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Contents...

Kerala Journal of Psychiatry - Instructions to Authors

Submission of Manuscripts

All submissions should be e-mailed to editoripskerala@gmail.com. Submitted manuscripts that do not follow our "Instructions to Authors" will be returned to the authors for necessary corrections.

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All manuscripts should be structured in the following order

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This page should include

1. Title (no more than 12 words)
2. Name, highest degree, and affiliation of each author
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4. Type of manuscript (original article, case report, review article, letter to editor, clinical images, etc.)
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2. Abstract

Abstracts should be constructed under the following headings:

a. Original Articles: structured abstract within 250 words under following headings
    1. Background (the rationale for the study)
    2. Methods (how the study was done)
    3. Results (major findings)
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c. Brief Communication: an unstructured abstract within 200 words.
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3. Text

The text of original articles should be divided into sections with the following headings:

1. Introduction
2. Material and Methods
3. Results
4. Discussion

Communications should be divided to

1. Introduction
2. Case report
3. Discussion

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g. Names of drugs: Use the official (generic) name throughout; trade (proprietary) names may be placed in parenthesis the first time the drug is mentioned, if necessary.
h. Numbers: Numerals from 1 to 10 are spelt out. Numerals at the beginning of the sentence are also spelt out. Numerical equivalents must precede all percentages eg: of 100 patients 30 (30%) had visual field changes.
i. Statistics: Whenever possible quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Authors should report losses to observation (such as, dropouts from a clinical trial). When data are summarized in the Results section, specify the statistical methods used to analyse them. Avoid non-technical uses of technical terms in statistics, such as 'random' (which implies a randomizing device), 'normal', 'significant', 'correlations', and 'sample'. Define statistical terms, abbreviations, and most symbols. Specify the computer software used. For all P values include the exact value and not less than 0.05 or 0.001. Mean differences in continuous variables, proportions

in categorical variables and relative risks including odds ratios and hazard ratios should be accompanied by their confidence intervals.

4. Acknowledgment

Acknowledgments should be listed on a separate page after text.

a. Granting and sponsoring agencies must be clearly acknowledged. Any source of funding must be mentioned here.
b. All contributors who do not meet the criteria for authorship should be listed in this section. Examples include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. People who have aided the author's work in any other important way may also be thanked in this section.

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Articles in Journals

Standard journal article

- Vinekar A, Dogra MR, Sangtam T, Narang A, Gupta A. Retinopathy of prematurity in Asian Indian babies weighing greater than 1250 grams at birth: Ten year data from a tertiary care center in a developing country. Indian J Ophthalmol 2007;55: 55:331-6

List the first six contributors followed by et al.

Volume with supplement

- Shen HM, Zhang QF. Risk assessment of nickel carcinogenicity and occupational lung cancer. Environ Health Perspect 1994; 102 Suppl 1:275-82.

Issue with supplement

- Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. Semin Oncol 1996; 23(1, Suppl 2):89-97.

Books and Other Monographs

Personal author(s):

- Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.

Editor(s), compiler(s) as author:

- Norman IJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

Chapter in a book

- Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: and management. 2nd ed. New York: Raven Press; 1995. pp. 465-78.

Electronic Sources as reference

Journal article on the Internet

- Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Aug 12]; 102(6): [about 3p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Monograph on the Internet

- Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National 2002 Jul 9] Available from: http://www.nap.edu/books/0309074029/html/.

Homepage of a Web site

- Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated Jul 9]. Available from: http://www.cancer-pain.org/.

Part of a homepage/Web site

- American Medical Association [homepage on the Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2 screens]. Available from: http://www.ama-assn.org/ama/pub/category/1736.html

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Type legends (maximum 40 words, excluding credit line)

a. Captions should briefly explain the figures / tables without the use of abbreviations and should be understandable without reference to the text.
b. Using double spacing, with Arabic numerals corresponding to the illustrations.
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b. Explain the internal scale (magnification) and identify the method of staining in photomicrographs.

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All submissions must be accompanied by a cover letter. Please write clearly the manuscript title. In the cover letter:

a. Mention whether the manuscript is being submitted as an Original Article, Review Article, Brief Communication, Letter to Editor, Abstract, or Other.
b. Include a statement to the editor that the paper being submitted has not been published, simultaneously submitted, or already accepted for publication elsewhere.
c. Include a statement that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.
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b. Type or print each table with double spacing on a separate sheet of paper.
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d. Number tables consecutively in the order of their first citation in the text and supply a brief title for each.
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f. For footnotes use the following symbols, in this sequence: *, †, ‡, §, ||, ¶, **, ††, ‡‡
g. Abbreviations should be explained. Place explanatory matter in footnotes, not in the heading
h. If means are used, the standard deviation (or error) and "n" should be included.
i. Report actual values of $p > 0.01$ to 2 decimal places and $p < 0.01$ to 3 decimal places; report $p < 0.001$ as "p < 0.001" only.
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The following guidelines must be followed.

a. For major revisions, the authors must provide a letter addressing each of the reviewers' comments separately and in point form by first recording the reviewer's comment and following it with the author's response.
b. The author must track all changes made in the revised manuscript.

Proofs

The editor reserves the right to correct grammar, spelling, and punctuation, to clarify obscurities and remove redundancies, to improve infelicities of style, to enhance or make appropriate the paper's organization, and to ensure that the paper (text and graphics) conforms overall to the requirements of the journal. No major changes will be made without consulting the author.

President's Page

Alcoholism and other menaces an action plan for IPS Kerala

C R Radhakrishnan
President IPS Kerala State Branch

Mental Health is gaining importance in public health due to many reasons. As per a recent WHO report 20-25% of the population suffer from mental or psychological disorders. Health is defined by WHO in its constitution as "a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity." Thus, WHO has given enough importance to mental health and social aspects in its definition of health.

Psychiatry and neurosciences and have shown tremendous growth in the last three decades. The advances in neuroimaging, biochemical research and pharmacological methods have given new hopes for better diagnosis and treatment of psychiatric illnesses. However, the common man and public still try to avoid Psychiatry due to the following reasons:

1. Stigma about psychiatric illnesses and Psychiatry itself.
2. Poor awareness about the speciality as a neuroscience.
3. Presence of fake practitioners and para-clinical personnel.
4. Fears about psychiatric drugs and ECT
5. Lack of proper laws to regulate modern psychiatric practice.

I feel that I.P.S will have to take the above problems into account to improve the practice of Psychiatry in our state.

India has a total of about 4000 psychiatrists and out of that about 400 are practising in Kerala. We have also got sufficient number of support staff like clinical psychologists, psychiatric social workers, and psychiatric nurses. Even then, a lot remains to be achieved in the field of mental health here.

Kerala government is doing a good job in the field of mental health with following services -

- Three mental hospitals
- Five medical colleges
- 14 district hospitals
- Thirty psychiatrists in taluk hospitals

National Mental Health Program is also being implemented in almost all the districts.Private sector institutions too are doing good service.

- Psychiatry is being accepted as a speciality in about 200 multispecialty hospitals.
- A big private mental hospital functions in Idukki Dt.
- Twenty self-financing medical colleges have got established Psychiatry departments.
- A huge number of psychiatric rehabilitation centres are functional in the state.

Despite all this, still we have to go so many more miles to ensure that the people of our state have good mental health.

Alcoholism

Alcoholism is one of the major menaces affecting the state of Kerala in many ways. For last 45years, after lifting of the partial control of alcohol ban by the then government in 1967, the problem of alcoholism has been increasing day by day. We have held the national first rank for literacy, population density, suicide rate, health indices, etc. But, on the other hand, we have overtaken Punjab and now hold the first place for highest per capita consumption of alcohol. Our per capita consumption of alcohol is 8.3 litres - four times the national average. The calculated per capita consumption may go further up if we exclude women and children below 15 years. As per media reports, we are now competing with France and Luxemburg. 16% of foreign liquor produced in the country is being sold in Kerala. Foreign liquor from military canteens, foreign liquor brought by NRIS, toddy and spurious liquor are also in plenty here. Reports also indicate that alcohol consumption is increasing in women and adolescents.

What is Alcohol Dependence?

Alcohol has been there with human beings as a pleasure giving substance from the beginning of history. Alcohol dependence is a chronic and progressive disease that includes difficulties in controlling one's drinking, excessive preoccupation with alcohol, continuing alcohol use despite significant harmful consequences, presence of excessive craving, and appearance of withdrawal symptoms while trying to stop or reduce alcohol use. Common withdrawal symptoms include tremors, sleep problems, irritability, etc.

Withdrawal may also progress to delirium, a condition characterized by disorientation, irrelevant talk, memory disturbances, aggressiveness, etc.

Causes and Risk Factors

Alcoholism is reported to have genetic, psychological, social and environmental causes. The common risk factors for development of alcoholism are:

1. Age of first use- there is higher risk of development of dependence if alcohol use starts at an early age.
2. Family history- there is a higher risk if one's close relatives suffer from alcohol dependence.
3. Mood disorders- especially depression.
4. Social and cultural factors- like the current situation in Kerala.

Consequences of excessive alcohol use

Alcohol affects all vital organs of body.

CNS- Alcohol depresses CNS and causes sedation, disinhibition, muscular incoordination and slurring of speech

LIVER- Continuous alcohol use leads to fatty hepatomegaly and liver fibrosis. These may gradually progress to cirrhosis of liver.

GIT- Alcohol increases the chances of development of peptic ulcers in stomach and duodenum.

Sexual-Erectile dysfunction is frequently reported in alcoholics.

Birth defects- Use of alcohol by pregnant women can lead to foetal alcoholic syndrome.

Accidents- Road traffic accidents are common in alcoholics. These usually lead to injuries like subdural haematoma.

Management of alcoholism

There are three components to the management of alcoholism. They are - Medical management, Psychosocial treatments, and Rehabilitation.

the extent of physical damage caused by chronic alcohol use, detoxification treatment to control the withdrawal symptoms, and administration of intravenous fluids and vitamin supplements to compensate for the dehydration and nutritional deficiencies. Subsequently, medications like acamprosate, disulfiram, etc. can be used to reduce craving and prevent relapses. Medications also have a role in management of comorbid psychiatric disorders.

Psychosocial treatments

Individual and group counselling and family counselling can be provided by clinical psychologists and medical social workers. Rehabilitation treatment and follow up is also important.

Kerala is facing a big problem due to increasing number of patients with alcohol dependence. I.P.S. should take lead in the fight against this problem which causes occupational crisis, social issues, and financial problems. I would like to put forward the following suggestions.

1. Legal age of consumption may be raised to 25
2. Alcohol shops and bars may function only between 3 PM and 11 PM
3. No more new shops or bars may be sanctioned.
4. As the government and beverages cooperation are making crores of rupees, they should also give importance to de-addiction and rehabilitation of patients.
5. Government should start a centre of excellence that can take up the lead role in management, training, and research on alcoholism in the state.
6. Government should start measures against fake practitioners who cheat patients and their families.

Editorial

Neurosurgical Treatment of Refractory Psychiatric Disease: A Review

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Keywords : Deep brain stimulation (DBS), psychosurgery, functional neurosurgery, lesioning

Introduction

Functional neurosurgery is that branch of neurosurgery which involves the surgical alteration of the nervous system to treat neurological disease. Functional neurosurgical approaches can also be highly effective in the treatment of psychiatric illness refractory to standard medical therapy. The safety and effectiveness of psychiatric neurosurgery are highly dependent on appropriate patient selection, high-resolution preoperative neuroimaging and intra-operative brain mapping, target selection, and surgical execution by appropriately trained functional neurosurgeons. In this article, we briefly review the intriguing history and evolution of psychiatric neurosurgery. We begin by considering early lesioning procedures, which were refined by the development of the concept of stereotaxy. We then move on to consider the modern treatment of psychiatric illness using radiosurgery as well as the current leading technique in the functional neurosurgeon's armamentarium, deep brain stimulation (DBS). We conclude with a consideration of some of the key ethical concerns underlying surgery for psychiatric illness with which psychiatrists and neurosurgeons alike must be familiar.

