ at 535 nm and expressed as nM / mL of plasma.

Protein carbonyl assay in plasma: Protein carbonyl contents were measured using a 2,4-dinitrophenyhydrazine (DNPH) based procedure in accordance with Ayedmir *et al* 2007.[19] Values were expressed as nM /mg of protein using molar

absorption coefficient of hydrazone: $ÄE_{450nm}$ = 22000 $M^{-1}cm^{-1}$.

Reduced glutathione assay in blood: The level of erythrocyte reduced glutathione was assayed in accordance with Beutler et al 1963.[20] Briefly, whole blood was hemolysed; the lysate was precipitated, filtered and then treated with 55 Dithiobis-2-nitrobenzoic acid (DTNB). Absorbance was read at 412 nm. The GSH concentration was calculated as µM/g hemoglobin.

Nitric oxide assay in plasma: Nitric oxide was estimated by using Griess Reagent containing sulphanilamide and N-napthyelenediamine dihydrochloride under acidic conditions. The absorbance was read at 540 nm. The results were expressed as µM/mL.

Statistical Analysis

The variables (age, MDA, PC, NO and GSH levels) were normally distributed as tested by the Kolmogrov-Smirnov Test. The biochemical markers in subject groups and healthy controls were compared by the analysis of variance (ANOVA) followed by post hoc Tukey's analysis. The biochemical parameters were also compared in a model with age, sex and severity of depression as covariates (analysis of covariance), followed by Bonferroni post hoc analysis in the subject groups. Linear correlation among the psychiatric parameters and the biochemical parameters were assessed by the Pearson correlation to explore the relationship between biochemical parameters and psychiatric parameters in suicidal behaviour. Multiple linear regression models were applied by taking biochemical parameters as dependant variable and psychiatric parameters as independent variables. Separate multiple regression models were applied for each biochemical parameter and psychiatric parameter after adjusting for age and sex. All the statistical analysis was performed using SPSS 16 for Windows.

Results

A total of 105 (one hundred and five) subjects with suicidal behaviour (suicide ideaters, n = 59 and suicide attempters, n = 46), along with 50 MDD patients (without any suicidal behaviour) and 60 controls were enrolled in the study. The socio-demographic-profiles and details of all the participants are listed in Table 1. Patients with depression were significantly older in comparison with those having suicidal tendencies (Table 1). The detailed psychiatric assessments of enrolled patients are listed in Table 2. The severity of depression (as assessed by the Hamilton rating scale for depression, HRSD), suicide intent (assessed by the suicide intent questionnaire) and risk for suicide (assessed by the California risk estimator for suicide) were significantly higher in patients having suicidal behaviour in comparison to depressive patients without suicidal behaviour. HRSD score and suicide intent was significantly higher in suicide attempters than suicide ideaters. The future risk for suicide was 60% higher in suicide attempters and 30% higher in suicide ideaters in comparison to patients having depression and without any suicidal behaviour (Table 2).

We measured oxidative stress parameters namely Malonyldialdehyde, protein carbonyl content, reduced glutathione, and nitric oxide and

Table 1: Details of the study subjects and controls

Characteristics	Control (n = 60)	MDD (n = 50)	SI (n = 59)	SA (n = 46)
Age (Mean ± SD)	28.1 ± 6.6	43.4 ± 11.2	33.4 ± 11.4	31.1 ± 10.8
Sex (M/F in %)	36.4 / 63.6	36.4 / 63.6	50.8 / 49.2	36.9 / 63.1
Education Status				
Uneducated	49.6%	35.0%	63.3%	21.5%
Educated	50.4%	65.0%	36.7%	78.6%
Marital Status				
(Married %)	35%	61.2%	65.1%	66.6%
Employment Status				
Unemployed (%)	2%	13%	13.2%	12.5%

MDD=Major depressive disorder, SI= Suicide ideaters, SA= suicide attempters, SD= Standard Deviation, M=Males and F= Females, n= number of enrolled subjects.

Table-2. Detailed psychiatric assessment of the study subjects

Characteristics of Patients	Suicide Attempters (n = 44)	Suicide Ideaters (n = 59)	Depressive patients (n = 50)
HRSD(Mean ± SD)	24.0 ± 8.1[a]	22.5 ± 6.1 [a]	10.1 ± 8.1
SIQ (Mean ± SD)	13.4 ± 4.7 [a,b]	10.6 ± 4.6 [a]	2.0 ± 1.6
CRES (Mean ± SD)	560.7 ± 104.8 [a]	499.1 ± 144.9 [a]	215.7 ± 127.7
Stress Factors			
Unfriendly environment	2.0%	10.2%	12.5%
Prolonged illness	5.0%	18.2%	8.3%
Failure	15.0%	14.2%	13.4%
Domestic Violence / Physical abuse	35.0%	16.3%	2.0%
Financial issues	29.0%	15.2%	34.0%
Bereavement	7.0%	14.1%	25.0%
Betrayal in love / business	10.0%	12.0%	3.0%
History of depression	33.0%	20.4%	5.0%
Family history of depression/SA	5.3%	0.1%	—
Multiple suicide attempts	62.5%	—	—
Methods of suicide attempts*			
Drug over dose	10.2	—	—
Burning	4.1	—	—
Jumping	6.1	—	—
Hanging	8.1	—	—
Cutting	10.2	—	—
Electric Shock	2.1	—	—
Poisoning	65.3	—	—

HRSD = Hamilton Rating Scale for Depression. SIQ = Suicide Intent Questionnaire. CRES= California risk estimator for suicide attempt. [a] significance of p< 0.001 with reference to depressive patients, [b] significance of p< 0.001 with reference to suicide ideater, *percentage sum exceeds 100 as many patients have applied multiple modes for attempting suicides. n= number of enrolled subjects, SA represents suicide attempts

the results are shown in Table 3.The plasma MDA levels were significantly higher in the three patient groups in comparison to healthy controls. In patients having suicidal tendencies, the plasma MDA levels were 65% higher in suicide ideaters and 80% higher in suicide attempters in comparison to healthy controls. With reference to depressive patients, the MDA levels were found to be significantly higher in patients with suicidal behaviour; however, there was no difference in MDA levels between the suicide ideaters and suicide attempters.

The levels of the protein carbonyl (PC) were raised in the three patient groups. However, the rise did not reach statistical significance in case of MDD patients without suicidal behaviour. In case of suicide ideaters and suicide attempters' significant increase accounting to 20% and 50% respectively in the levels of protein carbonyl were observed in comparison to healthy controls. Substantial increase in PC levels was observed in patients with suicidal behaviour as compared to patients having depression. In between the two groups with suicidal

Table-3. Oxidative stress parameters of study subjects and controls

Parameter	Control (Mean ± SEM)	MDD (Mean ± SEM)	SI (Mean ± SEM)	SA (Mean ± SEM)
MDA (nM/mL plasma)	1.05 ± 0.02	1.23 ± 0.09	1.74 ± 0.07[a,b]	1.89 ± 0.07 [a,b]
GSH (mg/g%Hb)	10.44 ± 0.35	5.07 ± 0.23 [a]	4.34 ± 0.26 [a,b]	2.17 ± 0.20 [a,b]
PCo (nM/mg protein)	0.95 ± 0.05	1.03 ± 0.05	1.16 ± 0.05	1. 45 ± 0.13 [a,b]
NO (nM/mL plasma)	24.27 ± 0.41	12.71 ± 0.56 [a]	15.93 ± 0.41 [a,b]	12.91 ± 0.46 [a]

MDD=Major depressive disorder, SI= Suicide ideaters, SA= suicide attempters, SEM= Standard error mean, MDA = Malonyldialdehyde, GSH= reduced glutathione, PC = protein carbonyl, NO = nitric oxide, [a] significance of p< 0.001 with reference to controls, [b] significance of p<0.001 with reference to MDD, hb = hemoglobin.

Table-4. Association between biochemical markers and psychiatric parameters in patients having suicidal behaviour

	MDA			PC			NO			GSH		
	Adjusted analysis*			Adjusted analysis*			Adjusted analysis*			Adjusted analysis*		
Psychiatric Parameters	**β**	**t**	**p**	**β**	**t**	**p**	**β**	**t**	**p**	**β**	**t**	**p**
Severity of depression	0.245	2.392	0.019	0.248	2.325	0.022	0.183	1.703	0.092	0.056	0.524	0.601
Suicide Intent	0.125	1.193	0.236	0.144	1.323	0.189	-.0133	-1.205	0.231	-0.160	-1.457	0.148
Risk of suicide	0.225	1.993	0.049	-0.055	-0.466	0.642	-0.051	-0.429	0.669	0.136	1.149	0.253

β represents the standardized regression coefficient , t denotes the t distribution value, p represents level of significance. The negative sign represent inverse relation. MDA = Malonyldialdehyde, GSH= reduced glutathione, PC protein carbonyl, NO= nitric oxide. *Multiple linear regression models adjusted for age and sex.

behaviour, suicide attempter were found to have significantly elevated levels of PC as compared to suicide ideaters. Reduced glutathione (GSH) levels in the study subjects were significantly decreased in three patient groups in comparison to healthy controls. The decrease in GSH levels was found to be 14% in case of suicidal ideaters and 50% in suicide attempters as compared to depressive patients. Plasma nitric oxide (NO) levels were reduced significantly in the depressive subjects with or without suicidal behaviour in comparison to healthy controls (Table 3). Among the three patient groups (patients having depression, suicide ideaters and suicide attempters), NO levels were found to be significantly less in patients having depression and in patients with suicide attempts than suicide ideaters. The significant alterations in the biochemical parameters namely MDA, PC, GSH and NO remained unaltered on adjusting for age, sex and severity of depression.

The relationship between the oxidative stress markers and psychiatric parameters was assessed by the Pearson linear correlation. MDA was found to be significantly and positively correlated with the severity of depression ($r = 0.382$, $p < 0.001$), severity of suicide intent ($r = 0.401$, $p < 0.001$) and with the future suicide risk ($r = 0.211$, $p < 0.001$). Protein carbonyl (PC) levels in plasma was found to be positively correlated with severity of depression ($r = 0.082$, $p = 0.313$), suicide intent ($r = 0,182$, $p < 0.05$) and future risk for suicide ($r = 0.134$, $p = 0.420$) in the depressive patients and the relationship was significantly positive with suicide intent. Glutathione levels were found to be negatively correlated with psychiatric parameters. The relationship was significant with the suicidal intent ($r = 0.106$, $p < 0.001$) and future risk for suicide ($r = 0.439$, $p < 0.001$). Nitric oxide levels were positively correlated with the psychiatric parameters; however, the correlation was significant only with severity of depression ($r = -0.169$, $p < 0.05$). To further ascertain the relationship between the biochemical parameters and the psychiatric parameters, multiple linear regression analysis was performed with psychiatric parameters as independent variables and biochemical parameters as dependent variables (Table 4). The standardised regression coefficient (â) indicated that severity of depression remained significantly correlated with MDA levels ($â = 0.245$, $p = 0.019$, $R^2 = 0.137$).