Early Lesioning Neurosurgery

For many, the concept of the neurosurgical management of psychiatric illness evokes a visceral reactionperhaps even overt oppositionbecause of the negative connotations of prefrontal lobotomy as championed by Freeman and Watts[15]. However, prefrontal lobotomy was preceded by several earlier attempts to use neurosurgical techniques to treat patients with psychiatric disorders.

Modern efforts at cerebral localization commenced in the 19th century as scientists began exploring the brain-behaviour link through the study of patients who had sustained focal brain injuries. Familiar cases such as that of Phineas Gage (who exhibited disinhibition due to prefrontal cortical damage), and the aphasia case series of Broca and Wernicke[7,24,85], opened the door to the possibility of treating neurological conditions by removing or damaging the dysfunctional regions of the brain which caused them.

In 1886, the neurosurgical pioneer, sir Victor Horsley, carried out the first open focal resections of the motor cortex to relieve involuntary movements[28,82]. Shortly thereafter, in 1891, Gottlieb Burckhardt, a Swiss psychiatrist, applied lesioning to patients with psychiatric disturbances. He published the results of a series of six "topectomy" procedures which involved multiple focal cortical resections of the frontal, temporal, and parietal lobes in the treatment of agitation[16,33]. Unfortunately, his work, widely criticised for a lack of efficacy and its failure to employ systematic assessments, was abandoned until neurosurgeons such as Puusepp in 1910, and later Penfield, rekindled interest into the effects of frontal lobe lesioning[41,84]. Despite considerable opposition, it was at this point, near the start of the 20th century, that the notion that focal cerebral resections could bring specific therapeutic effect against psychiatric disorders began to gain popularity.

The Legacy of Frontal Lobotomy

Based on the work of Fulton and Jacobsen which uncovered the anxiolytic effect of damaging the frontal lobe white matter in chimpanzees, neurologist Egas Moniz and his neurosurgeon colleague Almeida Lima carried out experimental investigation of a similar approach in humans, performing over 100 open frontal leukotomy procedures on institutionalized patients[13]. Thereafter, Walter Freeman and James Watts enthusiastically promoted and performed a modified version of the Moniz lobotomy which ultimately came to be executed via a transorbital approach (i.e., the now infamous "ice pick" lobotomy). This procedure became wildly popular in the United States, in part due to the lack of effective psychiatric medications and heavy burden of housing psychiatric inpatients in asylums of the time. As the popularity of the approach grew, operators alarmingly came to include non-surgeons and eventually even non-physicians, with a commensurate decrease in attention to technique and sterility[55]. It was this questionable, overly exuberant application of transorbital lobotomy combined with the frequent side effectssuch as abulia, inattention, disinhibition, infection, coma or deathwhich resulted in a considerable and nearly fatal backlash against psychiatric surgery from medical and lay communities.

Stereotactic Neurosurgery

Psychiatric surgery was effectively kept alive from the 1930s by the developmentin parallel with open lesioning proceduresof the concept of neurosurgical stereotaxis. In stereotactic surgery, the brain is defined in relation to a three-dimensional Cartesian coordinate system which permits the highly accurate delivery of an intracranial probe to a specific target while minimizing damage to surrounding brain structures[17]. Frame-based stereotactic procedures require temporary attachment of a stereotactic frame to the patient's skull such that it remains fixed in space relative to bony anatomy of the skull (and by extension the intracranial brain matter) throughout the operation[80]. The first stereotactic frame, the Horsley-Clarke apparatus, was designed by Victor Horsley and Robert Clarke in 1908 to be used primarily in animal experimental work. The first human stereotactic frames were developed in the 1940s concurrently by Leksell in Europe, and Spiegel and Wycis in North America. Initially, targeting was based on known relationships between extracranial landmarks and internal neuroanatomy. However, because the concordance between extracranial and intracranial anatomy is highly variable between individuals, targeting was refined by using intraoperative ventriculography to identify consistent neuroanatomical structures such as the anterior and posterior commissures, which went on to become the standard origin in most stereotactic coordinate systems. Eventually, stereotactic atlases of the human brain were developedsuch as one by Schaltenbrand and Wahren published in 1977allowing navigation to particular intracranial coordinates corresponding to particular structures in the *average* brain[75]. Currently, stereotactic neurosurgical procedures involve imaging patients with MRI or CT once the frame has been applied; sophisticated targeting software is then used to determine the coordinatesin so-called stereotactic frame spaceof target structures identified visually on acquired images.

Lesioning Procedures for Psychiatric Conditions

Frame-based stereotactic ablative procedures were developed during the 1950s and were employed at selected centres for the next three decades to treat medically refractory psychiatric conditions, including anxiety disorders and mood disorders. Though understanding of the neuroanatomical underpinnings of psychiatric illness remained somewhat primitive, common psychosurgical lesioning procedures were nominally based on disrupting orbitofrontal, prefrontal and/or cingulate cortical connections to the basal ganglia or thalamus. Lesions were generated using heat, alcohol injection, mechanical trauma or radiation (see below for more details on this last modality)[6]. Specific lesioning procedures included anterior cingulotomy, capsulotomy, subcaudate tractotomy and limbic leucotomy (see Table 1 for indications, target, potential side effects and efficacy)[8,12,18,22,25,26,34-36,43,62,68,70,79]. Currently, conventional stereotactic lesioning procedures remain an effective option for carefully selected patients without suitable medical alternatives who are prepared to accept the small but real risk of intracerebral hemorrhage (on the order of 2%) which can produce permanent neurological deficits. However, they have largely been replaced by radiosurgical and neuromodulatory approaches which are described below.

Radiosurgery

Targeted lesions of the brain can also be created through incisionless stereotactic radiosurgery (SRS). SRS involves the focused application of ionizing radiation to a specific target defined by high-resolution imaging using either a rigidly attached stereotactic cranial reference frame or a stereotactic image-guidance system in up to a maximum of five distinct sessions[5]. The targeted tissue is either completely destroyed or inactivated via radiation-induced injury, while adjacent structures are spared of damage due to steep dose gradients. Unlike conventional neurosurgical lesioning, SRS does not pose a risk of intracerebral hemorrhage since it does not involve the passage of any probes into the brain. Modern radiosurgery is commonly performed using fixed source of cobalt gamma radiation (Gamma Knife), or a frameless linear-accelerator (LINAC)-based device (e.g., Cyber-Knife).

Radiosurgery for psychiatric disorders was first performed in the early 1950s by Lars Leksell to lesion the anterior limb of the internal capsule (ALIC) in a patient with refractory obsessive-compulsive disorder (OCD) following the success achieved by Jean Talairach with open anterior capsulotomy as a less drastic alternative to prefrontal lobotomy[44,45]. Capsulotomy lesions are reported to disrupt fibers connecting the mediodorsal thalamus and the prefrontal cortex[72]. The accumulated evidence to date is limited to a number of case series that report improvement in 53 73% of patients following gamma knife bilateral anterior capsulotomy, although targeting, dose and outcome assessment are quite heterogeneous[20,37,46,49,60,61,71-73,78]. In an uncontrolled, retrospective comparison of conventional neurosurgical capsulotomy versus radiosurgical gamma capsulotomy there was no significant difference in the observed reduction of mean Yale-Brown Obsessive Compulsive Rating Scale (Y-BOCS)[72,73]. A clinically meaningful response (≥35% reduction of Y-BOCS score relative to baseline) was seen in 12 of 25 patients at long-term follow up. Consensus does not yet exist across several technical and methodological issues, such as the ideal number of radiation isocentres ("shots") within the target, or ideal radiation dose. Some groups advocate a bilateral, single isocentre technique,[72,73,78] while others support a bilateral, double isocentre approach[37,49].

Typical radiation dose varies from 140 180 Gy, although doses of up to 200 Gy have been reported albeit with greater propensity for side effects and evidence of expansion of the lesion beyond the planned target volume[45,78].

Potential adverse effects of gamma capsulotomy may include weight gain, executive dysfunction, apathy, emotional blunting, fatigue, urinary incontinence or disinhibition (Table 1)[45,74]. Post-operative MRI analysis of radiosurgical lesions suggests that minimizing the lateral extent of the lesion may improve OCD symptom relief while reduction of the posteromedial extent of the lesion may mitigate adverse events[73].

Although radiosurgical treatment of OCD and potentially other refractory psychiatric conditions clearly requires further investigation to clarify the ideal target volume, dose and technique radiosurgery currently does play a role in treatment of these challenging conditions in centres where equipment and expertise are available. Further randomized-controlled studies will be required to assess true efficacy and to compare SRS with reversible, neuromodulatory treatments such as DBS, which we address below.

Deep Brain Stimulation (DBS)

DBS is the chronic, reversible use of high-frequency (typically 100Hz or greater) direct electrical current, applied to a group of neural elements (neurons, axons, dendrites) in order to bring about functional alteration of the stimulated structures within the context of larger dysfunctional circuits to which they belong[38]. DBS is a well-established and widely used therapy in the treatment of patients with movement disorders such as Parkinson's Disease, dystonia, and Essential Tremor. In addition to being reversible, a key advantage of DBS over lesioning is it can be fined-tuned by the changing stimulation parameters such as voltage/current, pulse width, frequency and electrode configuration. Together, these can influence the size and shape of the electrical field which is generated (and therefore the clinical effect). Practically, the key components to a DBS system include a platinum-iridium DBS lead with four or more electrode contacts that is implanted in brain and attached to a lead extension that connects subcutaneously to a battery-powered pulse generator housed in the subclavicular region.

Neurosurgical implantation of the DBS lead to that target is accomplished via stereotaxy using MRI scans with the patient typically in a stereotactic frame. Intraoperative neurophysiological recording or stimulation (with an awake patient) may also be used to help verify the correct lead location and to ensure no early stimulation-related side effects. Thereafter, the lead is fixed to the skull, connected to a lead extension, and tunneled subcutaneously to the pulse generator.

Potential side effects of DBS implantation include intracerebral hemorrhage (1-2%), infection, hardware malfunction, stimulation-related side effects or emergence of stimulation tolerance[87].

The exact mechanism of action of DBS remains unknown. At the synaptic level DBS has also been shown to influence release or accumulation of neurotransmitter[42], but at a wider level DBS was initially thought to work simply by creating a reversible lesion that decreased local neural activity at the stimulation target[50]. In fact, this explanation appears to be an oversimplification and the current leading putative mechanism is that DBS modulates pathological activity within brain circuits by acting on specific nodes within the network[58]. In certain targets and in certain disease states, DBS has been demonstrated to decrease circuit-wide neurotransmission by "neural jamming" within affected circuits. In other circumstances, however, stimulation results in potentiated transmission via stochastic resonance[23,63]. Therefore, as Lozano and Lipsman put it, DBS can either help restore a more normal pattern of activity within pathological circuits, either directly or indirectly by substituting pathologic network activity with a more adaptive pattern both locally and at a distance from the stimulation region[23,50].

DBS for psychiatric disorders is still very much in its infancy; to date the most commonly studied indications include treatment-resistant depression (TRD) and OCD. DBS for TRD is still completely investigational, with all patients to date treated either in the context of a clinical trial, or with permission for off-label use. The most commonly used definition for TRD includes those patients with a diagnosis of major depressive disorder (MDD) with concurrent major depressive episode (MDE) of at least 1 year duration, who have failed to respond to at least 4 adequate treatment trials (which may include antidepressant medications, psychotherapy, or electroconvulsive therapy) who are not acutely suicidal. Although a number of DBS targets have been studied (see Table 2 for summary), the most rigorously investigated so far has been the subcallosal cingulate (SCG) region. Functional imaging studies have shown that depressed patients exhibit overactivity in the SCG region with an accompanying decrease in activity in the prefrontal cortex[56,57]. It has also been found that normal prefrontal cortex activity is restored by bilateral DBS in SCG. Clinically, long-term follow of TRD patients with SCG DBS has found remarkable anti-depressant response rates of 50 92% ("response" is typically defined by a decrease of Hamilton Depression Rating Score (HDRS) from baseline of 50% or more) and remission rates between 33 58% (typically defined as HDRS of less than 8). A recent randomized, single-blinded, sham-stimulation study of TRD (including both MDD and bipolar II disorder patients) found response in

7/17 (41%) and remission in 3/17 (18%) patients at 24 weeks follow-up improving to 11/12 (92%) and 7/12 (58%) at 2 years follow-up[27]. Notably these authors describe only a minimal sham stimulation effect following surgical implantation preceding the active stimulation phase, suggesting that the effect of SCG DBS is more than merely due to placebo.

Refractory OCD has also been treated with DBS, under a so-called Humanitarian Device Exemption (HDE) in North America and Europe. A current definition of medically refractory OCD is: the failure of at least three adequate trials of Serotonin Reuptake Inhibitors (SRI) (including clomipramine as one trial) along with two or more atypical antipsychotics as augmenting agents, as well as the failure of behavioural therapy while on a therapeutic dose of one SRI, to produce a decline of Y-BOCS score of 25% or more or to meaningfully alleviate functional impairment from their illness[31]. There are several case series and some randomized trials of DBS for OCD at several stimulation targets, including the ALIC[1,65,66], nucleus accumbens (NAcc)[10,30,81], ventral caudate/ventral striatum (VC/VS)[19,21,67], inferior thalamic peduncle (ITP)[32], and subthalamic nucleus (STN)[52] (summarized in Table 2).

The success of DBS in the treatment of refractory movement disorders and psychiatric conditions mentioned above has encouraged investigation into potential utility of DBS in other psychiatric conditions such as addiction (bilateral NAcc[39,53,64,86]), Anorexia Nervosa (SCG[48]) and Tourette syndrome (bilateral thalamic[2-4,29,51,69,76,77,83], pallidal[3,9,11,54,59], ALIC[14,40], and NAcc[40]). In Tourette syndrome in particular, four randomized controlled trials have been completed and all of them found statistically significant benefit in Y-BOCS scores, though there is still debate over the ideal DBS target.

Ethical considerations

Patients considering functional surgery for the treatment of medically refractory psychiatric disease are frequently a vulnerable group. This, coupled with the well-intentioned enthusiasm of psychiatrists and neurosurgeons to recruit these patients into clinical trials, demands the development of clear-cut guidelines and oversight regarding inclusion criteria, supervision of patients enrolled in trials, and assessment of the capacity to provide informed consent. A recent review on the topic of consent in clinical trials of psychiatric DBS by Lipsman and colleagues summarizes salient issues such as patient understanding of the research-therapy distinction, establishing clear expectations, and rigorous assessment of reality testing and cognitive ability in order to establish appropriate informed consent from patients with psychiatric illness[47]. The complex neuroethical landscape of the surgical treatment of refractory psychiatric disease demands the diverse skills of a multidisciplinary team. It is critical that the decision to proceed with surgerywhether within or outside the confines of a clinical trialis made in close consultation with the patient and only with the consensus of several different team members including the implanting neurosurgeon, psychiatrists, social workers, mental health nurses, and occasionally a clinical ethicist.

Conclusions

Functional neurosurgery is an exciting, rapidly-changing field that provides several targeted approaches to rectifying dysfunction of the nervous system in patients with refractory psychiatric conditions. Technological advancements, in particular in the areas of high-resolution anatomical and functional brain mapping, coupled with a greater understanding of the neuroanatomical and neurochemical basis of psychiatric diseases, will continue to push the field forward. Practitioners in the fieldincluding both neurosurgeons and psychiatrists alikemust continue to investigate the safety and efficacy of new and existing functional surgery techniques using sound scientific approaches, while always remaining aware of vital ethical principles which will ensure the renewed and continued confidence of patients suffering from severe psychiatric illness, and the public at large.

References

1. Abelson J, Curtis G, Sagher O, Albucher R, Harrigan M, Taylor S, et al: Deep brain stimulation for refractory obsessive-compulsive disorder. **Biological Psychiatry 57:**510-516, 2005
2. Ackermans L, Duits A, Temel Y, Winogrodzka A, Peeters F, Beuls E, et al: Long-term outcome of thalamic deep brain stimulation in two patients with Tourette syndrome. **Journal of Neurology Neurosurgery and Psychiatry 81:**1068-1072, 2010
3. Ackermans L, Temel Y, Cath D, van der Linden C, Bruggeman R, Kleijer M, et al: Deep brain stimulation in Tourette's syndrome: Two targets? **Movement Disorders 21:**709-713, 2006
4. Bajwa R, de Lotbiniere A, King R, Jabbari B, Quatrano S, Kunze K, et al: Deep brain stimulation in Tourette's syndrome. **Movement Disorders 22:**1346-1350, 2007
5. Barnett G, Linskey M, Adler J, Cozzens J, Friedman W, Heilbrun M, et al: Stereotactic radiosurgery - an organized neurosurgery-sanctioned definition. **Journal of Neurosurgery 106:**1-5, 2007
6. Benabid A, Chabardes S, Seigneuret E: Deep-brain stimulation in Parkinson's disease: long-term efficacy and safety - What happened this year? **Current Opinion in Neurology 18:**623-630, 2005
7. Broca P: Sur le liege de la faculte due language article. **Bull. Soc. Anthropol:**377 - 393, 1865
8. Cho D, Lee W, Chen C: Limbic leukotomy for intractable major affective disorders: A 7-year follow-up study using nine comprehensive psychiatric test evaluations. **Journal of Clinical Neuroscience 15:**138-142, 2008
9. Dehning S, Mehrkens J, Muller N, Botzel K: Therapy-refractory Tourette syndrome: Beneficial outcome with globus pallidus internus deep brain stimulation. **Movement Disorders 23:**1300-1302, 2008
10. Denys D, Mantione M, Figee M, van den Munckhof P, Koerselman F, Westenberg H, et al: Deep Brain Stimulation of the Nucleus Accumbens for Treatment-Refractory Obsessive-Compulsive Disorder. **Archives of General Psychiatry 67:**1061-1068, 2010

11. Diederich N, Kalteis K, Stamenkovic M, Pieri V, Alesch F: Efficient internal pallidal stimulation in Gilles de la Tourette syndrome: A case report. **Movement Disorders 20:**1496-1499, 2005
12. Dougherty D, Baer L, Cosgrove G, Cassem E, Price B, Nierenberg A, et al: Prospective long-term follow-up of 44 patients who received cingulotomy for treatment-refractory obsessive-compulsive disorder. **American Journal of Psychiatry 159:**269-275, 2002
13. Moniz E: Prefrontal leucotomy in the treatment of mental disorders. **Am. J. Psychiatry 93:**1379 - 1385, 1937
14. Flaherty A, Williams Z, Amirnovin R, Kasper E, Rauch S, Cosgrove G, et al: Deep brain stimulation of the anterior internal capsule for the treatment of tourette syndrome: technical case report. **Neurosurgery 57**, 2005
15. Freeman W, Watts JW: An Interpretation of the Functions of the Frontal Lobe: Based upon Observations in Forty-Eight Cases of Prefrontal Lobotomy. **Yale J Biol Med 11:**527-539, 1939
16. Burckhardt G: Uber rindexcisionen, als beitrag zur operativen therapie der psychosen. **Allg. Z. Psychiatr. Psych. Med. 47:**463 - 548, 1891
17. Gildenberg PL: Where have we been? Where are we going? **Stereotact Funct Neurosurg 68:**1-9, 1997
18. Goktepe E, Young L, Bridges P: Further review of results of stereotactic subcaudate tractotomy. **British Journal of Psychiatry 126:**270-280, 1975
19. Goodman W, Foote K, Greenberg B, Ricciuti N, Bauer R, Ward H, et al: Deep Brain Stimulation for Intractable Obsessive Compulsive Disorder: Pilot Study Using a Blinded, Staggered-Onset Design. **Biological Psychiatry 67:**535-542, 2010
20. Gouvea F, Lopes A, Greenberg B, Canteras M, Taub A, Mathis M, et al: Response to sham and active gamma ventral capsulotomy in otherwise intractable obsessive-compulsive disorder. **Stereotact Funct Neurosurg 88:**177-182, 2010
21. Greenberg B, Gabriels L, Malone D, Rezai A, Friehs G, Okun M, et al: Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. **Molecular Psychiatry 15:**64-79, 2010
22. Greenberg B, Rauch S, Haber S: Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. **Neuropsychopharmacology 35:**317 - 336, 2009
23. Greenberg B, Rezai A: Mechanisms and the current state of deep brain stimulation in neuropsychiatry. **Cns Spectrums 8:**522-526, 2003
24. Harlow J: Recovery from the passage of an iron bar through the head. **N. Eng. J. Med.:**389 - 392, 1848
25. Hay P, Sachdev P, Cumming S, Smith J, Lee T, Kitchener P, Et Al: Treatment of obsessive-compulsive disorder by psychosurgery. **Acta Psychiatrica Scandinavica 87:**197-207, 1993
26. Hodgkiss A, Malizia A, Bartlett J, Bridges P: Outcome after the psychosurgical operation of stereotaxic subcaudate tractotomy. **Journal of Neuropsychiatry and Clinical Neurosciences 7:**230-234, 1995
27. Holtzheimer P, Kelley M, Gross R, Filkowski M, Garlow S, Barrocas A, et al: Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Unipolar and Bipolar Depression. **Archives of General Psychiatry 69:**150-158, 2012
28. Horsley V: Brain surgery. **British Medical Journal 2:**670 - 675, 1886
29. Houeto J, Karachi C, Mallet L, Pillon B, Damier P, Agid Y: Tourette disorders and deep brain stimulation. **Movement Disorders 20:**S156-S156, 2005
30. Huff W, Lenartz D, Schormann M, Lee S, Kuhn J, Koulousakis A, et al: Unilateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: Outcomes after one year. **Clinical Neurology and Neurosurgery 112:**137-143, 2010
31. Husted D, Shapira N: A review of the treatment for refractory obsessive-compulsive disorder: From medicine to deep brain stimulation. **Cns Spectrums 9:**833-847, 2004
32. Jimenez F, Nicolini H, Lozano A, Piedimonte F, Salin R, Velasco F: Electrical Stimulation of the Inferior Thalamic Peduncle in the Treatment of Major Depression and Obsessive Compulsive Disorders. **World Neurosurgery 80**, 2013
33. Joanette Y, Stemmer B, Assal G, Whitaker H: From theory to practice - the unconventional contribution of burckhardt,gottlieb to psychosurgery. **Brain and Language 45:**572-587, 1993
34. Jung H, Kim C, Chang J, Park Y, Chung S, Chang J: Bilateral anterior cingulotomy for refractory obsessive-compulsive disorder: Long-term follow-up results. **Stereotactic and Functional Neurosurgery 84:**184-189, 2006
35. Kelly D, Richardson N, Mitchell-Higgs N, Greenup J, Chen C, RJ H: Stereotactic limbic leucotomy: a preliminary report on forty patients. **Br J Pscyhiatry 123:**141 - 148, 1973
36. Kim M, Lee T, Choi C: Review of long-term results of stereotactic psychosurgery. **Neurologia Medico-Chirurgica 42:**365-371, 2002
37. Kondziolka D, Flickinger JC, Hudak R: Results following gamma knife radiosurgical anterior capsulotomies for obsessive compulsive disorder. **Neurosurgery 68:**28-32; discussion 23-23, 2011
38. Kringelbach M, Jenkinson N, Owen S, Aziz T: Translational principles of deep brain stimulation. **Nature Reviews Neuroscience 8:**623-635, 2007
39. Kuhn J, Lenartz D, Huff W, Lee S, Koulousakis A, Klosterkoetter J, et al: Remission of alcohol dependency following deep brain stimulation of the nucleus accumbens: valuable therapeutic implications? **Journal of Neurology Neurosurgery and Psychiatry 78:**1152-1153, 2007
40. Kuhn J, Lenartz D, Mai J, Huff W, Lee S, Koulousakis A, et al: Deep brain stimulation of the nucleus accumbens and the internal capsule in therapeutically refractory Tourette-syndrome. **Journal of Neurology 254:**963-965, 2007
41. Puusepp L: Alcune considerazioni sugli interventi chirugici nelle malattie mentali. **G. Accad. Med. Torino 100:**3 - 16, 1937
42. Lee K, Chang S, Roberts D, Kim U: Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. **Journal of Neurosurgery 101:**511-517, 2004
43. Leiphart J, Valone F: Stereotactic lesions for the treatment of psychiatric disorders. **Journal of Neurosurgery 113:**1204-1211, 2010
44. Leksell L: stereotactic radiosurgery. **Journal of Neurology Neurosurgery and Psychiatry 46:**797-803, 1983
45. Leveque M, Carron R, Regis J: Radiosurgery for the Treatment of Psychiatric Disorders: A Review. **World Neurosurgery 80**, 2013
46.Lippitz B, Mindus P, Meyerson B, Kihlstrom L, Lindquist C: Lesion topography and outcome after thermocapsulotomy or gamma knife capsulotomy for obsessive-compulsive disorder: Relevance of the right hemisphere. **Neurosurgery 44:**452-458, 1999
47. Lipsman N, Giacobbe P, Bernstein M, Lozano A: Informed consent for clinical trials of deep brain stimulation in psychiatric disease: challenges and implications for trial design. **Journal of Medical Ethics 38:**107-111, 2012
48. Lipsman N, Woodside D, Giacobbe P, Hamani C, Carter J, Norwood S, et al: Subcallosal cingulate deep brain stimulation for treatment-refractory anorexia nervosa: a phase 1 pilot trial. **Lancet 381:**1361-1370, 2013
49. Lopes AC, Greenberg BD, Norén G, Canteras MM, Busatto GF, de Mathis ME, et al: Treatment of resistant obsessive-compulsive disorder with ventral capsular/ventral striatal gamma capsulotomy: a pilot prospective study. **J Neuropsychiatry Clin Neurosci 21:**381-392, 2009
50. Lozano A, Lipsman N: Probing and Regulating Dysfunctional Circuits Using Deep Brain Stimulation. **Neuron 77:**406-424, 2013
51. Maciunas R, Maddux B, Riley D, Whitney C, Schoenberg M, Ogrocki P, et al: Prospective randomized double-blind trial of bilateral thalamic deep brain stimulation in adults with Tourette