Discussion

We have studied the oxidative stress parameters namely, MDA, PC, GSH and NO in depressive patients in relation to suicidal behaviour either in the form of ideation or attempt. The results indicate that the patients having suicidal behaviour have significantly increased levels of MDA and PC and significantly decreased levels of GSH in comparison to patients having depression and healthy controls. Nitric oxide levels were decreased in three patient groups in comparison with healthy controls; whereas the patients having suicide ideations have increased nitric oxide levels in comparison with MDD. Correlation analysis also showed significant association with various

psychiatric parameters and oxidative stress parameters. The regression model also suggested positive and significant association of MDA with severity of depression after adjusting age and sex, indicating that as the oxidative stress is raised, the degree of suicidal behaviour also increases. Our results therefore showed significant alterations in the oxidative stress markers in suicidal behaviour in comparison to healthy controls and MDD.

Various studies on MDD patients have reported increased concentration of MDA and decreased total antioxidant activity (TAS) in the plasma of depressed patients.[6-8,21-24] It has been proposed that the multiple etiological trigger by psychological stress may induce oxidative stress in depression.[21] Psychological stressors have been shown to induce a pro-oxidant state and lipid peroxidation. Even relatively minor stressors, such as examination stress, have been reported to be associated with oxidative damage to DNA, sensitivity to lipid oxidation and decreased plasma antioxidant activity.[22-25] Decreased level of erythrocyte glutathione has been observed in suicidal behaviour in this study, and in accordance with our observations decreased levels of reduced GSH levels have also been reported in the prefrontal cortex of patients with various psychiatric disorders in comparison to age and sex matched non-psychiatric controls.[26] Recently, Magalhaes et al,[27] in a nested population based case-control study have shown that protein oxidative damage is present from early stages of depression and can be seen as a sign of early activity in mood disorders. Our findings of low levels of plasma nitric oxide in patients having depression and suicidal behaviour in comparison to healthy controls are also in line with those of Kim et al,[14] who reported significantly increased levels of plasma nitric oxide metabolites in the depressive patients who had recently attempted suicide than healthy controls. Decreased levels of plasma nitric oxide synthase have also been reported in depressive patients in comparison to healthy controls.[28]

This study indicates the probable role of enhanced oxidative stress in the aetiopathology of suicidal behaviour. It highlights the involvement of lipid peroxidation and reduction in the levels of glutathione in stress induced suicidal behaviour MDD patients especially in suicide attempters. It is well known that, oxidative stress induced lipid peroxidation in the lipid rich constitution of brain results in the decrease membrane fluidity, damage in membrane proteins, inactivation of receptors, enzymes and ion channels.[29] As a result, oxidative stress can alter neurotransmission, neuronal function and over all brain activity and there by development of suicidal behaviour.[22,29] However, prospective study is required to establish the exact role of oxidative stress in induction of suicidal behaviour.

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Declaration of interest

None to declare.

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Case Report

Psychosis and Hyperthyroidism, the Interface of Endocrinology and Psychiatry: A case report of multidisciplinary approach

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Introduction

Psychiatric manifestations are not uncommon in patients with underlying thyroid abnormalities (Hyper or Hypothyroidism).[1] The manifestation ranges from affective instability, memory disturbances to psychotic presentation and the psychotic presentation is often recognized as organic psychosis.[1–5] Hyperthyroid states are known to have presentation like paranoid psychosis, which is temporally correlated with very high level of circulating thyroid hormones and subside with the correction in the level of hormones.[1,5] It is also reported that sudden alteration or fluctuation in the thyroid hormone level, precipitates psychosis.[6,7] Presence of physical symptoms, psycho-social stressors and other medical or psychiatric comorbidities, further colours the clinical picture and creates diagnostic dilemmas.

Case history

Mrs Z, 27 years old, high school pass, married housewife presented with sudden onset behavioural change since four days, characterized by strange hand movements, constant clapping, running around, tearing her clothes, assaulting her children, destroying household articles, taking out various animal sounds with loss of sleep and poor self care. At the time of presentation in the Psychiatry Emergency, her pulse was 98/min with a Blood pressure of 130/80mm Hg and had an observable thyroid swelling which would move on deglutition. She had been receiving Carbimazole 45 mg/d with Propanolol 80mg/d in divided dosages for the last 4 years (since 2008), however had been irregular with treatment in the last three months. The Ultrasound of the neck (done two months before) revealed enlarged heterogeneously hyper-echoic Right Lobe of Thyroid measuring 6.7 × 2.4 × 3 cm^3 and enlarged Left lobe measuring 7.3 × 2.7 × 3.2 cm^3. The Isthmus was 2.3 cm and showed heterogenous pattern. No obvious enlargement of cervical nodes was noted along Internal Jugular vein. Her TPO antibody level was elevated with serum TSH of 0.04μIU/ml and Free T4 3.22 ng/dl done six weeks prior to presentation. She was due for I^{131} Thyroid ablation and had been informed of isolation from the family following the procedure.

There was history of six similar episodes in the last eight years, each lasting for 1-7 days and had precipitated following stressful life events. Three of the episodes occurred during the last trimister of gestation preceding the birth of her three children. One episode occurred following the still birth of her fourth child, and the precipitating factors for the other two episodes were insignificant.

In the first 72 hours of her stay in the Emergency, she was not communicative although appeared to comprehend questions put to her and obeyed commands, she would mimic the actions of doctors, would close her eyes and make swaying movements with her hands during service rounds, would stretch her legs as if to kick at the doctors. She was shifted to the padded room in the Psychiatry Intensive Care Unit whenever she would get agitated and would make flinging movements, would clutch her own throat and shout and scream almost throughout the day.

The husband of the patient who was living away would visit the patient only once in 4 months informed that they had been residing in an

independent accommodation since last 2 years close to the in-laws, following frequent quarrels with them over trivial issues and the patient had recently been expressing her desire to move to Mumbai with him. The Family as a whole ascribed the current state of the patient to black magic or possibly because of stopping of her anti-thyroid medication.

During the first five days of admission she was only administered oral Lorazepam 6mg/d in divided dosages and Risperidone 6mg/d and Injectable Lorazepam 2mg whenever agitated on sos basis and started showing some improvement in her condition.

Her routine investigations were done and found to be normal. Her Free T3 was 18.9 pg/ml (2.0-4.4 pg/ml), Free T4 was 7.5 ng/ml (0.93-1.7 ng/dl) and TSH 0.01uIU (0.27-4.2 uIU /mg).

One week after the admission, she developed marked tachycardia (110/min) with elevated blood pressure (140/90 mm Hg) and pyrexia (upto 103 ^{o}F) with T wave inversion in II, III and aVF leads lasting 2 days. During this period she would remain restless throughout the day, pace helplessly in and out of ward and was irritable on minimal provocation. She was diagnosed with 'Thyroid Storm' by the Endocrinologist and Carbimazole was increased to 50mg/d with Propanolol 80mg/d. The patient was given injectable Lorazepam 2mg/d qid to control her agitation.

At the end of one week she became amenable to dialogue and Supportive Psychotherapy. She reported that she had been struggling with her thyroid problem for the last 3 years, but her husband and her in-laws had been very reluctant to spend on her medication and passed critical comments pertaining to the amount they had to spend on the same.

Individual sessions were held with the patient with the aim of ventilating her feelings and improving coping strategies and sessions with the family were held with the aim of cutting down secondary gains. During the supportive sessions she expressed anger towards the husband and the in-laws. She showed dramatic improvement and sessions were continued. She was discharged after one month of admission.

Discussion

This case highlights the interface of Endocrinology and Psychiatry. Most studies done in the past suggest no causative role of hyperthyroidism in the development of psychosis[8,9] although it's role in aggravating and colouring psychosis is well established. Psychosis can occur as an 'acute organic reaction' to thyroid storm or may be independent of the thyroid status.

This patient was diagnosed with Graves's disease based on the history of hyperthyroidism, uniform and enlarged goitrous swelling, elevated Free T4 and decreased TSH levels with positive Anti-TPO antibody. Most of the brief episodes of psychosis were precipitated following significant life events. The Interpersonal problems with family members, husband living away and possibly having a second home, financial constraints and the thought of being separated following radiotherapy acted as a precipitant for the current psychotic episode.

This patient developed Thyroid crises during the course of admission which mimicked psychotic agitation. Altered sensorium, elevated blood pressure, markedly elevated pulse, fever in the presence of significantly elevated FT4 were indicators of a thyroid crises and it improved following increase in the dose of anti-thyroid medication and supportive treatment.

The patient was diagnosed with Organic Psychosis with Graves's disease and was treated with antipsychotics and benzodiazepines. With the manifestations of Dissociative symptoms, attempts were made to develop a rapport with the patient which facilitated ventilation of the patient during sessions. This brought about dramatic improvement in her behaviour with brief fluctuations. Family sessions were taken to cut down secondary gains. By the end of the third week, the patient was clinically stable with no oddities in behaviour and was advised stay with her parents and but was lost on follow up after discharge.

The first person to diagnose a psychotic state in a patient with exopthalamic goiter was Basedow in 1840.[3] Originally, two kinds of psychotic states are described in Thyrotoxicosis (1) Confusional state (2) Affective disorder, commonly Mania. Other than these, Apathetic hyperthyroidism and Schizophrenia like reactions are known to occur but the incidence of these is low.

This patient fits the classical description of 'Hysterical Psychosis'. Janet believed that if the Dissociative element of psychosis can be established then that psychosis may be considered

to be hysterical in nature. The concept was popular in the 19th century but lost importance with the emergence of Schizophrenia in the early 20th century. Hollander and Hirsch described 'Hysterical Psychosis' with the following characteristics (1) Sudden Onset (2) Onset of event profoundly upsetting (3) Manifestations in the form of Delusions, hallucinations, depersonalization or grossly unusual behaviour (4) Affectivity is not usually altered, usually in direction of volatility and not flattening (5) Disorder is generally circumscribed and transient, even though there are delusions and hallucinations, they are usually like simple distortions of reality seen in very angry or fearful child which disappear when emotional control is achieved (6) Acute episode seldom lasts longer than 1-3 weeks (7) Psychosis recedes as dramatically as it began leaving no residue (8) Prognosis is good (9) 2nd, 3rd episode may occur (10) Response to psychotherapy is good (11) Common in hysterical personality and in women (10). The 9th edition of ICD included the term under 'Other and Unspecified Reactive Psychosis' but does not find place in the current classificatory system.[11]

The sudden behavioural change akin to psychosis in the background of Hyperthyroidism and thyroid crises and psychosocial stressors posed a diagnostic dilemma. The brief psychotic episode lasted a week. The importance of optimizing her anti-thyroid medication and non-pharmacological management of her stressors emphasizes the need for a Bio-psychosocial approach in management.