syndrome. **Journal of Neurosurgery 107:**1004-1014, 2007

52. Mallet L, Polosan M, Jaafari N, Baup N, Welter M, Fontaine D, et al: Subthalamic Nucleus Stimulation in Severe Obsessive-Compulsive Disorder. **New England Journal of Medicine 359:**2121-2134, 2008
53. Mantione M, van de Brink W, Schuurman P, Denys D: Smoking Cessation and Weight Loss After Chronic Deep Brain Stimulation of the Nucleus Accumbens: Therapeutic and Research Implications: Case Report. **Neurosurgery 66:**218-218, 2010
54. Martinez-Fernandez R, Zrinzo L, Aviles-Olmos I, Hariz M, Martinez-Torres I, Joyce E, et al: Deep Brain Stimulation for Gilles de la Tourette Syndrome: A Case Series Targeting Subregions of the Globus Pallidus Internus. **Movement Disorders 26:**1922-1930, 2011
55. Mashour G, Walker E, Martuza R: Psychosurgery: past, present, and future. **Brain Research Reviews 48:**409-419, 2005
56. Mayberg H, Liotti M, Brannan S, McGinnis S, Mahurin R, Jerabek P, et al: Reciprocal limbic-cortical function and negative mood: Converging PET findings in depression and normal sadness. **American Journal of Psychiatry 156:**675-682, 1999
57. Mayberg H, Lozano A, Voon V, McNeely H, Seminowicz D, Hamani C, et al: Deep brain stimulation for treatment-resistant depression. **Neuron 45:**651-660, 2005
58. McIntyre C, Hahn P: Network perspectives on the mechanisms of deep brain stimulation. **Neurobiology of Disease 38:**329-337, 2010
59. Mehrkens J, Boetzel K, Leitner B, Feddersen B, Muller N, Dehning S: Successful GPi-Deep brain stimulation in Tourette syndrome (GTS) - Much more than improvement of tics. **Movement Disorders 27:**S319-S319, 2012
60. Mindus P, Bergstrom K, Levander S, Noren G, Hindmarsh T, Thuomas K: Magnetic-resonance images related to clinical outcome after psychosurgical intervention in severe anxiety disorder. **Journal of Neurology Neurosurgery and Psychiatry 50:**1288-1293, 1987
61. Mindus P, Levander S, Nyman H, Bergstrom K, Noren G: Stereotaxic gamma-capsulotomy in anxiety and obsessive-compulsive states - a prospective, multidisciplinary assessment. **International Journal of Neuroscience 32:**486-486, 1987
62. Mitchell-Higgs N, Kelly D, Richardson A: Stereotactic limbic leukotomy--a follow-up at 16 months. **Br J Psychiatry 128:**226 - 240, 1976
63. Montgomery E, Baker K: Mechanisms of deep brain stimulation and future technical developments. **Neurological Research 22:**259-266, 2000
64. Muller U, Sturm V, Voges J, Heinze H, Galazky I, Heldmann M, et al: Successful Treatment of Chronic Resistant Alcoholism by Deep Brain Stimulation of Nucleus Accumbens: First Experience with Three Cases. **Pharmacopsychiatry 42:**288-291, 2009
65. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B: Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. **Lancet 354:**1526-1526, 1999
66. Nuttin B, Gabriels L, van Kuyck K, Cosyns P: Electrical stimulation of the anterior limbs of the internal capsules in patients with severe obsessive-compulsive disorder: anecdotal reports. **Neurosurgery Clinics of North America 14:**267-+, 2003
67. Okun M, Mann G, Foote K, Shapira N, Bowers D, Springer U, et al: Deep brain stimulation in the internal capsule and nucleus accumbens region: responses observed during active and sham programming. **Journal of Neurology Neurosurgery and Psychiatry 78:**310-314, 2007
68. Patel S, Aronson J, Sheth S, Eskandar E: Lesion Procedures in Psychiatric Neurosurgery. **World Neurosurgery 80**, 2013
69. Porta M, Brambilla A, Cavanna A, Servello D, Sassi M, Rickards H, et al: Thalamic deep brain stimulation for treatment-refractory Tourette syndrome Two-year outcome. **Neurology 73:**1375-1380, 200970. Poynton A, Bridges P, Bartlett J: Resistant bipolar affective-disorder treated by stereotactic subcaudate tractotomy. **British Journal of Psychiatry 152:**354-358, 1988
71. RA DV, SR G, E A, M P-P: Psychiatric radiosurgery by gamma-knife. **Salud mental 29:**18-27, 2006
72. Ruck C, Andreewitch S, Flyckt K, Edman G, Nyman H, Meyerson B, et al: Capsulotomy for refractory anxiety disorders: Long-term follow-up of 26 patients. **American Journal of Psychiatry 160:**513-521, 2003
73. Ruck C, Karlsson A, Steele J, Edman G, Meyerson B, Ericson K, et al: Capsulotomy for obsessive-compulsive disorder - Long-term follow-up of 25 patients. **Archives of General Psychiatry 65:**914-922, 2008
74. Rück C, Karlsson A, Steele JD, Edman G, Meyerson BA, Ericson K, et al: Capsulotomy for obsessive-compulsive disorder: long-term follow-up of 25 patients. **Arch Gen Psychiatry 65:**914-921, 2008
75. Schaltenbrand G, Wahren W: **Atlas for stereotaxy of the human brain**: Thieme, 1977
76. Servello D, Porta M, Sassi M, Brambilla A, Robertson M: Deep brain stimulation in 18 patients with severe Gilles de la Tourette syndrome refractory to treatment: the surgery and stimulation. **Journal of Neurology Neurosurgery and Psychiatry 79:**136-142, 2008
77. Servello D, Sassi M, Brambilla A, Defendi S, Porta M: Long-Term, Post-Deep Brain Stimulation Management of a Series of 36 Patients Affected With Refractory Gilles de la Tourette Syndrome. **Neuromodulation 13:**187-194, 2010
78. Sheehan JP, Patterson G, Schlesinger D, Xu Z: γ knife surgery anterior capsulotomy for severe and refractory obsessive-compulsive disorder. **J Neurosurg 119:**1112-1118, 2013
79. Spangler W, Cosgrove G, Ballantine H, Cassem E, Rauch S, Nierenberg A, et al: Magnetic resonance image-guided stereotactic cingulotomy for intractable psychiatric disease. **Neurosurgery 38:**1071-1076, 1996
80. Spiegel E, Wycis H, Marks M, Lee A: Stereotaxic apparatus for operations on the human brain. **Science 106:**349-350, 1947
81. Sturm V, Lenartz D, Koulousakis A, Treuer H, Herholz K, Klein J, et al: The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. **Journal of Chemical Neuroanatomy 26:**293-299, 2003
82. Horsley V: Remarks on ten consequtive cases of operations upon the brain and cranial cavity to illustrate the details and safety of the method employed. **British medical journal 1:**863 - 865, 1887
83. Vandewalle V, van der Linden C, Groenewegen H, Caemaert J: Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. **Lancet 353:**724-724, 1999
84. Penfield W, Evans J: The frontal lobe in man: a clinical study of maximal removals. **Brain 58:**115 - 133, 1935
85. Wernicke C: **Aphasische Symptomen Complex.** Breslau: Max Cohn & Weigert, 1874
86. Zhou H, Xu J, Jiang J: Deep Brain Stimulation of Nucleus Accumbens on Heroin-Seeking Behaviors: A Case Report. **Biological Psychiatry 69:**E41-E42, 2011
87. Zrinzo L, Foltynie T, Limousin P, Hariz M: Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review Clinical article. **Journal of Neurosurgery 116:**84-94, 2012

Table 1: Summary of stereotactic lesioning procedures for psychiatric conditions

Procedure	Specific Target	Methods Available	Diseases	Potential Side Effects	Efficacy
Capsulotomy	ALIC	Thermocoagulation, Radiosurgery	OCD	Transient: headache, confusion. Long-term: weight gain, fatigue, amnesia, suicidality, lethargy, delayed cyst formation (radiosurgery only)	35 - 70% improvement[1-4]
Cingulotomy	Anterior cingulate white matter	Electrocoagulation	OCD MDD BPD	Long-term: incontinence, seizures	OCD: 32 - 48% reduction in YBOCS[5-6] MDD: 60% respond[2] BPD: 77% respond[2]
Subcaudate tractotomy	Substantia innominata (immediately inferior to head of the caudate)	Electrocoagulation, Radiosurgery, Radioactive yttrium-90 rods	OCD MDD BPD	Transient: edema, disorientation. Long-term: seizures, negative personality change.	OCD: 50% improve[7] MDD: 32% improve[8] BPD: 56% improve[9]
Limbic leucotomy	Anterior cingulate white matter, substantia innominata	Mechanical, Thermal, Radiofrequency,	OCD MDD BPD	Transient: headache, confusion, perseveration, incontinence, somnolence, apathy, seizure. Long-term: cognitive decline	OCD: 38 - 98% improve[10-12] MDD: 33% symptom-free, 22% improve[13] BPD: 68% improve[14]