In our case, some questions still remain unanswered, whether the previous episodes had any relationship with thyroid dysfunction could not be established. Although the patient was managed on the lines of acute psychosis in view of the agitation and disorganization, there were no clear reality distortions. In view of the symptoms abating with the subsistence of the 'Thyroid Storm' it remained a diagnostic dilemma as to whether the psychotic condition was a result of the thyroid anomaly or independent in nature. Systematic research would be needed in patients diagnosed with 'Thyroid Storm' preferably in Endocrinology Intensive Care Units and studying various psychiatric manifestations in them, to further elucidate this clinical dilemma. To the best of our knowledge, there is dearth of such studies in India.

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Case Report

Priapism with Risperidone use : A Rare but Important Side Effect

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Introduction

Priapism is a prolonged, painful, and persistent penile erection usually not associated with sexual stimulation. Only the corpora cavernosa are turgid without affecting the other glans penis and corpora spongiosa. It is this finding that distinguishes priapism from a normal penile erection.[1] Two types of priapism are described. (1) high flow (arterial) priapism: which is usually secondary to a rupture of a cavernous artery and unregulated flow into the lacunar spaces, this type of priapism is usually not painful and has a favorable prognosis, and is generally not considered a true emergency[2] (2) low-flow (veno-occlusive) priapism: There is a reduction or absence of the venous drainage from the emissary venules, which results in hypoxia, acidosis, and ischemia. This subtype is painful, accounts for the majority of the cases, and can lead to irreversible fibrosis of the cavernosal spaces if not treated urgently. Low-flow priapism is associated with the use of antipsychotic medications. Priapism is a relatively rare condition, but due to its potentially serious and long-term consequences and its potential as an adverse effect of many common medications, it is a matter of serious concern for clinicians. Impotence may occur in 50% of patients with an episode of priapism.[3] Although priapism can occur in all age groups, it occurs more frequently in the third and fourth decades, often early in the morning, and is noticed on waking.[4] The cause is unknown 50% of the time, and the rate of recurrence is 30%–40%.[4] The exact pathophysiology is still unclear, and it is considered to be multifactorial in origin. Different causes associated with priapism are: haematological (sickle cell disease, leukemia and thalassemia), neurological (spinal cord injury), renal, local causes (trauma, infection), drug abuse (alcohol, cocaine and marijuana) and drug therapy (psychotropic, phenytoin, and heparin).[4-6] Drug-induced priapism is associated with antipsychotics, antidepressants, antihypertensive medications, and accounts for approximately 15% to 41% of all cases, of which antipsychotics-induced priapism is most common.[7,8] Twenty percent of all reports of drug-induced priapism are induced by antipsychotic drugs[9] most commonly chlorpromazine,[10-12] thioridazine[13] which occurs within 28 days of initiation of drug therapy.[9] All atypical agents are associated with priapism. Risperidone is more frequently reported. There have been recent reports of priapism associated with the usage of clozapine,[14-20] olanzapine[21-23] and risperidone.[24-26] Quetiapine and ziprasidone, however, have not been reported to cause priapism. Priapism has been associated with atypical antidepressant drugs mainly trazodone and selective seretonin reuptake inhibitor (SSRI) fluoxetine[9] while tricyclic antidepressant have not been associated with priapism[27] probably due to their anticholinergic properties. Priapism may occur at any time during the treatment course of psychotropic medications and may occur even without a change in the medication dosage.[28] The commonly proposed mechanism of antipsychotic-induced priapism is related to the α-adrenergic system. Arterioles in the penis that supply blood to the corpora cavernosa are in a tonic state of contraction during the flaccid state of penis, a condition mediated by the α-adrenergic activity.[29] During erection, there is a relaxation of the cavernous and

the arteriolar smooth muscle leading to an increase in the blood flow into the sinusoidal spaces[30] Priapism is proposed to be mediated by α receptors located in the corpora cavernosa of the penis[31] and the α-adrenergic antagonist properties found in many psychotropic medications[7] could very well explain the mechanism underlying priapism induced by these medications. It has also been proposed that the corpora cavernosa in some men are exceptionally sensitive to α-blocking agents. Of the antipsychotics still commonly prescribed, ziprasidone and risperidone have the highest affinity for α_1-adrenergic receptor blockade; quetiapine and olanzapine have the weakest[32-34] Thus, of the frequently prescribed antipsychotics, ziprasidone and risperidone theoretically would be the drugs most likely to induce priapism. (Chlorpromazine also has a high affinity but is not prescribed by most clinicians.) Clozapine, which has a lower affinity, has been associated with priapism more often; the reason for this is unclear. The paucity of reported cases of priapism associated with ziprasidone could be explained by this drug's relatively recent introduction to the market.However, priapism is a rare sequel of antipsychotics. It is considered as an urologic urgency and 40-50 % of these patients become impotent even after surgical treatments. Therefore, clinicians should be familiar with this infrequent and serious antipsychotic side effect and inform patients about priapism signs.This case presents how a treatment regimen was finally established balancing antipsychotic efficacy to acceptable side effects andoffers guidance to physicians regarding how antipsychotic-induced priapism may be resolved.

Case History

Mr. A., 28-year-old Hindu male presented to the emergency room with a history of a persistent and painful penile erection from last 4 hours. It was sudden in onset while the patient was slept, and he awoke with a painful erection. The patient was not sexually active; there was no history of penile, genital, or pelvic trauma; and there was no evidence of any infection or malignancy. Routine laboratory tests were performed that included complete blood count, basic metabolic profile, and a coagulation study, and all the results were within normal limits. The drug history revealed that the patient was taking 6 mg of risperidone per day from last 2 years for his psychiatric illness from a private psychiatrist. There was no change in his current medication and no reported use of any over-the-counter medication or any herbal preparation. A diagnosis of priapism was made, and the urology service was consulted. They performed irrigation with normal saline followed by an injection of phenylephrine to the corpora cavernosa to reduce the priapism. There was no improvement in the patient's symptoms. So he was immediately transferred to the operating room where a shunt was placed between corpora cavernosa and corpora spongiosa to relieve his symptoms. His priapism resolved completely within a few hours with the shunt placement. His risperidone was stopped by the department of urology . Psychiatric consultation was sought by the department of urology on evaluation of psychiatric history and mental status examination a diagnosis of paranoid schizophrenia (F20.0) was made as per International Classification of Diseases - 10th Edition criteria (World Health Organization, 1992)[35] Risperidone was the only known causative factor for priapism in this patient. So he was started on amisulpride which has less α_1-adrenergic receptor blockade property. The patient was followed-up monthly and for last 6 months there was no complain suggestive of priapism and his psychotic symptoms are also controlled.

Discussion

Risperidone is an established cause of priapism. Our patient, for unknown reasons, may have been more susceptible than most patients to the effects of risperidone that produced priapism. (15%–26%) of all reports of drug-induced priapism are induced by antipsychotic drugs[36] Certain patients may be more vulnerable than others to this adverse effect. Patients commonly delay reporting both prolonged erections and priapism possibly due to emotional trauma, embarrassment and lack of knowledge as to the emergency nature of priapism or the misconception that prolonged erection is a favorable side effect of psychotropic medications.[36] Patients with a history of priapism associated with antipsychotic treatment should be carefully educated and monitored for signs or symptoms of priapism when therapy with an antipsychotic is started. Priapism is not a dose-or duration-specific complication. The

physician prescribing medications associated with priapism should be aware of a history of prolonged erections and patients should be informed about this complication. Further investigation is needed regarding the mechanisms of erectile disturbances related to administration of antipsychotics and other psychotropic agents.

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Case Report

Eagle's Syndrome Co-Morbid with Depression and Insomnia

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Introduction

Watt W. Eagle in 1937 first described stylalgia, which later came to be known as Eagle syndrome[1]. Stylalgia due to elongated styloid process (long styloid process syndrome, Eagle's syndrome) is related to abnormal length of the styloid process, to mineralization of the styloid ligament complex[1], or to calcification of digastric muscles[2].

The normal length of the styloid process may vary, however, a 30 mm or longer process is generally accepted as anomalous and responsible for the so-called Eagle syndrome. The epidemiological incidence has been reported to be somewhere between 1.4-30%[3, 4]. Eagle's syndrome is generally characterized by the following symptoms: pharyngeal pain localized in the tonsillar fossa, radiating to the oesophagus, to the hyoid bone, painful head rotation and lingual movements. The pain is exacerbated by swallowing and chewing. Other symptoms include foreign body sensation (globus hystericus)[5] and voice change lasting for only a few minutes. A variety of additional symptoms have been reported such as clicking jaw[6], unilateral pain, pain radiating to the neck, to the tongue, chest or temporo-mandibular joint (TMJ) and facial paraesthesia, hypersalivation, sometimes visual problems, dysphagia and pharyngeal spasm.

Though there have been case reports by various authors on Eagle's syndrome[5-8], to the best of author's knowledge, till date there have been only one report[9] on psychiatric co-morbidity with Eagle's syndrome. We hereby present a case report of a young male presenting with features of Depression and insomnia along with Eagle's syndrome.

Case Report

Socio-Demographic details and History of Present Illness

A 30 year old Hindu Male, educated up-to 12th standard, salesman by occupation, married and belonging to low-socio-economic status family presented to psychiatry OPD with chief complaints of persistent pain in left angle of the mandible, radiating to neck along with discomfort while swallowing and chewing for past 3 years. These complaints would subside whenever the patient would go to his home for holidays and take rest while these problems would get aggravated whenever he would spend long hours working on his sales job. Along with these complaints the patient reported gradually progressing sadness of mood, decreased interest in work and hobbies, fatigability, decreased self confidence and reduced concentration for past 8 months and decreased sleep for past 1.5 years. The sadness of mood and insomnia symptoms were progressive, pervasive and persistent and had no specific aggravating and relieving factors and had no particular relation to his pain symptoms. For past 8 months the patient reported worsening of insomnia symptoms along with sadness of mood. The patient also reported occasional concern about his pain symptoms and at times would worry that he might be developing a throat cancer.

The patient reported visiting multiple doctors for his neck pain in the past 3 years ranging from physicians to ENT surgeons and dentists. The patient reported having been told various diagnosis ranging from throat infection to dental caries and occasional doctor also raised a possibility of

possible throat malignancy. The patient reported that he has been prescribed various medications by various doctors for these symptoms but as per the reports of the patient he has never felt any real symptom relief from any of the medications except for occasional improvement in insomnia on taking alprazolam 0.25 mg. The patient had not consulted any doctor for his mood symptoms. There is no history of any other co-morbid medical or surgical illness.

Family History

No history of any similar complaints or any Neuro-psychiatric illness in the family. The patient was married for past 8 years and had 2 children. There was no evidence of any chronic conflicts or stressors at home.

Pre-Morbid Adjustment

The patient's pre-morbid adjustment was good. The patient shared good interpersonal relationships and was working as a sales executive for past 7 years. The patient had a history of nicotine dependence (cigarette smoking 1 bundle per day) for past 10 years.

General Physical And Systemic Examination

Patient's general physical and systemic examination were within normal limits except for mild pallor.

Mental Status Examination

The patient was appropriately dressed for his socio-economic background and his speech and psychomotor activity was within normal limits. He was co-operative and rapport could be established. The patient reported his mood to be sad and his thinking revealed evidence of decreased self confidence, helplessness and worthlessness along with persistent concern about his pain problem and its implications on his health and the future of his family if it turns out to be a cancer. The patient reported being excessively worried about his death. There was no evidence of any delusions, obsessions, compulsions or any hallucinations. His concentration was impaired. Insight and Judgement were found to be intact.

Management

The patient's medical records were evaluated systematically to find out the possible causes of these symptoms. All baseline blood investigations, X-Rays and ultrasonograms did not reveal any abnormality. A non-contrast CT Scan head was ordered which revealed elongated left styloid process of length 3.70 cm. On the basis of patient's symptomatology and CT findings a provisional diagnosis of Eagle's Syndrome with moderate depression and insomnia was made.

The patient was started on Duloxetine (in view of his depression and pain symptoms) 40 mg/day which was gradually increased to 60 mg/day and was prescribed NSAIDs to be taken if there were acute pain exacerbations. The patient was also prescribed Zolpidem- extended release tablet 6.25 mg to be taken at bed-time for his insomnia. On these medications, the patient reported improvement in his depressive and insomnia symptoms but reported only slight improvement in his pain symptoms.

The patient was thus referred to department of ENT for surgical removal of the patient's styloid process. In the meanwhile patient was psycho-educated about the nature of his problems and the cause of his symptoms and was informed that these symptoms are unlikely to be due to malignancy. The patient was counseled regarding sleep hygiene and was taught deep breathing and progressive muscle relaxation techniques.

Over subsequent follow-ups it was observed that even though there was not much relief in his pain symptoms but his depressive and insomnia symptoms were under remission for last 4 months. His Zolpidem was gradually stopped and he is currently maintained on once daily dose of 60 mg Duloxetine which he has been advised to continue for another 3 months.

Discussion

This case highlights the association of depression and insomnia symptoms with Eagle's syndrome and the approach to its management. We hypothesize that the patient developed depression and insomnia as a reaction to the demoralization resulting from uncertainty of the his diagnosis and lack of proper explanation of his pain symptoms and equally unnecessary repeated investigations he was subjected to and his perceived threat to his life and its implications for his family as a result of the

whole process.

Eagle's syndrome is a rare diagnosis and is generally difficult to arrive at. However the whole process of arriving at a rare diagnosis can be a distressing experience for the patient and his family and can have psychological sequelae. These should be considered and treated at the earliest to reduce the morbidity and the burden of the illness and for improving the quality of patient's life.

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Case Report

Acute Nocturnal Akathisia with Clozapine

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Introduction

Akathisia is a subjectively unpleasant state of inner restlessness where there is a strong desire or compulsion to move. It is the most common acute manifestation of neuroleptic-induced extra-pyramidal side effects and often the most distressing. Early detection and rapid amelioration of akathisia is essential since it may may lead to personal distress, worsening of psychosis, noncompliance, impulsive disruptive behavior, and increased suicide risk.[1,2,3] Akathisia is a common side-effect of the dopamine-blocking agents such as antipsychotics, antiemetics (metoclopramide, prochlorperazine),[4] and antidepressants, particularly selective serotonin reuptake inhibitors.5 Akathisia has also been described in patients with idiopathic parkinsonism, uremia, idiopathic restless legs syndrome, congestive heart failure, encephalitis, and sub thalamic abscess.[6] 20 to 75 percent of patients treated with antipsychotics experience akathisia, especially in the first 3 months of treatment.[1,7,8] Although low propensity to induce extrapyramidal side-effects (EPS) is a defining feature of second-generation antipsychotics (SGAs), this seems not to hold true for akathisia.[9] The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) revealed no significant differences between the intermediate-potency FGA perphenazine and four SGAs (olanzapine, quetiapine, risperidone, ziprasidone) in the percentage of patients with chronic schizophrenia who developed akathisia.[10] SGAs are not alike in their propensity to provoke akathisia. Risperidone, ziprasidone and aripiprazole possess a higher risk than olanzapine, whereas quetiapine and clozapine present the lowest risk, although explicit comparative evaluation is lacking.[9] A variety of akathisia subtypes have been described: acute, withdrawal, tardive and chronic.[11] These types resemble each other phenomenologically, but may have different pharmacological profiles in terms of treatment and, possibly, aetiology. Nocturnal akathisia differs significantly from other types of akathisia in terms of its presentation and also it is less commonly reported compared to other types. To date, there is two case reports[12,13] of nocturnal akathisia induced by clozapine. One of them was tardive nocturnal akathisia[12] and other case was of acute nocturnal akathisia induced by clozapine reported from India.[13] We are reporting a case of acute nocturnal akathisia induced by clozapine and its successful treatment by the use of B-blockers.

Case History:

Mr. A. 22 year old unmarried, Indian male diagnosed with schizophrenia, paranoid type as per the as per International Classification of Diseases-10th Edition criteria (World Health Organization, 1992)[14] was hospitalized in the department of psychiatry. His Positive and Negative Symptom Scale[15] score at admission was 114. He did not have any family history of restless legs syndrome and no significant past medical or psychiatric history. His laboratory data revealed no abnormalities, including no anemia and normal biochemical tests. He was started on tablet clozapine and the dose was increased 50 mg on every alterative day. One week after when he was on 200 mg per day of clozapine he complained of impaired sleep in the night due to pain in the both lower limbs and

restlessness. However, during daytime, these symptoms were not marked and the patient was able to carry out his routine ward activities normally. Over the next 2days his complaints of pain in both the lower limbs increased along with this he developed desire to move most of the time and paced around the ward from 10PM to 3 AM. These symptoms were considered to be acute nocturnal akathisia due to use of clozapine because it appeared only within the limited time at night. Rating with Barnes Akathisia Rating Scale[3] revealed a score rating of 15. He was started on tablet Propranolol 20 mg twice daily. There was significant reduction in the symptoms of akathisia on the third day (Rating with Barnes Akathisia Rating Scale was of 7) of starting propranolol. After 7 days there was complete resolution of the symptoms of akathisia. Then the dose of clozapine was increased to 300 mg / day and propranolol was continued as 40 mg/ day, which was tapered off over the next 14 days and stopped, without any reemergence of akathisia. The patient's psychotic symptoms gradually improved, and his Positive and Negative Symptom Scale score was 54 when he was discharged after 1 months on 300 mg/d clozapine.

Discussion

Nocturnal akathisia may develop after acute neuroleptic treatment.[12,13] Though our patient was receiving clozapine on a twice-daily dosage, but akathisia developed in the night only. This may be due to pharmacodynamics interaction at serotonin-dopamine and a-receptors. This case showed that short term treatment with propranolol can be helpful in complete resolution of nocturnal akathisia due to clozapine. Previously it is well known that appearance of acute akathisia on an antipsychotic has been reported to predict poor response to the drug,[16] but our patient's schizophrenia improved with continued treatment with clozapine. Prevalence of akathisia with clozapine is lowest among all second generation antipsychotics and occurrence of nocturnal akathisia is itself also rare. So it should be kept in mind while treating patients with clozapine that acute nocturnal akathisia can occur with clozapine treatment and it is easily treatable with propranolol.

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Case Report

Paliperidone induced Tardive Dyskinesia treated with Clozapine

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Introduction

Tardive dyskinesia (TD) is a severe side effect often induced by conventional antipsychotics and affects approximately 20-30% of patients with schizophrenia.[1] Although usually mild, 5% of patients may develop severe TD.[2] Atypical antipsychotics cause TD less often when compared to conventional antipsychotics[3] though drugs like Risperidone and Quetiapine have been implicated in TD.[4] Both conventional and atypical antipsychotics cause an up-regulation of dopamine-2 receptors and have been associated with tardive dyskinesia.[5] However, studies of adult and elderly subjects have shown a greater incidence of tardive dyskinesia among patients who were administered conventional antipsychotic drugs than those given atypical antipsychotic drugs.[6] Second-generation antipsychotics conferred a lower risk for tardive dyskinesia at 6 months than first-generation antipsychotics. In addition, patients with tardive dyskinesia at baseline who were receiving second-generation antipsychotics were less likely than patients receiving first-generation antipsychotics to have tardive dyskinesia symptoms at 6 months.[7-8] Pailperidone is a new antipsychotic that has been used in the treatment of schizophrenia.[9] Tardive dyskinesia has been reported recently with oral and injectable Paliperidone.[10-11] We add to the existing literature on the same with this case report of two cases of tardive dyskinesia, following treatment with Paliperidone both of which responded well to Clozapine.

Case 1

A 35 year old male was brought with complains of abnormal behaviour in the form of abusive aggressive behaviour, disinhibition in form of removing clothes and moving around naked in the house in front of his 7 year old daughter. He fulfilled the DSM IV criteria for Schizophrenia – Undifferentiated type. Patient was started on Paliperidone extended release tablet at a dose of 3mg at night. He improved considerably with the treatment as reported by his wife. After around four months of treatment patient was found to have Tardive Dyskinesia. Other causes of orofacial dyskinesia were ruled out.The patient was referred to neurologist and blood screening for movement disorders was negative while an MRI study of brain revealed no abnormality.Paliperidone was stopped and patient was started on Clozapine. The dose was titrated up to 100 mg at night. Clozapine was started with a view to help both the schizophrenia and TD. The patient showed improvement in his Tardive Dyskinesia as well as schizophrenic symptoms.

Case 2

A 49 year old female had come with complains of insomnia and sadness. The reason for her insomnia and sadness was suspiciousness on her husband since last six months. She fulfilled the DSM IV criteria for Delusional Disorder as she had no symptoms suggestive of major depression while the suspiciousness which was delusional in nature was the only predominant symptom. She was started on Olanzapine 5mg twice a day and Fluoxetine 20

mg per day following which she improved. This combination was started to combat both her delusions and sadness. On follow up her lipid profile was found to be elevated. We do not know whether lipid profile was elevated prior to starting olanzapine but as a precautionary measure olanzapine was discontinued. She was started on Paliperidone extended release oral tablet at a dose of 3 mg which was gradually increased to 6 mg in 10 days. After two months of treatment she developed Tardive Dyskinesia. Neurological reference was done and other causes of orofacial dyskinesia were ruled out. Brain imaging study revealed no abnormality. Paliperidone was stopped and Clozapine was startedwithagradual increase in dose upto 100mg at night. The patient showed improvement in her delusions and her tardive dyskinesia.