ALIC, Anterior Limb of the Internal Capsule; BPD, Bipolar Disorder; MDD, Major Depressive Disorder; OCD, obsessive-compulsive disorder; YBOCS, Yale-Brown Obsessive Compulsive Scale

[1]Patel et al., 2013; [2]Spangler et al., 1996; [3]Greenberg et al., 2003; [4]Leiphart & Valone, 2010; [5]Dougherty et al., 2002; [6]Jung et al., 2006; [7]Goktepe et al., 1975; [8]Hodgkiss et al., 1995; [9]Poynton et al., 1988; [10]Kelly et al., 1973; [11]Hay et al., 1993; [12]Kim et al., 2002 ; [13]Mitchell-Heggs et al., 1976 ; [14]Cho et al., 2008

Table 2: Trials of Deep Brain Stimulation (DBS) for psychiatric illness

Diagnosis	Target	Author, Year	# Patients	Outcome	Potential Side Effects
MDD	SCG/SCC	Mayberg, 2005	6	66% remission rate (@6 months)	Wound infection, suicidality, headache, agitation, weight gain, nausea and vomiting, gastrointestinal discomfort, hardware-related problems.
		Lozano, 2008	20	60% response rate, 35% remission (@12 months) 62.5% response rate, 33% remission (@12 months)	
		Kennedy, 2011	20	62.5% response rate, 50% remission (@12 months) 92% response rate, 58% remission (@ 2 years)	
		Puigdemont, 2011	8	62% response rate (@12 months)	
		Holtzheimer, 2012	12		
		Lozano, 2012	21		
	VC/VS	Malone, 2009	17	71% response rate, 35% remission (variable follow-up)	
	NAcc	Schlaepfer, 2008	3	All patients showed improvement in anhedonia 45% response rate (@ 4 years)	
		Bewernick, 2010/2012	11		
OCD	ALIC	Nuttin, 1999	4	75% response rate (variable follow-up)	Short-term: olfactory, gustatory, and motor sensations; autonomic changes; fear and panic; hypomania Long-term: cognitive decline, disinhibition
		Nuttin, 2003	6	50% response rate (variable follow-up)	
		Abelson, 2005	4	50% response rate (@ 3 weeks)	
	NAcc	Sturm, 2003	4	75% response rate	
		Denys, 2010	16	56% response rate (@ 8 months)	
		Huff, 2010	10	50% had reduction of Y-BOCS score of = 25% (@ 12 months)	
	VC/VS	Greenberg, 2010	26	60% clinically significant symptom reduction (variable)	
		Goodman, 2010	6	33% response rate (@ 12 months)	
	ITP	Jimenez, 2009	6	100% response rate (@ 12 months)	
	STN	Mallet, 2008	16	75% response rate (@ 6 months)	

ALIC, anterior limb of internal capsule; ITP, inferior thalamic peduncle; MDD, major depressive disorder; NAcc, nucleus accumbens; SCG, subcallosal cingulate; STN, subthalamic nucleus; VC/VS, ventral caudate/ventral striatum

View Point

Specific Learning Disability- Is it a disability?

Thomas John
Editor: Branch of Indian Psychiatric Society (Kerala)

Prof Samuel Kirk coined the term Specific Learning Disability (SLD) in 1963 by combining the domains of dyslexia, dysgraphia and dyscalculia; and gave it much publicity in the educational field. In our country, advent of the child psychiatry movement has popularized the concept of SLD, and there is a movement for its inclusion under the Persons with Disabilities (PWD) Act. SLD is one amongst the eight disabilities included in the draft form of this newly proposed bill (PWD Bill 2012).

Definition of SLD

PwD Bill (2012) defines 'Specific Learning Disability' as a heterogeneous group of conditions wherein there is a deficit in processing language, spoken or written, that may manifest itself as a difficulty to comprehend, speak, read, write, spell, or do mathematical calculations. The term includes such conditions as perceptual disabilities, dyslexia, dysgraphia, dyscalculia, dyspraxia and developmental aphasia. This definition is almost similar to the one by U.S. Federal Register, Department of Education (Part 3, 34, CFR 300.7).

Perceptual Disorder - Inability to recognize, discriminate and interpret auditory and visual sensation. (NIMHANS Publication No 48, 3rd edition, p-62). Visual discrimination, visual memory, auditory discrimination and auditory memory are affected here. This condition is not specified as a disorder in ICD or DSM.

Dyslexia - Inaccurate or slow and effortful word reading. Equivalent term in ICD-10 is Specific Reading Disorder (F81.0) and in DSM-5 is Specific Learning Disorder with Impairment in Reading.

Dysgraphia - Difficulties with written expression. No equivalent term in ICD-10, but Specific Spelling Disorder (F81.1) can be considered. In DSM-5, its equivalent term is Specific Learning Disorder with Impairment in Written Expression.

Dyscalculia - Difficulties with mathematical reasoning and calculation. Equivalent term in ICD-10 is Specific Disorder of Arithmetical Skills (F81.2) and in DSM-5 is Specific Learning Disorder with Impairment in Mathematics.

Dyspraxia - Severe impairment in motor coordination in the absence of any diagnosable neurological disorder. Equivalent term in ICD-10 is Specific Developmental Disorder of Motor Function (F82) and in DSM-5 is Developmental Coordination Disorder (Motor Disorders).

Developmental Aphasia - Persistent difficulties in the acquisition and usage of language characterized by reduced vocabulary, limited sentence structure, etc. Equivalent terms in ICD-10 are Expressive Language Disorder (F80.1) and Receptive Language Disorder (F80.2) and in DSM-5 is Language Disorder.

In short, Specific Learning Disability is not a single entity but a cluster of disorders under Neurodevelopmental Disorders in DSM-5 and Disorders of Psychological Development (F80-F82) in ICD-10.

Is it a disability?

A student with a disability of ≥40%, like MR or Autism, will have impairments in various aspects of day to day living. However, a student with SLD per se is disadvantaged only in academics. If children with SLD are helped to develop their other skills, they can have a life of quality. Hence it is not socially justifiable to consider children with SLD under disability category, and to give them all the benefits provided under PwD Act. Hence, any movement to include SLD under disability category will be a social injustice. At the same time, there is no doubt that SLD children need academic help.

Message

Is it necessary for Psychiatry to be Dynamic?

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In a way, present-day medical practice is becoming somewhat like mechanical engineering! Doctors tend to view patients as complex machines. With more and more sophisticated tools available to 'repair', 'professional work' for many doctors means functioning like highly skilled technologists. Often with a tunnel vision which they acquire from their particular specialty, they are unable to view human predicaments beyond a narrow 'bio-medical' frame!

Coming to Psychiatry, our academic programs these days are mostly high-flown discourses on topics from Biological Psychiatry. True, this is understandable and may be necessary, with such fascinating research data emerging from fields like psychopharmacology and molecular biology. But, in the process, are we practicing psychiatrists getting a bit carried away?

Anyone with a sense of history cannot fail to notice that despite many scientific achievements, during the past few decades medical practitioners have lost the special place in the hearts of their patients. The attitude of doctors has became "cold and clinical", as the saying goes! Sensitive old timers among clinicians would certainly feel that if Medicine is to regain its old humane touch, a paradigm shift is necessary. A new vision of reality is needed for all medical practitioners: in perceptions, thoughts, and values.

Let us proudly recall that in the early decades of the twentieth century, when mainstream Medicine was getting a little carried away by its new found image as "Medical Science", Psychiatry emerged as a much needed corrective force. Its many doyens, with their robust theories, provided a new approach for Medicine to go beyond its machine-model conceptualization.

Most of the integrating holistic views about human beings were acquired by Psychiatry from psychoanalytic theory and techniques. The greatest attraction of Freud's theory was that it covered all aspects of human existence. Also, all of Freud's basic postulates have very strong explanatory power. For practicing clinicians, sayings like "every symptom has a cause, purpose, economy and meaning" provide insights into certain dark and deep recesses in the human psyche that no ingenious biological concept could explain! Also, dictums such as "Meaning resides in the domain of the mind" or "It is not the phenomena themselves that are inherently mental or physical, but rather our ways of describing and conceptualizing them that lead to categorization and polarization" could well be remembered by practicing doctors to their advantage.

Besides Psychoanalysis, theoretical positions like Adolf Meyer's Psycho-biology, Existentialism, and Cybernetics offered comprehensive models to help doctors go beyond their narrow Reductionism and Mind-Brain dualism. In the West, throughout the twentieth century holistic views influenced medical practice in significant ways and the 'Reductionistic strait-jacket' in the thinking of doctors got modified to a good extent. But in India, it is an altogether different story. Psychoanalysis or other holistic concepts failed to permeate into the thinking of academicians in main-stream Medicine. And Psychiatry, for most of our fellow medical professionals, was merely a specialty that would take over their disturbed patients who occasionally create an ugly scene!

Today, with the emergence of more and more 'sub' and 'super' specialization in many areas of medical practice, things have deteriorated further. Academicians across all branches of Medicine do not even consider that there is anything worthwhile in dynamic theories. Ideas from such fields do not find a place in medical education at the graduate level. Not only dynamic theories, even basic clinical psychiatry is not given its due place when it comes to training a doctor! The net result is here for everyone to see: Many medical practitioners today are not able to even strongly suspect common disorders like Depressive Disorders or Schizophrenia!

The situation is not different at post-graduate level. In many centers, learned professors do not consider that a brief posting in Psychiatry would be useful as part of MD [General Medicine] training! Even in fields like Neurology, which is closely related to Psychiatry, basic clinical skills in Psychiatry are not taught as part of training, despite the fact that Neurologists in our country are 'managing' a lot of primary psychiatric disorders. After all, owing to widespread stigma, most people would take mentally ill to them, rather than to psychiatrists!

Let us, for the time being, leave aside Neurologists and other doctors. What are Psychiatrists, in general, doing about these kinds of things? In the 1960s, exercises such

as psychodynamic formulation were very much part of postgraduate training. But slowly Psychiatrists started wondering "how much of this 'dynamic quality' is really needed for Psychiatry"? And over the years Psychiatrists lost whatever rudimentary interest they had in dynamic theories! In the present times, with more and more of biological orientation, the question has got apparently modified into, 'is it necessary at all for Psychiatry to be dynamic?"

True, we have a small section of psychiatrists who meticulously practice good psychotherapy. Also there may be some individual psychiatrists who make use of the bio-psycho-social frame in an effort to understand their patients. But these are isolated instances.

Currently, during their postgraduation, trainees are seldom required to make any psychodynamic formulations. The job of clinicians, it seems, is to just affix labels for various psychiatric disorders! And for this they have classification manuals that make everything appear so deceptively simple. It is no more necessary to acquire any in-depth understanding of the patients! Nobody wants a trainee in psychiatry to imbibe an ability to build a 'psychotherapeutic doctor-patient relationship', or view his patient as a collaborator who is willing to take a voyage to the depth of un-consciousness, along with the therapist! Nobody wants a patient to take an 'active' role in the right tradition of psychotherapy.