Discussion

There are various studies which say that the incidence of TD was higher with second-generation antipsychotics than previously reported. This is possibly due to recent studies with relatively short mean durations and use of non-standard tardive dyskinesia definitions.[12] The incidence of tardive dyskinesia with recent exposure to atypical antipsychotics alone was more similar to that for conventional antipsychotics than in most previous studies.[13] Despite a high penetration of atypical antipsychotics into clinical practice, the incidence and prevalence of tardive dyskinesia appeared relatively unchanged since the 1980s. Clinicians should continue to monitor for tardive dyskinesia, and researchers should continue to pursue efforts to treat or prevent it.[6] Results from 11 long-term studies support the idea that second-generation antipsychotics have a reduced risk for tardive dyskinesia, compared to first-generation antipsychotics, although the doses of haloperidol used in the comparator studies were relatively high.[14] More carefully designed studies, ideally lasting beyond 1 year and comparing the effects of different second-generation antipsychotics in patients who have never taken first-generation antipsychotics, are needed to estimate the true risk.[15] It is important for clinicians to consider these findings in making long-term treatment decisions.[2] Clozapine has been considered safer than other antipsychotic drugs in the causation of drug induced movement disorders and TD.[16] Recent researchers have implicated Clozapine in the management of TD.[17] In the cases mentioned above, an interesting facet was that none of the patients had acute extrapyramidal reactions, but rather developed TD directly. The cases above illustrate the same and suggest that clinicians must be watchful of TD in all the newer antipsychotics and consider alternate treatment strategies once TD has been detected.

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Case Report

Post Dengue Psychosis

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Dengue fever is a well-known mosquito borne viral infection commonly seen in tropical countries, commonly present as fever, backache, headache, malaise and in complicated form may lead to hemorrhage (gastro-intestinal, cerebral or gum bleeding, etc) and shock.[1] Neuropsychiatric manifestations are not uncommon in patients suffering from dengue fever, though these areas are less emphasized.[2–5] Infection with dengue virus leads to inflammatory changes in the cerebral cortex (encephalitis / encephalopathy) which are responsible for the neuropsychiatric manifestations.[2–6] There is scarcity of literature regarding psychiatric manifestations of dengue fever. In this case, a rare acute psychotic presentation immediately following recovery from dengue fever is reported.

Case history

A 35 years old male of low socioeconomic status with insignificant family and personal history, presented in psychiatric emergency with reduced sleep, suspiciousness, fear of being harmed by others, agitation, poor self-care and emotional lability. There symptoms were present approximately one week prior to consultation in our institution. This episode was preceded by physical illness during which he had fever, myalgia and reduced appetite. He had been investigated and found to be sero-positive (positive IgM antibodies) for dengue. MRI of the brain did not reveal any abnormality. As fever started subsiding, his platelet count fell down to 43,000/mm^3 but with conservative treatment and one unit platelet transfusion, he had improved. After 3 to 4 days, he developed the psychiatric symptoms. At time of presentation to psychiatric emergency, patient was conscious and oriented to time, place and person. There was no evidence of impairment of cognitive function (Mini Mental Status Examination score-26). He was having irritable affect, persecutory delusion with impaired judgment and insight. At that time, he was afebrile. His platelet count was 1, 47, 000/mm^3. The patient was diagnosed with "Acute and transient psychotic disorder" as per the ICD-10, diagnostic criteria. He was prescribed olanzapine 10mg/day and lorazepam 2mg at bed time for sleep. With these medications, there was significant improve-ment in one week.

Discussion

Dengue fever is associated with neuropsychiatric manifestations. Even in the post dengue convalescence phase, psychiatric disorders emerge. This area is poorly studied. Recently, the focus is shifting towards the neuropsychiatric manifestations and different forms of psychiatric presentations of dengue patients. In this case, unlike other cases reported in the literature[2–5] didn't have any psychiatric symptoms during the phase of illness (dengue fever). The patient had developed psychotic features after recovery from dengue. Now, development of acute and transient psychotic disorder in this case raises questions–*whether psychosis was a late complication of dengue fever or just a coincidence?*

Patients suffering from dengue fever need to be evaluated for psychiatric symptoms during the illness as well as after recovery for early diagnosis, appropriate intervention and simultaneously to substantiate the evidence in this poorly studied domain.

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Case Report

Occlusal dysesthesia responded to Escitalopram

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Introduction

Dysesthesia is defined as an unpleasant abnormal sense of touch.[1] It often presents as pain[1] but may also present as an inappropriate, but not discomforting, sensation. Term is derived from the Greek word "dys", meaning "not-normal" and "aesthesis", which means "sensation" (abnormal sensation).[2] It is caused by lesions of the nervous system, peripheral or central, and it involves sensations, whether spontaneous or evoked, such as burning, wetness, itching, electric shock, and pins and needles.[1] Dysesthesia can include sensations in any bodily tissue, including most often the mouth, scalp, skin, or legs.[1] Dysesthesia should not be confused with anesthesia or *hypesthesia*, which refer to a loss of sensation, or *paresthesia* which refers to a distorted sensation. Dysesthesia is distinct in that it can, but not necessarily, refer to spontaneous sensations in the absence of stimuli. Occlusal dysesthesia, or "phantom bite," is characterized by the feeling of a biting sensation in the absence of any apparent damage to oral or maxillofacial structures or tissue, usually in patients that have undergone recent dental surgery.[3]

The patient described developed persistent biting sensation following dental extraction and responded to an SSRI,escitalopram.

Case Report

We describe a case of 38-year-old housewife. She was living with husband and two children in semi urban area. She presented with a four months history of feeling of a biting sensation on the right side of the face over the temporo-mandibular area. It was sometimes associated with dull aching pain. This started about one month after dental extraction (right lower premolar tooth). She tried different types of analgesics, toothpaste and mouth washes but without any relief. Due to symptom, she had developed anxiety and sleeplessness and was unable to do her household activities perfectly. She did not believe the suggestion of her relatives including husband and children that there is no medical basis of her complaint. There were no known stressors. There was no past or family history of psychiatric disorder or chronic physical illness.

Detailed systemic examination including neurological examination and relevant hemato-logical and radiological investigations including CT scan (head) did not reveal any abnormality. Mental state examination revealed a middle-aged lady of endomorphic build. Psychomotor activity and speech were normal. There was no perceptual abnormality. She was preoccupied with the complaint. Higher mental functions were normal.

She was psycho-educated about the problem and was convinced with difficulty that it requires treatment with systemic psychotropic drugs.The patient was started on tablet carbamazepine 600 mg/dayin three divided doses, tablet gabapentin 300 mg at night and tablet methylcobalamine 1500 mcg/d..There was no improvement in 2 weeks. She was then started on tablet escitalopram 10 mg/day.

Tablet carbamazepine and tablet gabapentin 300 mg/day were gradually tapered off in another 2 weeks. The dose of escitalopram was gradually increased to 20 mg/day in four-weeks. There was improvement in the biting sensation and complete remission in six weeks. On following her up at twelve weeks,she did not develop the symptom again.

Discussion

Dysesthesia has been reported in Diabetes mellitus, Guillain-Barre syndrome, Lyme disease, Multiple sclerosis, GM2 Gangliosidosis, withdrawal from alcohol or other drugs, side-effect of chemotherapy drugs or after oral surgery.[4–10] Local conditions e.g. facial arthromyalgia, myofacial pain, masticatory muscle disorders also constitute the differential diagnosis.[6] In the present case, there was history of dental extraction one month prior to development of complaint.

There are a number of hypotheses regarding the basis of occlusal dysesthesia. Some researchers believe the disorder is a psychological one, while others classify it as a psychosomatic disorder.[7] *Joseph Marbach*[10] hypothesized that the symptoms were rooted in psychiatric disorders.

Similarly, Marbach[10] proposed that occlusal dysesthesia may be caused by the brain "talking to itself," causing abnormal oral sensations in the absence of external stimuli. According to this model, the symptoms of dysesthesia are catalyzed by dental "amputation," for example the extraction of a tooth, whereby the brain loses the ability to distinguish between its memory of the bite and the actual, new bite. Greene and Gelb[11] suggested that instead of having a psychological root, dysesthesia may be caused by a false signal being sent from the peripheral nervous system to the central nervous system. Chronic anxiety is often associated with dysesthesia[12,13]. Patients suffering from this anxiety may experience numbness or tingling in the face. In one study, those patients that were examined psychologically had symptoms of anxiety, depression, obsessive-compulsive personality disorder, or somatoform disorder.[7]

Daily oral muscle physical therapy, or the administration of antidepressants have been reported as effective therapy for patients with occlusal dysesthesia.[7] Tooth grinding, and the replacement or removal of all dental work should be avoided in patients with occlusal dysesthesia,[7,14] despite the frequent requests for further surgery often requested by these patients. The present case responded to SSRI, escitalopram.

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Forensic Psychiatry

Medico-legal issues in Prescription Errors

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Abstract

Errors in the prescriptions written to the patients by physician are commonly encountered in the medical/dental practice. There are different types of prescription errors such as: Illegible writing leading to delivery of different medicine other than desired; excess of dose; misreading by the pharmacist; prescribing a drug that may not be indicated as per standard treatment protocols. The prescription errors can at times lead to damages to the patients and can be a ground for medical negligence. There are both ethical and legal issues pertaining to the prescription errors that can call for both civil and criminal liability on the physicians. Both the issues have been discussed in the paper with few illustrative court judgments both from abroad and our own country.

Introduction

A definition of prescription error states that a 'clinically meaningful prescribing error occurs when… there is an unintentional significant reduction in the probability of treatment being timely and effective or increase in the risk of harm when compared with generally accepted practice'.[1] As per the statistics from the Centres of Disease Control and Prevention (National Center for Health Statistics). Births and Death: preliminary data for 1998, more people die in a given year as a result of medical errors that from motor vehicles accidents, breast cancer or AIDS.[1] The adverse drug events cause more than 7,70,000 injuries and death each year and cost up to $5.6 million per hospital.[2]

Medication/prescription errors happen. Unfortunately they represent a fact of life in virtually every health care institution. Medication errors involve a variety of health professions, from the physicians who prescribe medication, to pharmacists who have responsibility for dispensing it, to nursing staff who administer it. Determining the causes for medication errors and the means/ ways of minimizing these errors is a difficult task. It is a fact of life that most nurses and physicians will be involved in a medication error at some point in their careers. Medication errors usually do not involve any lack of competence on the part of the health care practitioner. Nevertheless, the pressures of daily practice or a moment of inattention may result in a patient not receiving the required medication in a timely manner or giving a higher dose of the medicine. Health practitioners who are involved in a medication incident may learn the important lesson that they are not immune from this type of error. This, in turn, can have a positive impact to ensure that this type of incident does not recur.

Legal Consequences of Prescription Error

Prescription/ Medication errors usually don't lead to any permanent health problem. Unfortunately, in a small percentage of cases medication errors result in serious injury or death. For health practitioners who are involved in a serious medication incident resulting in patient injury or death, the impact on their professional life can be devastating. In addition to the emotional impact of having to come to grips with a serious incident, a civil claim for damages will follow. The incident

could also result in discipline in the employment setting or, if a physician is involved, could result in a review of privileges to practice in a particular institution. There is also the potential for a regulatory college to become involved and to impose discipline which could limit an individual's right to practice in the future.

Illustrative Court Judgments

1. Dr. (Mrs.) V.C. Bendale Vs. Leela Veerajaneyulu, National Consumer Disputes Redressal Commission, New Delhi

Revision Petition No. 586 of 2006, Judgment dated 16th December, 2010

The case pertains to a patient who was suffering from fever and was prescribed *Reziz* (a combination of Sulphadoxine and Pyrimethamine) who immediately had a reaction after the medication and died 16 days later. The patient's family sued the physician, the hospital, and the nursing, clerical and pharmacy staff.

The Court in its verdict stated, "However, a perusal of her first prescription dated 30th of September, 1997 betrays complete lack of professional conduct, inasmuch as the prescription does not indicate the age of the child nor does it indicate as to whether he was running fever at the time of examination and whether there were other symptoms from which she could arrive at a proper conclusion that the child was suffering from Malaria. Fever has manifestation e.g. viral, dengue, chikungunya etc. and the doctor should have recorded some details as to why she straightaway diagnosed it to be a case of Malaria. Blood smear tests facilities are now a days available in every PHC and health center and she should have asked for a test report before prescribing medicine without that. She has not stated a single word with regard to the history of the patient and has gone on to prescribe the medicines in a very routine manner. Her contention that she has diagnosed it to be a case of Malaria is now based on the prescription of Reziz rather than on any clinical history. This by itself constitutes negligence. However, even if the case is taken to be that of Malaria, straightaway prescribing Reziz without any investigation will not be justified. In fact it runs counter to the treatment protocol on Malaria prescribed by the National Drug Policy on Malaria of the Government of India. Further, with regard, however, to Reziz, the medical literature states that Reziz is a combination of two drugs such as Sulphadoxine and Pyrimethamine. No doubt, it is used to treat Malaria but only if it has been established that the Malaria is chloroquine resistant and the attack is acute in nature. With regard to the dosage, it states that while adults can take 2-3 tablets as a single dose, the children from 5-10 years age group with 20-30 kgs. body weight can be given 1½ tablets as a single dose. It clearly stipulates that the dose should not be repeated for at least seven days. In the case in hand, Dr. Bendale has prescribed four tablets of Reziz at the rate of two tablets per day for two consecutive days as against the recommended dose of 1½ tablets as a single dose. It cannot, therefore, be said that the dosage prescribed was not in excess. It is admitted that even on the 15th of October, 1997 Dr. Bendale has repeated the Reziz and, therefore, it is fully established that Reziz had been administered to the child far in excess of the requirement".[3] Therefore, the commission did not gave any relief to the appellant and upheld the trial court verdict.

In this case at trial, it was learned that the defendants relied on a computer generated Medication Administration Record (MAR) which listed "no allergies" for the patient. The defendants failed to thoroughly review the patient's medical records for allergies or check the MARs for any inconsistencies. The court concluded that the defendant health care providers had failed their responsibilities to verify the appropriateness of the patient's prescriptions and to bring potential problems to the attention of the prescriber. The plaintiffs were awarded $350,000 in damages.

2. In 1983 the Court of Appeal in U.K., in the case of Dwyer Roderick and others,' emphasised the serious consequences of negligently writing and dispensing medical prescriptions. Those consequences were re-emphasised in the recent High Court decision in the case of Prendergast v Sam and Dee Ltd. Wrong dosage Dr Ian Roderick wrote a prescription for Mrs Joan Dwyer, who had complained to him of severe headaches, for a pain killing drug which was proved successful in the treatment of migraine. The drug, ergotamine tartrate (Migril), is extremely dangerous if not taken in proper doses. It can produce gangrene. Dr Roderick did not prescribe the drug in the proper doses. Mrs

Dwyer took the prescription to the pharmacy of Cross Chemists (Banbury) Ltd. There she was given ergotamine tartrate in a container displaying the exact dosage as recommended by Dr Roderick. Mrs Dwyer began to take the drug as directed and rapidly became very ill. During this time she was seen by a partner of Dr Roderick, Dr Jackson, who called to see Mrs Dwyer from his own home and therefore did not have her medical notes with him. He gave evidence that he was unaware that Mrs Dwyer was taking ergotamine tartrate. He stated that he had examined drugs that were on her bedside table but had not seen ergotamine tartrate. By the time that the mistake was discovered Mrs Dwyer was suffering from gangrene and her toes had to be amputated. As a result she became permanently crippled. In the High Court Mr Justice Stuart-Smith noted that negligence was admitted by Dr Roderick who had written the prescription and by the pharmacy which had dispensed it. There were therefore two main issues for the judge to decide. Firstly, he had to consider whether any further liability lay with Dr Jackson. In an attempt to limit its liability the pharmacy had joined Dr Jackson as another defendant. The judge held that the overwhelming likelihood was that on Dr Jackson's first visit to Mrs Dwyer a bottle containing ergotamine tartrate was by her bedside. Dr Jackson had persuaded himself, during the eight years which it took for the case to come to trial, that he could not have known that the plaintiff was taking the drug. Having concluded that Dr Jackson had also been negligent, the judge had to decide what the proper apportionment of liability should be. Accordingly, Mr Justice Stuart-Smith awarded damages of £100000 against Dr Roderick, Dr Jackson, and the pharmacy to be apportioned as to 45% to Dr Roderick, 15% to Dr Jackson, and 40% to the pharmacy.[4]

3. There are number of other judicial pronouncements deals with different aspects of prescription errors such as:

Strangeways v Clayton 1936

Nurses misread px of Paraldehyde and gave a lethal dose[5]

Collins v Hertfordshire CC 1947[6]

There was failure in communication. Mistook procaine for cocaine

Smith v Brighton & Lewes HMC 1958

Patient received 4 injections of streptomycin above 30 prescribed. Caused loss of balance

Prendergast v Sam & Dee Ltd 1989[7]

Illegibly written script resulted in supply of wrong drug.

4. A US jury has found that a Texas doctor's poor penmanship was partly to blame for the death of a 42-year-old man. *American Medical News* (Nov. 22/29, 1999, p. 1) reports that the verdict is probably the first in the US in which a physician was found negligent solely on the basis of poor handwriting.

Cardiologist Ramachandra Kolluru of Odessa, Texas, allegedly wrote a prescription that called for Ramon Vasquez to take 20 mg of Isordil (isosorbide) every 6 hours. However, the illegibility of the prescription caused a pharmacist to dispense the same dosage of Plendil (felodipine), although the maximum daily dose was only 10 mg. (In Canada the maximum recommended daily dose is 20 mg.) Vasquez had a heart attack a day after taking the Plendil and died several days later. Jurors attributed his death to the drug and found the physician and pharmacy equally liable for the fatal error. Each was ordered to pay $225 000. "This is a wake-up call," said Max Wright, the attorney for Kolluru. "[It is] another reminder that doctors . . .need to ensure that they have communicated what they meant to communicate to their patients."[8]

Ethical & Legal Issues in Prescription Errors

As per the Indian Medical Council Regulations called as, "The Indian Medical Council (Professional conduct, Etiquette and Ethics) Regulations, 2002",[9] there is Section 1, Sub-section-5 related to the prescription writing and the same is reproduced below:

1.5. *Use of Generic names of drugs:* Every physician should, as far as possible, prescribe drugs with generic names and he / she shall ensure that there is a rational prescription and use of drugs.

Therefore any physician disgracing from the above guidelines violates the provisions of the prescription writings and can be punished with the ethical wrong if the same is brought to the notice of State Medical Council/ Medical Council of India.

As far as The Information Technology Act 2000 (ITA-2000) is concerned it is silent on electronic prescription. However, more and more physicians

are using electronically generated prescriptions especially in the corporate hospitals.

Newer outpatient electronic prescribing software programs produce typewritten paper prescriptions with electronically created signatures. Current Canadian federal legislation forbids static (unchanging) signature images on prescriptions.

As far as civil and criminal liability resulting from prescription errors are concerned, they will depend upon the extent of the damages caused to the patient. If the loss the patient is not severe than it can be compensated monetarily and for that the patient has to approach either the civil court or the consumer dispute forum/commission depending upon the amount of compensation sought. If damage is in the form of death of the patient than even a criminal charge can be brought against the doctor under Section 304A of the Indian Penal Code. **Causing death by negligence-**Whoever causes the death of any person by doing any rash or negligent act not amounting to culpable homicide, shall be punished with imprisonment of either description for a term which may extend to two years, or with fine, or with both. In other non-fatal criminal cases there are two legal provisions:

Section 337 - Causing hurt by act endangering life or personal safety of others Whoever causes hurt to any person by doing any act so rashly or negligently as to endanger human life, or the personal safety of others, shall be punished with imprisonment of either description for term which may extend to six months, or with fine which may extend to five hundred rupees, or with both; and

Section 338 - Causing grievous hurt by act endangering life or personal safety of others

Whoever causes grievous hurt to any person to doing any act so rashly or negligently as to endanger human life, or the personal safety of others, shall be punished with imprisonment of either description for a term which may extend to two years, or with fine which may extend to one thousand rupees, or with both.[10]

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2. Centres of Disease Control and Prevention (National Center for Health Statistics). Births and Death: preliminary data for 1998. National Vital Statistics Reports 1999; 47(25) : 6.
3. Dr. (Mrs.) V.C. Bendale Vs Leela Veerajaneyulu, Revision Petition No. 586/2006, National Consumer Dispute Redressal Commission, N-Delhi, Judgment dated December, 16, 2010.
4. Dwyer v Roderick (1983) 127 SJ 806
5. Strangeways-Lesmere v Clayton [1936] 2 KB 11, [1936)1 All ER 484
6. Collins v Hertfordshire CC [1947] 1 All ER 633
7. Prendergast v. Sam & Dee Ltd [1989], 1 Med LR 36
8. Hirshhorn C. Poor Penmanship cost MD $ 2,25,000. CMAJ 2000; 62 : 91
9. The Indian Medical Council (Professional conduct, Etiquette and Ethics) Regulations, 2002. Available at www.mci.org
10. Indian Penal Code, 1860. Available at www. advocatekhoj.com