The new-millennium psychiatrists' efforts are to ensure that their patients are just as passive and obedient as those being treated by 'successful and famous' doctors in other branches of medicine. Many seem keen to acquire a new identity as a 'Neuro-Psychiatrist' or a 'Biological Psychiatrist'. May be they want to shed a pejorative, 'alienist' label, which is traditionally attached to terms like "Psychiatrist" and "Dynamic Psychiatrist"! Their paramount aim seems just to be counted 'on par with' all other medical specialists!

For this, they are all too willing to reduce themselves as specialists handling that particular part of 'Man-Machine' called 'Mind'! They are happy with a new over-simplified, restrictive conceptualization of Mind: namely, only whatever is revealed by new high-tech studies as part of 'brain function' is the 'real' Mind! Rest of the things about human existence that have been taught to us by our great doyens they would just ignore!

We have a related issue of having many Psychologists who are also in a hardcore reductionistic mindset. They seem to believe that they have an exclusive right to 'repair' that particular part of the 'Man-machine', called 'Mind'! To justify this claim they make use the good old "Conflict model", borrowed from psychoanalysis, to have a 'complete' explanation for "mental diseases" as though mind is an entity separate and quite independent of human body and biology! Preposterous ideas like "psychogenic diseases have nothing to do with body" generated by such Psychologists have takers not only among 'enlightened' public, but even among many medical professionals!

In recent times, many fascinating research findings have emerged in Psychiatry. Like the one by Eric Kandel where he established that calcium influx in presynaptic terminals get modulated when the marine snail 'experiences' its environment. Or the study by Post et al. on infant monkeys establishing that separation in early life might sensitize receptor sites, elevate plasma cortisol level, alter opiate receptors in the brain, increase catecholamine synthesizing enzymes in adrenals and so on. Studies have also shown that maternal deprivation at 90 days makes striking impact in infant monkeys, but not when the deprivation occurred at either 60 days or 120 days!

Findings like these actually validate some of Freud's postulations. But are we viewing it that way? Practicing psychiatrists are by and large unable to integrate these kinds of research findings in an inclusive holistic hypothesis. On the contrary, at least a considerable section of them are really getting hardened in their Biological-Medical mindsets! Nobody seems to remember an old dictum that a "psycho-dynamically oriented psychiatrist who ignores the biological dimension of experience and a biologically oriented Psychiatrist who neglects the psychological realm are both guilty of narrow-minded reductionism"!

Psychodynamic Psychiatry, as Glen Gabbard has elegantly put, "is an approach to diagnosis and treatment characterized by a way of thinking about both patient and clinician that includes unconscious conflict, deficits and distortions of intra-psychic 'structures', and internal object relations". Kernberg has observed, "The polarization between the biological and psychodynamic perspectives arises from a failure to appreciate the complex relationship between psychosocial and neuro-physiological factors in the etiology and pathogenesis of psychiatric disorders".

Not only are psychodynamic theories ignored, today the tripartite Psychiatric explanatory structure, "Bio-Psycho-Social", to which we pay lip service, is quietly getting de-emphasized! Also in the name of being more "objective" and more "scientific", the unique value of 'subjective experience', which ought to be quite central to a Psychiatrist's understanding of a patient, is totally ignored!

This brief essay should not be mistaken as an attempt to downplay the importance of advances in the biological frontier. The objective is far from it. We learn a lot of

fascinating new things from this field almost everyday. What we need to do is to integrate knowledge from biology to a comprehensive dynamic theory. Let us not forget that the historical mission of Psychiatry is to replace the popular reductionistic world-view of Descartes and Newton by a holistic and ecological view.

In an era when doctors have given up much of their humane concerns that used to be the hallmark of the healing profession, Psychiatry has certain responsibilities like bringing a psychotherapeutic fragrance to doctor-patient relationship and making every medical practitioner know the usefulness of a bio-psycho-social attitude in clinical practice. For this, first and foremost, Psychiatrists themselves must be able to think beyond a narrow biological conceptualization of human predicaments. We would be able to fulfill these historic obligations only by imbibing psychodynamic theories and keeping an eclectic mindset.

Commentary

The gastroenterology-psychiatry interface: a comparison of medical practice in India with the West

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As a practicing gastroenterologist, I have an endless fascination for the mind-gut axis and its implications in patient management. A large proportion of patients who visit gastroenterology clinics have significant psychiatric illnesses which either are coexisting, contributing to, or at times are even caused by the gastroenterological problem.

Functional dyspepsia is a common problem among young adults, with disabling symptoms that can affect quality of life and productivity at work. While the purpose of performing an endoscopy on these patients is largely to rule out an unlikely organic etiology, it does have some role in reassuring the patient. Continued treatment, however, must be initiated with psychopharmacological agents for lasting relief of symptoms.

Having spent more than a decade working in western countries, I enjoy the camaraderie I share with my psychiatrist colleagues in India more than during my time abroad. In India, especially in a multispecialty hospital setting, I often meet my Psychiatry/Psychology colleagues socially during tea- break or elsewhere. At other times, they are just a phone call away. Several of the patients who see me also require an evaluation by the Psychiatrist or counseling by a Psychologist, and our system in India makes it easy for our patients to achieve these in short time.

In comparison, the healthcare system abroad involves a lot more "red-tape" as defined by restrictions in the "menu" of medications that one can prescribe, and the difficulties in obtaining an appointment with a Psychiatrist. In the town that I practiced in the Northeastern US, there were numerous gastroenterologists, but very few Psychiatrists, none of whom I got a chance to meet, let alone discuss in detail about our mutual patients.

Communications between consultants abroad occur mostly through dictated letters that arrive by mail. Besides, it takes several weeks of waiting to get an appointment, regardless of the specialty being Gastroenterology or Psychiatry. I had noticed often that by the time the patient sees the intended specialist abroad, the problem may have gone away on its own!

Switching back to practice in India, doctors often communicate freely between themselves about their mutual patients, and the waiting period to see the next doctor could be just a few minutes! Instead of dictating printed letters and mailing them to the referring doctor, here in India, problems are solved with a real conversation between doctors either in person or by phone.

From a patients' perspective, it is my opinion that it is much better to be a patient in India than abroad. Here is why: you can choose any doctor you want to see, and most doctors in India see walk-in patients, so you don't spend weeks waiting for an appointment. Besides, in India, the patient can choose the doctor, while in the US, the insurance company chooses for the patient. Healthcare is still very cheap here considering that we use, for the most part, the same equipment and skill set that patients abroad receive. Besides, the wide range of medications available in India is unparalleled. I felt like a kid in a large toy store as I moved from USA back to India! The sheer range and choice of medications here is an absolute luxury for someone like me who practiced with an extremely short menu of "approved" medications abroad for each condition, not to mention the fear of litigation, if, even out of good faith, you choose to prescribe outside your specialty.

In summary, despite its shortcomings, India is a wonderful place to practice medicine. We must appreciate and nurture the camaraderie, communication and teamwork among doctors which is a major factor that will continue to drive excellence in our healthcare system.

Research Article

Impact of self-esteem on life satisfaction among alcoholics and non-alcoholics

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Abstract

Background: Human life is like a crystal very beautiful and precious. Starting from the embryo stage to the old age, it gets purified and becomes sparkler through various roles performed. Apart from other factors, the concept self, starts developing from the childhood onwards. Self- esteem of individuals enhances which triggers appropriate behavior pattern from the person concerned. But, in reality the fast moving present day world along with high competitiveness induce number of problem in everyone's life. Most of them choose external methods to either escape or avoid the problems which they faced. In fact, many persons resort to alcohol and to drugs for easy remedy. The alcoholism or drug dependency affects not only the person who is engaging in these types of activities but it affects their family in a narrow sense but the entire society in a larger levels. Alcoholism becomes a threat to the self-esteem of the alcoholics and it shatters the satisfaction of life of the alcoholics. The aim of the current study was to identify the impact of Self-esteem on Life-satisfaction of young and middle adulthood alcoholics and non-alcoholics.

Material and Method: sample consisting of 30 alcoholic and 30 non-alcoholic young and middle adulthood men. Alcoholic samples were collected from IQRAA International Hospital & Research Center, Kozhikode and non-alcoholic samples were collected from different places of Kozhikode district. They were evaluated by using Rosenberg Self-esteem scale and Prameela Singh and George Joseph Life Satisfaction Scale.

Result: The analysis reported that there is significant difference between alcoholic and non-alcoholic young and middle adults with respect to their levels of life satisfaction. The non-alcoholics found to have greater levels of life satisfaction.There is no difference between levels of self-esteem with reference to life satisfaction. And finally there is no interaction effect between levels of self-esteem, alcoholics and non-alcoholics on their life satisfaction.

Conclusion: Alcoholic behavior disturbs and minimize the life satisfaction of individuals. Interestingly self-esteem as not shown any significant impact on life satisfaction of individuals in respective of whether they are alcoholic or non-alcoholic.

Key Words: *Self-esteem, Life satisfaction, Alcoholism*

INTRODUCTION

The positive and negative evaluation people make about themself has been the subject matter in psychology from the very early period of history. High self- esteem people were more likely to report having this ability if told it was very important than if told it was useless. Feeling good about oneself in a general way, it seems, casts a rosy glow over one's specific self- schemas and possible selves. Self- esteem is the degree to which one perceive themselves positively or negatively, overall attitude towards themselves. It can be measured explicitly or implicitly. An existential perspective on the person begins with the concrete and specific consciousness of a single human being existing at a particular moment in time and space. Existentialists suggest that everyone exist as a being in the world consciously and painfully aware of them existence and eventual nonexistence. A person is either a product of heredity factors or environmental influences, everyone is responsible for who they are and what they become. (Myer-2005)

Diener, (1984) defined Life satisfaction as an overall assessment of feelings and attitudes about one's life at a particular point in time ranging from negative to positive. It is one of three major indicators of well-being: life satisfaction, positive affect, and negative affect. Life-satisfaction is a result of individual's deep examination or evaluation about their own life situations and total outcomes of their life. These evaluations are different from person to person based on their perceptions of their life. These perception and evaluation also consisting the future thought of a person about their life. Life-satisfaction can create in a person life a favorable attitude toward his/her life as a whole. In an individual life there are numbers of certain factors influencing individual life-satisfaction, such as amount of education, experiences, and the people economic and residence as well as many other topics

Alcoholism is a broad term for problems with alcohol, and is generally used to mean compulsive and uncontrolled consumption of alcoholic beverages, usually to the detriment of the drinker's health, personal relationships, and social standing. It is medically considered a disease, specifically an addictive illness. In psychiatry several other terms have been used,

specifically alcohol abuse, alcohol dependence, and alcohol use disorder. The biological mechanisms that cause alcoholism are not well understood. Social environment, stress, mental health, family history, age, ethnic group, and gender all influence the risk for the condition. It is characterized by an increased tolerance of and physical dependence on alcohol, affecting an individual's ability to control alcohol consumption safely. These characteristics are believed to play a role in impeding an alcoholic's ability to stop drinking (Sadocks 2007). The social problems arising from alcoholism are serious, caused by the pathological changes in the brain and the intoxicating effects of alcohol. Alcohol abuse is associated with an increased risk of committing criminal offences.

Objectives of the study

1. To find out the influence of self-esteem on life satisfaction of the young and middle adulthood alcoholics.
2. To find out the impact of self-esteem on life satisfaction of the young and middle adulthood non-alcoholics.

Tools

1. The Rosenberg Self-Esteem Scale (Rosenberg 1965)
2. Life Satisfaction Scale (L-S Scale:Pramila Singh and George Joseph -2009)

The Rosenberg Self-Esteem Scale

The Rosenberg Self-Esteem Scale Is developed by Rosenberg in 1965. The scale is believed to be uni-dimensional and it consists of 10 items. All items are answered using a 4-point Likert-type format ranging from strongly agree to strongly disagree. It measures personal worth, self-confidence, self-satisfaction, self-respect, and self-deprecation. The pattern of functioning of the items was examined with respect to their content, and observations.