Fourthcoming Events

(A) International Psychiatry Conferences

30 Sep 2013 – 01 Oct 2013, San Antonio, United States, PsychoAAD-2013 would lay a platform for the interaction between experts around the world and aims in accelerating scientific discoveries. The main theme of the conference is Global Perspectives and current trends in Psychology Psychology, Psychiatry, Autism, Alzheimer's, Alzheimer's Disease, Psychotherapy, Current Research, Addiction, Addiction Psychology, Aging Psychology, Social Psychology, Family Psychology , Personal Psychology, Sport Psychology, Abnormal Psychology, Diagnostics and Analysis, Clinical aspects & Case Studies, Parkinsonism, sleeping disorder, positive psychology, stress, absue, aggression, animal abuse, EGO, Animal Model, Anger, Cognition, Behavioural Psychology, Trauma, Neurology, Bipolar, Anxiety disorders, Schizophrenia, Eating disorder, Work, Brain, Internet http://www.omicsgroup.com/conferences/psychology-autism-alzheimers-2013/ Phone: [6502689744]; Email: psychoaad2013@omicsgroup.com

01 Oct 2013 – 04 Oct 2013, Seoul, South Korea, IPA has held International Congresses since it was founded in 1982. As the most highly acclaimed meeting in the field of the mental health and aging for old people, IPA 2013 is expected to draw over 1,000 participants from around the world. http:// www.ipa2013.com Rosa Jeong; Phone: [+82-2-566-5920]; Email: seoul@ipa2013.com Geriatrics

17 Oct 2013 – 19 Oct 2013, Alpbach, Austria Ziel des Kongresses ist es, den aktuellen Stand der Forschung, Behandlung und Prävention von Essstörungen und Adipositas darzustellen und den wissenschaftlichen und klinisch-therapeutischen Austausch zu fördern. http://www.netzwerk-essstoerungen.at/kongress13

Phone: [(+43-512-57 60 26)]; Email: info@netzwerk-essstoerungen.at

23 Oct 2013 – 26 Oct 2013, Barcelona, Spain**,** The 3rd International Congress on Dual Disorders will be the best opportunity for psychiatrist sspecialized in Dual Pathology to meet, share and find the last advances in the field. Psychiatry, Dual Disorders, Dual Pathology, Psychologist, International Congress on Dual Disorders, ICDD, ICDD2013, Mental Health, Mental disorders, Suicide, Co-morbid mental and physical illness, psychotic http://www.cipd2013.com/ Natalia Ribas Londres, 17 28028 Madrid, Spain; Phone: [+34 91 361 2600]; Email: secretariat@cipd2013.com

(B) International Psychology Conferences

September 2013

1st 3rd Global Conference: The value of work, Oxford, United Kingdom.

5th Death Dying & Disposal 11, Where theory meets practice, Milton Keynes, United Kingdom.

14th 12th Asian Oceanian Congress on Child Neurology, Riyadh, Saudi Arabia.

19th "Dreams, Phantasms and Memories" Interdisciplinary Conference, Gdansk, Pland.

19th 6th Global Conference: Making Sense of : Madness Oxford, United Kingdom.

23rd 3rd Global Conference: Making Sense of: Chronicity, Oxford, United Kingdom.

30th International Conference on Psychology, Autism and Alzheimer's Disease, San Antonio, United States of America.

October 2013

23rd 3rd International Congress on Dual Disorders, Barcelona, Spain.
31st 4th WA Transcultural Mental Health & 2nd Australasian Refugee Health Conference, Perth, Australia.

(c) National Conferences

- 38th Annual Conference of IPS (North Zone) on October 26 & 27, 2013 at Delhi (Contact: Dr. Dinesh Kataria at drdineshkataria@yahoo.com and Prof. R.C. Jiloha at rcjiloha@hotmail.com)
- 7th Congress of Asian Society for Child and Adolescent Psychiatry & Allied Professions and 12th Biennial Conference of Indian Association for Child and Adolescent Mental Health, New Delhi on 25-28th September 2013. (Contact: Dr. Savita Malhotra at savita.pgi@gmail.com)
- 66th Annual Conference of Indian Psychiatric Society to be held at Pune on 16-19 January 2014 (Contact: contactus@ancips2014.com Dr. Kishor Gujar/Dr. Vidyadhar Vatve).

WPA CONFERENCES

2013

WPA Co-Sponsored Meeting (Zone 9) — Best practice in psychological therapies for psychosis Poland / Warsaw 22.08.2013 – 25.08.2013.
WPA Co-Sponsored Meeting (Zone 5) — 2013 World Mental Health Congress of the World Federation for Mental Health "Social Inclusion through Interdisciplinary Interventions" Argentina / Buenos Aires 25.08.2013 – 28.08.2013.
WPA Thematic Conference (Zone 10) — Armenia / Yerevan 29.08.2013 – 31.08.2013.
WPA Co-Sponsored Meeting (Zone 8) — "9th European Congress of Mental Health in Intellectual Disability" "New horizons for mental health in intellectual and developmental disabilities" Portugal / Estoril, Lisbon 12.09.2013 – 14.09.2013.
WPA Regional Congress (Zone 3) — WPA Regional Congress and XXIII. APM National Congress México / Guadalajara, Jalisco 12.09.2013 - 16.09.2013
WPA Co-Sponsored Meeting (Zone 7) — The International Society on the Study of Personality Disorders (ISSPD), XIII International Congress on Disorders of Personality - Bridging Personality and Psychopathology: The Person Behind the Illness Denmark / Copenhagen 16.09.2013 – 19.09.2013
WPA Co-Sponsored Meeting (Zone 12) — "First Psychiatry Up date 2013 International Mental Health Conference" UAE / Abu Dhabi 20.09.2013 – 21.09.2013.
WPA Co-Sponsored Meeting (Zone 8) — Spanish Society of Psychiatry National Meeting with the theme Spain / Seville 24.09.2013 – 27.09.2013.
WPA Co-Sponsored Meeting (Zone 11) : Group Psychotherapy and Group Processes "Hope in Critical Times" Egypt / Giza 24.09.2013 – 27.09.2013.
WPA Co-Sponsored Meeting (Zone 9) — 1st International Conference on Creative Psycho-pharmacotherapy "Psychopharmacology, new insights, philosophies of treatment and stigma and human rights of patients" Croatia / Dubrovnik 25.09.2013 – 28.09.2013.
WPA Co-Sponsored Meeting (Zone 16) : 7th Congress of the Asian Society for Child and Adolescent Psychiatry and Allied Professions (ASCAPAP) and the 12th Biennial Conference of the Indian Association for Child and Adolescent Mental Health with the theme "B India / New Delhi 25.09.2013 – 28.09.2013.
WPA Co-Sponsored Meeting (Zone 6) — "4th European Conference on Schizophrenia Research (ECSR)" "Together for better treatment and care" Germany / Berlin 26.09.2013 – 28.09.2013.
WPA Co-Sponsored Meeting (Zone 1) — 63rd Annual Conference Canadian Psychiatric Association Canada / Ottawa 26.09.2013 – 28.09.2013.
WPA Co-Sponsored Meeting (Zone 8) — 1st International Brain Storming School : Focus on long term treatment Greece / Chalkidiki 27.09.2013 – 29.09.2013.
WPA Thematic Conference (Zone 18) — Human Factors in Crisis and Disasters - Future Proofing of Crisis and Disaster Management Australia / Melbourne 30.09.2013 – 02.10.2013.
WPA Co-Sponsored Meeting (Zone 9) — 2nd congress on Treatment in Psychiatry Czech Republic /

Ostrava 10.10.2013 – 13.10.2013.
WPA Co-Sponsored Meeting (Zone 15) — 30th Annual Congress of Iranian Psychiatric Association "Psychosomatic Medicine" Iran / Tehran 22.10.2013 – 25.10.2013.
WPA Co-Sponsored Meeting (Zone 5) — 31st Brazilian Congress of Psychiatry Brazil / Curitiba, Paraná 23.10.2013 – 26.10.2013.
WPA Co-Sponsored Meeting (Zone 6) — 8th European Congress on Violence in Clinical Psychiatry with the theme Belgium / Ghent 23.10.2013 – 26.10.2013.
WPA Co-Sponsored Meeting (Zone 8): III International Congress Dual Disorders: Addictions and Other Mental Disorders Spain / Barcelona 23.10.2013 – 26.10.2013.
WPA International Congress (Zone 8) — Future Psychiatry: Challenges and Opportunities Austria / Vienna 27.10.2013 - 30.10.2013
WPA Co-Sponsored Meeting (Zone 15) — 3rd Asia Pacific Conference on Psychosocial Pakistan / Lahore 01.11.2013 – 03.11.2013.
WPA Co-Sponsored Meeting (Zone 2) — Perinatal Mental Health: Optimizing Treatment to Improve Infant Outcomes USA / Chicago 06.11.2013 – 08.11.2013.
WPA Co-Sponsored Meeting (Zone 8) — "UNESCO Chair in Bioethics 9th World Conference" "Bioethics, Medical Ethics & Health Law; Towards the 21st Century" Italy / Naples 19.11.2013 – 21.11.2013
WPA Co-Sponsored Meeting (Zone 16) — 7th International Conference on Psychiatry Bangladesh / Dhaka 23.11.2013 – 25.11.2013.
WPA Co-Sponsored Meeting (Zone 12) — 2nd Prince Sultan Military Medical City (PSMMC) International Psychiatry Conference "Mood Disorders Across Age Groups" Saudi Arabia / Riyadh 26.11.2013 – 27.11.2013.
WPA Co-Sponsored Meeting (Zone 8) — Temperament, character, personality and the mood disorders spectrum Greece / Thessaloniki 15.12.2013 – 15.12.2013.

2014

WPA Co-Sponsored Meeting (Zone 8) — "15th edition of the Virtual Congress of Psiquiatria.com (Interpsiquis 2014)" On line / 01.02.2014 – 28.02.2014
WPA Regional Meeting (Zone 14) — WPA Regional Meeting Uganda / Kampala 06.02.2014 - 08.02.2014
WPA Regional Meeting (Zone 9) — "WPA Regional Meeting" "Addressing mental health needs in the Alps-Adria-Danube Region: Stigma, Community Based Care, Stress and Suicidality Slovenia / Ljubljana 09.04.2014 – 12.04.2014
WPA Co-Sponsored Meeting (Zone 12) — "10th International conference on Psychiatry" "Psychiatric Models; Biological and Psychological perspectives" Kingdom of Saudi Arabia / Jeddah 15.04.2014 - 17.04.2014
WPA Co-Sponsored Meeting (Zone 1) — National Association on Dual Diagnosis (NADD) International Congress USA / Miami, Florida 07.05.2014 – 09.05.2014
WPA Co-Sponsored Meeting (Zone 10) — Congress of World Association for Dynamic Psychiatry - Multidisciplinary Approach to and Treatment of Mental Disorders: Myth or Reality? Russia / St. Petersburg 14.05.2014 – 17.05.2014
WPA Co-Sponsored Meeting (Zone 5) — "Forum Specialists in Mental Health" "Critical Thinking and Psychiatry" Argentina / Buenos Aires 04.06.2014 - 05.06.2014
WPA Thematic Conference (Zone 9) — WPA Thematic Conference "Neurobiology and treatment of psychiatric disorders and addiction" Poland / Warsaw 05.06.2014 – 07.06.2014
WPA Co-Sponsored Meeting (Zone 9) — 16th International Conference for Philosophy, Psychiatry and Psychology "Neuroscience, Logics and Mental Development" Bulgaria / Varna 26.06.2014 - 29.06.2014 Read More
WPA Co-Sponsored Meeting (Zone 17) — "110th Annual Meeting of the Japanese Society of Psychiatry

and Neurology" "Psychiatry to change the world: from community psychiatry to global psychiatry" Japan / Yokohama 26.06.2014 – 28.06.2014

16th World Congress of Psychiatry (Zone 8) — WPA 16th World Congress of Psychiatry - Focusing on Quality, Access and Humane Care, Spain / Madrid 14.09.2014 - 18.09.2014

WPA Regional Congress (Zone 17) — WPA Regional Congress"Ying and Yang of Mental Health in Asia – Balancing Priorities" China / Hong Kong 12.12.2014 - 14.12.2014

OTHER CONFERENCES

September 2013

- ISMRM Workshop on Dynamic MR Imaging & Spectroscopy of Psychiatric Illness 2013Sat 7th Sep 2013 to Tue 10th Sep 2013 Lisbon, Portugal
- European Society for Biomedical Research on Alcoholism 15th Congress 2013 Sun 8th Sep 2013 to Wed 11th Sep 2013 Warsaw, Poland
- Swiss Society for Psychiatry and Psychotherapy Annual Congress 2013 Wed 11th Sep 2013 to Fri 13th Sep 2013 Montreux, Switzerland
- Mexican Association of Psychiatry 23rd National Congress 2013 Thu 12th Sep 2013 to Mon 16th Sep 2013 Guadalajara, Mexico
- RANZCP New Zealand Conference 2013 Mon 16th Sep 2013 to Wed 18th Sep 2013 Auckland, New Zealand
- International "Stress and Behavior" PTSD Symposium 2013 Fri 20th Sep 2013 to Sat 21st Sep 2013 Yerevan, Armenia
- Treating Depression 2013 Fri 20th Sep 2013 to Fri 20th Sep 2013 London, United Kingdom.
- International Association for Suicide Prevention 27th World Congress 2013 Tue 24th Sep 2013 to Sat 28th Sep 2013 Oslo, Norway
- 49th Turkey National Psychiatry Congress 2013 Tue 24th Sep 2013 to Sat 28th Sep 2013 Izmir, Turkey
- European Association For Behavioural and Cognitive Therapy 2013 Wed 25th Sep 2013 to Sat 28th Sep 2013 Marrakech, Morocco
- 17th Spanish National Congress of Psychiatry 2013 Thu 26th Sep 2013 to Sat 28th Sep 2013 Seville, Spain
- Canadian Psychiatric Association Annual Conference 2013 Thu 26th Sep 2013 to Sat 28th Sep 2013 Ottawa, Canada
- 26th U.S. Psychiatric and Mental Health Congress 2013 Mon 30th Sep 2013 to Thu 3rd Oct 2013 Las Vegas, United States

October 2013

- European College of Neuropsychopharmacology 26th Congress 2013 Sat 5th Oct 2013 to Wed 9th Oct 2013 Barcelona, Spain
- Argentine Association of Psychiatry 21st International Congress 2013 Mon 7th Oct 2013 to Wed 9th Oct 2013 Buenos Aires, Argentina
- Faculty of General Adult Psychiatry Annual Conference 2013 Thu 10th Oct 2013 to Fri 11th Oct 2013 Manchester, United Kingdom
- Columbian Congress of Psychiatry 2013 Thu 10th Oct 2013 to Mon 14th Oct 2013 Bolívar, Colombia
- Colombian Congress of Psychiatry 2013Thu 10th Oct 2013 to Mon 14th Oct 2013 Cartagena De Indias, Colombia
- Inflammation: Emerging Therapeutic Targets in Psychiatry 2013 Sat 12th Oct 2013 to Sun 20th Oct 2013 Cortona, Italy
- 21st World Congress of Psychiatric Genetics 2013 Thu 17th Oct 2013 to Mon 21st Oct 2013 Boston, United States

- American Academy of Psychiatry and the Law Forensic Psychiatry Review Course/44th Annual Meeting 2013Mon 21st Oct 2013 to Sun 27th Oct 2013 Coronado, United States
- 3rd International Congress on Dual Disorders 2013 Wed 23rd Oct 2013 to Sat 26th Oct 2013 Barcelona, Spain
- 8th European Congress on Violence in Clinical Psychiatry 2013 Wed 23rd Oct 2013 to Sat 26th Oct 2013 Ghent, Belgium
- Brazilian Congress of Psychiatry 2013 Wed 23rd Oct 2013 to Sat 26th Oct 2013 Curitiba, Brazil
- 12th Annual Psychopharmacology Update 2013 Sat 26th Oct 2013 to Sat 26th Oct 2013 Cincinnati, United States

November 2013

- International Society for Traumatic Stress Studies 29th Annual Meeting 2013 Thu 7th Nov 2013 to Sat 9th Nov 2013 Philadelphia, United States
- Children and Adults with Attention Deficit/Hyperactivity Disorder (CHADD) 25th Annual International Conference on ADHD 7th Nov-9th Nov 2013, Crystal city, DC.
- College of Psychiatrists of Ireland Winter Conference 2013 Thu 7th Nov 2013 to Fri 8th Nov 2013 Malahide, Ireland
- Indian Association For Social Psychiatry 20th National Conference 2013 Fri 8th Nov 2013 to Sun 10th Nov 2013 Kolkata, India
- 13th International Forum on Mood and Anxiety Disorders 2013 Wed 20th Nov 2013 to Fri 22nd Nov 2013 Monte Carlo, Monaco
- International Society for Addiction Medicine 15th Annual Meeting 2013 Thu 21st Nov 2013 to Sat 23rd Nov 2013 Kuala Lumpur, Malaysia
- German Association for Psychiatry and Psychotherapy Congress 2013 Wed 27th Nov 2013 to Sat 30th Nov 2013 Berlin, Germany.

December 2013

- Australasian Society For Psychiatric Research 2013 Wed 4th Dec 2013 to Fri 6th Dec 2013 Melbourne, Australia
- American Academy of Addiction Psychiatry 24th Annual Meeting and Symposium 2013 Thu 5th Dec 2013 to Sun 8th Dec 2013 Scottsdale, United States
- 9th National Conference: Bipolar Disorder 2013 Fri 13th Dec 2013 to Fri 13th Dec 2013 London, United Kingdom

January 2014

- Annual National Conference of Indian Psychiatric Society 2014 Thu 16th Jan 2014 to Sun 19th Jan 2014, Pune, India
- 29th CINP World Congress, 22-26th June 2014, Vancouver, Canada.

Interesting Articles

- Patrick F, et al. *Genetic architectures of psychiatric disorders: the emerging picture and its implications.* Nature Reviews Genetics 2012; 13 : 537–551.
- MU - Hong Chen, et al. *Higher risk of developing mood disorders among adolescents with comorbidity of attention deficit hyperactivity disorder and disruptive behavior disorder: A nationwide prospective study.* Journal of Psychiatric Research 2013; 47 : 1019–1023.
- Schmidt SC. *Ethical Perspectives Regarding Antidepressant Drug Therapy During Pregnancy.* Journal of Student Psychiatric Nursing 2013;6: Available at: http://repository.upenn.edu/josnr/vol6/iss1/1
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- Mc Grath J, et al. *Prevention and Schizophrenia—The Role of Dietary Factors*. Schizophrenia Bulletin 2011; 37 : 272–283.
- Calvo MS, et al. *Vitamin D intake: a global perspective of current status.* J Nutr 2005; 135 : 310–316.
- Bernard P, et al. *Smoking Cessation, Depression, and Exercise: Empirical Evidence, Clinical Needs, and Mechanisms.* Nicotine Tobacco Research 2013. doi: 10.1093/ntr/ntt042
- Mentzel CL, et al. *Efficacy and Safety of Deep Brain Stimulation in Patients with Medication-Induced ardive Dyskinesia and/or Dystonia: A Systematic Review.* J Clin Psychiatry 2012; 73 : 1395-1434-1442.
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- Sharma V, Pope CJ. *Pregnancy and Bipolar Disorder: A Systematic Review.* J Clin Psychiatry 2012; 1447-1455.
- Frey et al. *Sensitivity and Specificity of the Mood Disorder Questionnaire as a Screening Tool for Bipolar Disorder During Pregnancy and the Postpartum Period.* J Clin Psychiatry 2012; 73 : 1456-1460.
- Manor I, et al. *A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Evaluating the Efficacy, Safety, and Tolerability of Extended-Release Metadoxine in Adults with attention-Deficit/ Hyperactivity Disorder* [FREE ACCESS]. J Clin Psychiatry 2012; 73 : 1517-1523.
- Szegedi A, et al. *Meta-Analyses of the Efficacy of Asenapine for Acute Schizophrenia: Comparisons With Placebo and other Antipsychotics* [FREE ACCESS]. J Clin Psychiatry 2012; 73 : 1533-1540.
- Andrade A. *Drug interactions in the Treatment of Depression in Patients with Ischemic Heart Disease.* J Clin Psychiatry 2012; 73 : e1475-e1477.
- Swartz HA, Faqiolini A. *Cardiovascular Disease and Bipolar Disorder : Risk and Clinical Implications.* J Clin Psychiatry 2012; 73 : 1563-1565.
- Rotella F, Mannucci E. *Depression as a Risk Factor for Diabetes: A Meta-Analysis of Longitudinal*

Studies. J Clin Psychiatry 2013; 74 : 31-37.

- Weiner R, et al. *Electroconvulsive Therapy Device Classification: Response to FDA Advisory Panel Hearing and Recommendations.* J Clin Psychiatry 2013; 74 : 38-42.
- Pathak S, et al. *Efficacy and Safety of Quetiapine in Children and Adolescents with Mania Associated with Bipolar I Disorder: A 3-week, Double-Blind, Placebo-Controlled Trial.* J Clin Psychiatry 2013; 74 : e100-e109.
- Yang S, et al. *Antipsychotic Drugs, Mood Stabilizers, and Risk of Pneumonia in Bipolar Disorder: A Nationwide Case-Control Study.* J Clin Psychiatry 2013; 74 : e79-e86.
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