Life Satisfaction Scale

Life satisfaction scale was developed by Pramila Singh and George Joseph (2009). The L-S Scale contains has35-items and it is designed to measure five current life satisfaction dimensions, such as, taking pleasure in everyday activities, considering life meaningful, holding a positive self- image, having a happy and optimistic outlook and feeling success in achieving goals. The scale has face and content validity since each item has been judged by the experts in the subject.

Data Collection

The objectives of the study demands that the sample should be both alcoholics and non-alcoholics. The samples are collected from Kozhikode district of Kerala. Using purposive sampling method 30 alcoholics were identified from Iqraa International Hospital Kozhikode and included as alcoholic sample for the study. The sample was the inpatients admitted for the de-addictionprogram. Using the same sampling procedure the investigator approached general public and enquired whether they are non-alcoholic or not. 30 non-alcoholics who accepted to serve as sample for the study were identified and included as sample for the non-alcoholic group. Their aged ranged from 30 to 55 years of age.

Statistical Analysis

The collected date of the present study tabulated and analyzed with the help of Statistical Package for Social Science researchers (SPSS). Two-way ANOVA technique was used in the present study. It is used when the data are classified on the basis of two factors. The ANOVA technique is little different in case of repeated measurements where we also compute the interaction variation.

RESULTS

Table 1 show that the Descriptive statistics of alcoholism and self-esteem with respect to life satisfaction. Sample, mean and standard deviation result in each group like alcoholic, non-alcoholic high and low self-esteem.

Table 1: *Descriptive statistics of alcoholism and self-esteem with respect tolife satisfaction. Sample, mean and standard deviation result in each group.*

Variable	Group	*N*	Mean	SD
Alcoholism	Alcoholic	27	137.69	16.78
	Non alcoholic	26	151.69	12.90
Self esteem	High	29	148.79	13.46
	Low	24	139.75	18.44

Table 2 shows that Test of normality and homogeneity of variance of life satisfaction. Shapiro-Wilk test enables to test the data is enable to further analysis or not. Or it checks the level of the normal distribution in current sample. Table 3 shows that Summary of two ways ANOVA of life satisfaction with respect to self-esteem and alcoholism

Table 2: *Test of normality and homogeneity of variance of life satisfaction*

Variable	Groups	Shapiro-Wilk			Test of Equality of Error Variances			
		W	Df	Sig.	*F*	df1	df2	Sig.
Self esteem	High	0.974	29	0.684	1.553	3	49	0.213
	Low	0.950	24	0.267				
Alcoholism	Alcoholics	0.941	27	0.131				
	Non alcoholics	0.967	26	0.550				

Table 3: *Summary of ANOVA of life satisfaction with respect to self-esteem and alcoholism*

Sources of variation	Type III Sum of Squares	Df	Mean Square	*F*	Sig.
High-Low Self-esteem	5.099	1	5.099	0.022	0.883
Alcoholics Non-alcoholics	1509.461	1	1509.461	6.491	0.014
Self Esteem * Alcoholism	70.099	1	70.099	0.301	0.585
Error	11395.519	49	232.562		
Total	1123669.000	53			

DISCUSSION

The results of the present study lead to interesting findings. The analysis reported that there is significant difference between alcoholic and non-alcoholic young and middle adults with respect to their levels of life satisfaction. The non-alcoholics found to have greater levels of life satisfaction. Life satisfaction refers to the subjective cognitive evaluations that people make with regard to the quality of their overall lives or the quality of specific domains within their lives (Diener et al., 1999; Gilman & Huebner, 2003; Huebner, 1991). There are different factors like family relationships, friendship, job environment, salary and other rewards they get etc. affecting ones' life satisfaction. Alcoholics cannot cope up with their life situations very easily it may leads to their lower level of life satisfaction. Alcoholic behavior is restrain them from positive aspects of life they become unsatisfactory in every aspects in their life. Society and family neglect their views and ideas by their drinking habit. One of the researches indicates that quartile drinker was negatively associated with satisfaction. (Massin& Kopp, 2014). Another study found that those who reported using alcohol and or other substances had higher levels of depression than those who reported not using substances, (Wise, Miller and Preussler 2003). These all indicates that alcoholics have very low level of satisfaction in their life. Hence there is significant difference; the hypothesis is accepted in this study. Whereas non-alcoholics have higher level of life satisfaction. They could be able to solve their problem in their life and make them happy. They also have so many problems, but they are capable to cope up with those problems and satisfy their next level of need as described by Maslow (1987) in his theory of hierarchy of needs. Hence there is significant difference; the hypothesis is accepted in this study.

The next finding of the study shows that there is no difference between levels of self-esteem with reference to life satisfaction. As discussed above there are different factors influencing ones' life satisfaction. Self-esteem is one of the factors which may or may not influence ones' life satisfaction with other factors. Researches show the high-low self-esteem affect people in different ways. One of the studies indicates that low self-esteem will lead to aggression, anti-social behavior and delinquency (Donnellan et. al. 2005). One research indicates that when unstable high self- esteem people experience failure, their underlying self-doubt is reflected in physiological responses indicative of threat (Seery, Blscovich, Weisbuch, & Vick, 2004). Hence the hypothesis is rejected in this present study.

Statistical analysis result indicates that there is no interaction effect between levels of self-esteem, alcoholics and non-alcoholics on their life satisfaction.As mentioned earlier, self-esteem is one of the factor which influence the life satisfaction. There are lots of other conditions or factors which affect individuals' life satisfaction. The previous researches show that there is an interactive effect between self-esteem and life satisfaction (Raboteg and Marija 2008). But the current study shows that no interaction effect between these two components, it may be due to the difference in demographic variable and culture of the present study samples. Though there is no interaction effect between level of self-esteem and alcoholics and non-alcoholics on their life satisfaction, hypothesis is rejected in this study.

CONCLUSION

Alcoholic behavior disturbs and minimizes the life satisfaction of individuals. Interestingly self-esteem is not shown any significant impact on life satisfaction of individuals in respective of whether they are alcoholic or non-alcoholic. Further study need to be clear these topics.

Limitations of the study

Even though the investigator tried the best to make the study as successful as possible, but there are certain limitations. They are:

- Samples only collected from the Kozhikode district in Kerala.
- Only 60 Samples are collected for this study.
- Study only focused on young and middle adults.

REFERENCES

Smith, E. R., Mackie, D. M. (2007). *Social Psychology* (3rd Ed.). Hove: Psychology Press.

Hjelle, L. A., Ziegler, D. J. (1992). *Personality theories: basic assumptions, research, and application.* (3rd Ed.). New York: McGraw- hill.

Baron, R. A., Branscombe, N. R., Byrne, D., and Bhardwaj. (2009). *Social Psychology.* (12th Ed.). New Delhi: Pearsson Education.

Myer, D.G. (2005). *Social psychology*. (8th Ed.).New Delhi: Tata McGraw-Hill.

Larsen,J.R., and Buss,D.M.(2005).*Personality psychology-domains of knowledge about human nature.* (2nd Ed.).New Delhi: Pearson publication.

Snyder, C. R., Lopez, S.J., Pedrotti, J. T. (2011). *Positive psychology, the scientific and practical exploration of human strengths.* (2nd Ed.). New Delhi: Sage Publication.

Frager, R., and Fadiman, J.(2005). *Personality and personal growth*. (6th Ed.). New Delhi: Pearson publication.

Seligman, M. (2002). *Positive emotions undo negative ones, authentic happiness*. New York: Simon & Schuster.

Kumar, T.P. (2011). *Positive psychology approach to education*. (1st Ed). Canada: Apple academic press.

Suh, et. al. (1999). Subjective well-being: Three decades of progress. *Psychological Bulletin*, Vol 125(2). 276-302. doi: 10.1037/0033-2909.125.2.276

Bailey, T., Eng, W., Frisch, M., & Snyder, C. R. (2007), Hope and optimism as related to life satisfaction. Journal of Positive Psychology, 2(3), 168-69 retrieved from, http://en.jstor.org/lifesatsfaction.

McCroskey, J. C., Richmond, V. P., Daly, J. A., Falclone, R. L. (1977). Studies of the relationship between communications apprehension and self-esteem. *Journal of Human Communication.*Vol 3 (3).

Case Series

Valproate Induced Hyperammonemic Encephalopathy: A Case Series in a Psychiatric Setting

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ABSTRACT
Sodium valproate or Valproate, an anticonvulsant, is a routinely used drug in the psychiatric setting. Asymptomatic hyperammonemia is found in patients on Valproate, and can rarely present as Valproate Induced Hyperammonemic Encephalopathy (VIHE). We present a series of six psychiatric patients with VIHE. All the patients developed VIHE within 2 days of initiating or escalating the dose of valproate. The presentations ranged from confusion, slurring of speech, disorientation, and gait disturbances to hallucinations and worsening of agitation. After withdrawal or tapering of Valproate, clinical improvement was noticed in 4-21 days. We suggest that VIHE should be strongly suspected in worsening or onset of new symptoms in a psychiatric patient. Various risk factors and drug interactions could play a role in the causation of VIHE. Prompt intervention and reduction or stoppage of valproate can lead to clinical improvement.

Keywords: Valproate, hyperammonemia, encephalopathy, bipolar affective disorder

INTRODUCTION

Valproic acid (*n*-dipropylacetic acid) is a simple branched-chain carboxylic acid, grouped under anticonvulsant mood stabilizers, widely used in the fields of Psychiatry, Neurology and Pediatrics. In Psychiatry, its sodium salt, Sodium valproate or Valproate, is one of the first line agents used in the management of numerous conditions including Bipolar Affective Disorder, Schizoaffective Disorder, etc. Asymptomatic hyperammonemia (Serum Ammonia being more than 40mmol/l) during valproate therapy has been documented (1) in the presence of normal liver function tests. It can rarely present with Valproate induced Hyperammonemic Encephalopathy (VIHE) (2)(3) too. While there are a multitude of studies ranging from case reports/series and studies (4)(5)(6)(7) from Pediatrics and Neurology, to our knowledge, only a single cohort study has been being published in a Psychiatric setting till date (1).

Here we present a series comprising six cases (Table 1) of VIHE, managed as inpatients in the Department of Psychiatry, Government TD Medical College Hospital, Alappuzha, Kerala, who were either newly started on Valproate or the dose at initial presentation was escalated to reach therapeutic efficacy as a part of the treatment of their psychiatric condition. During the course of treatment they developed confused behavior that was temporally correlated to dose initiation/ escalation and arterial ammonia levels. The condition improved in all cases following discontinuation of valproate or reducing its dose.

CASES

The case series is described in Table 1. All the patients were diagnosed with Bipolar Affective Disorder. Case 5 also had psychotic symptoms. They developed encephalopathy within two days of initiating or escalating the dose of valproate. Cases 3 and 4 were started with a high loading dose. In cases 1, 2, 5 and 6 the dose of Valproate was rapidly escalated for want of urgent symptom control. There was no history of fever, headache, vomiting, loss of consciousness, weakness, focal neurological deficits, hypertension, or diabetes in any of the cases. Family history suggestive of inborn errors of metabolism or neurological disorders was absent. The confused behavior was associated with hike in blood level of arterial ammonia. Serum Ammonia was taken from free flowing arterial blood, maintaining all precautions to prevent false positive results, and was transferred in icepacks within 15 minutes for analysis. All the patients had their hemoglobin, Total and Differential Count, Erythrocyte Sedimentation Rate, Liver and Renal Function Tests, Routine Blood Sugar, and Serum Sodium and Potassium levels within the normal limits. Tests for urea cycle disorders or Carnitine deficiency, serum valproate levels, neuroimaging and EEG were not done due to economic reasons. Valproate re-challenge was not done due to ethical reasons.

DISCUSSION

Valproate induced hyperammonemia is often an asymptomatic phenomenon found in more than 50 % of patients (1). Only rarely does it cause encephalopathy. VIHE was first described in 1980 by Coulter and Allen

(2) in a pediatric epilepsy patient treated with valproic acid. Settle probably described the first case of VIHE in a psychiatric setting (3) in 1995.Various mechanisms have been proposed in the pathogenesis of VIHE.

Valproic acid is metabolized via glucuronidation in the liver, beta oxidation in the mitochondria and omega oxidation in the cytosol, producing numerous metabolites in the process (4) (5). Sodium 2-propyl-4-pentenoate and sodium 2-propyl-2-pentenoate , metabolites of valproic acid formed through beta and omega oxidation respectively, has been experimentally found in animals to stimulate ammonia production by increasing the production and decreasing the renal uptake of ammonia (6). Sodium 2-propyl-4-pentenoate has been implicated to cause VIHE in humans (7). At the renal level, ammonia, which is essential for maintaining acid-base balance, is produced by the conversion of glutamine to glutamate with the help of glutaminase enzyme. Valproic acid has been implicated to increase glutamine levels across the mitochondrial membrane, thereby making it more available for ammonia production (8) Valproic acid been found to also decrease the renal uptake of ammoniagenesis inhibitors such as fatty acids, ketone bodies and α-ketoglutarate (6). In the brain, ammonia detoxification occurs in the astrocytes, where glutamine synthetase needed to produce glutamine from glutamate and ammonia and glutaminase is needed for the reverse reaction (9). Valproic acid has been implicated in increasing glutaminase and decreasing glutamine synthetase activity, leading to ammonia accumulation in the astrocytes in animal experiments. Increased ammonia in astrocyte leads to cerebral oedema and astrocyte dysfunction. Valproic acid and its reactive intermediate valproyl-CoA (VP-CoA) inhibit N-acetylglutamate synthase which synthesise N-acetylglutamate (NAG), a prime metabolite activator of the urea cycle (10). Ornithine Transcarbamoylase (OTC) is one of the mitochondrial enzymes involved in the urea cycle whose deficiency has been implicated in Valproate induced hyperammonemia (11). Valproic acid raises propionic acid levels, and in the process impairs the conversion of ammonia to urea by inhibiting Carbamoyl phosphate synthetase, the rate-limiting enzyme in the urea cycle (12). Carnitine is essential for beta oxidation and hence the proper metabolism of valproate. Its deficiency and depletion of its stores by valproic acid has also been proposed in the causation of hyperammonemia (4).

No relationship has been found between the daily dose of valproate or serum valproic acid level with severity of symptoms of VIHE (13). Long term valproate use has not been associated with VIHE.

Presentations of VIHE include confusion, slurring of speech, disorientation, gait disturbances and hallucinations (13). Worsening of agitation, a symptom reported by other authors, was not observed in our case series. All these symptoms could be misinterpreted as worsening of the primary psychiatric condition. Other reported symptoms also included asterixis, gastritis, perseveration, and non-convulsive status epilepticus. Autospy of fatal cases has shown cerebral oedema and herniation of brain structures (14). Laboratory investigations have usually shown VIHE occurring with normal hepatic function (15), and the same was observed in our case series too. Vossler et al has noted elevation of serum and CSF glutamine levels in VIHE (16). EEG findings include diffuse slowing and triphasic waves (15). MRI has shown brain atrophy on serial imaging (17) and bilateral hyperintense T2 images in cerebellum and globus pallidus. Magnetic Resonance Spectroscopy has demonstrated excess of glutamine and depletion of myonositol and choline (18). Hippocampal involvement has also been described (19).

Poor nutritional status and vegetarian diets are risk factors for development of hyperammonemia, with carbohydrate (8) and protein rich(20) intake influencing ammonia levels. Our case number 3 had a history of recent change to vegetarian diet.

Various complex adverse drug interactions have to be considered in the causation of VIHE. One patient in our case series was started with chlorpromazine and Valproate. Ishizaki et al has reported that chlorpromazine decreases the metabolism of Valproate (18). Risperidone (9) and Olanzapine(21) are known to increase the plasma level of valproate by replacing it from plasma proteins, and two of our cases were on a combination of Risperidone/Olanzapine and Valproate. Four of the cases were also on Lorazepam. Anderson et al has reported that Valproate inhibits the glucoronide conjugation of Lorazepam in liver, thereby decreasing its clearance and thus increasing the blood concentration (22).

Other psychotropic drug interactions possibly causing valproate induced hyperammonemia has been described with phenytoin, barbiturates (23), topiramate (24), lamotrigine (25) and quetiapine (26). Polytherapy with Valproate has been considered a risk factor in the causation of VIHE (27).

Mainline of treatment includes of supportive care and withdrawal/reduction of Valproate (28), and this was followed in our case series. Treatment with L-Carnitine has also been found to be useful (4) (29). Use of citrulline (30), lactulose (31) and carglumic acid (32) has also been described. Hemodialysis has been used in the management of severe cases of VIHE (33).

CONCLUSIONS

Due to the asymptomatic hyperammonemia common

in patients taking valproate, a diagnosis of VIHE should be based on clinical findings and not laboratory values. Psychiatrists managing patients with VIHE should remember that multiple risk factors could be interacting in its causation. As lack of treatment can lead to deaths and just a simple intervention of tapering or stopping the offending agent can be greatly rewarding, prompt diagnosis is warranted. Future research in clinical features and other risk factors in a psychiatric setting will helpful in understanding this rare adverse effect of a very commonly prescribed drug.

REFERENCES

1. Raja M, Azzoni A. Valproate-induced hyperammonaemia. J Clin Psychopharmacol. 2002 Dec;22(6):6313.
2. Sousa C. Valproic acid-induced hyperammonemic encephalopathy a potentially fatal adverse drug reaction. SpringerPlus. 2013 Jan 15;2(1):13.
3. Segura-Bruna N, Rodriguez-Campello A, Puente V, Roquer J. Valproate-induced hyperammonemic encephalopathy. Acta Neurol Scand. 2006 Jul;114(1):17.
4. Böhles H, Sewell AC, Wenzel D. The effect of carnitine supplementation in valproate-induced hyperammonaemia. Acta Paediatr Oslo Nor 1992. 1996 Apr;85(4):4469.
5. Murphy JV, Marquardt K. Asymptomatic hyperammonemia in patients receiving valproic acid. Arch Neurol. 1982 Sep;39(9):5912.
6. Williams CA, Tiefenbach S, McReynolds JW. Valproic acid-induced hyperammonemia in mentally retarded adults. Neurology. 1984 Apr;34(4):5503.
7. Altunbsak S, Baytok V, Tasouji M, Hergüner Ö, Burgut R, Kayrin L. Asymptomatic Hyperammonemia in Children Treated With Valproic Acid. J Child Neurol. 1997 Oct 1;12(7):4613.
8. Coulter D, Allen R. SECONDARY HYPERAMMONÆMIA: A POSSIBLE MECHANISM FOR VALPROATE ENCEPHALOPATHY. The Lancet. 1980 Jun;315(8181): 13101.
9. Settle EC Jr. Valproic acid-associated encephalopathy with coma. Am J Psychiatry. 1995 Aug;152(8):12367.
10. Lheureux PE, Penaloza A, Zahir S, Gris M. Science review: Carnitine in the treatment of valproic acid-induced toxicity - what is the evidence? Crit Care. 2005;9(5):43140.
11. Katiyar A, Aaron C. Case files of the Children's Hospital of Michigan Regional Poison Control Center: The use of carnitine for the management of acute valproic acid toxicity. J Med Toxicol. 2007 Sep;3(3):12938.
12. Elhamri M, Ferrier B, Martin M, Baverel G. Effect of valproate, sodium 2-propyl-4-pentenoate and sodium 2-propyl-2-pentenoate on renal substrate uptake and ammoniagenesis in the rat. J Pharmacol Exp Ther. 1993 Jul 1;266(1):8996.
13. Kondo T, Ishida M, Kaneko S, Hirano T, Otani K, Fukushima Y, et al. Is 2-propyl-4-pentenoic acid, a hepatotoxic metabolite of valproate, responsible for valproate-induced hyperammonemia? Epilepsia. 1992 Jun;33(3):5504.
14. Warter JM, Marescaux C, Chabrier G, Rumbach L, Micheletti G, Reitzer B, et al. Increase of valproate-induced hyperammonemia in normal subjects by carbohydrate intake. Neurology. 1984 Nov;34(11):14879.
15. Collins RM Jr, Zielke HR, Woody RC. Valproate increases glutaminase and decreases glutamine synthetase activities in primary cultures of rat brain astrocytes. J Neurochem. 1994 Mar;62(3):113743.
16. Cátia C P Aires A van C. New insights on the mechanisms of valproate-induced hyperammonemia: inhibition of hepatic N-acetylglutamate synthase activity by valproyl-CoA. J Hepatol. 2010;55(2):42634.
17. Honeycutt D, Callahan K, Rutledge L, Evans B. Heterozygote ornithine transcarbamylase deficiency presenting as symptomatic hyperammonemia during initiation of valproate therapy. Neurology. 1992 Mar;42(3 Pt 1):6668.
18. Clay AS, Hainline BE. Hyperammonemia in the ICU. Chest. 2007 Oct;132(4):136878.
19. Carr MD, Russell, Shrewsbury MD, Kerrie. Hyperammonemia Due to Valproic Acid in the Psychiatric Setting. Am J Psychiatry. 2007 Jul 1;164(7):10207.
20. Bega D, Vaitkevicius H, Boland TA, Murray M, Chou SH-Y. Fatal hyperammonemic brain injury from valproic Acid exposure. Case Rep Neurol. 2012 Sep;4(3):22430.
21. Vossler DG, Wilensky AJ, Cawthon DF, Kraemer DLA, Ojemann LM, Caylor LM, et al. Serum and CSF glutamine levels in valproate-related hyperammonemic encephalopathy. Epilepsia. 2002 Feb;43(2):1549.
22. Hantson P, Grandin C, Duprez T, Nassogne M-C, Guérit J-M. Comparison of clinical, magnetic resonance and evoked potentials data in a case of valproic-acid-related hyperammonemic coma. Eur Radiol. 2005 Jan;15(1):5964.
23. Ziyeh S, Thiel T, Spreer J, Klisch J, Schumacher M. Valproate-induced encephalopathy: assessment with MR imaging and 1H MR spectroscopy. Epilepsia. 2002 Sep;43(9): 11015.
24. Soares-Fernandes JP, Machado Á, Ribeiro M, Ferreira C, Figueiredo J, Rocha JF. HIppocampal involvement in valproate-induced acute hyperammonemic encephalopathy. Arch Neurol. 2006 Aug 1;63(8):12023.
25. Gidal BE, Inglese CM, Meyer JF, Pitterle ME, Antonopolous J, Rust RS. Diet- and valproate-induced transient hyperammonemia: effect of L-carnitine. Pediatr Neurol. 1997 May;16(4):3015.
26. Trojak B, de la Gastine B, Dollfus S. Valproate-induced encephalopathy related to concurrent antimanic medications. J Neuropsychiatry Clin Neurosci. 2011;23(1):E2223.
27. Anderson GD, Gidal BE, Kantor ED, Wilensky AJ. Lorazepam-valproate interaction: studies in normal subjects and isolated perfused rat liver. Epilepsia. 1994 Feb;35(1):2215.
28. Ratnaike RN, Schapel GJ, Purdie G, Rischbieth RH, Hoffmann S. Hyperammonaemia and hepatotoxicity during chronic valproate therapy: enhancement by combination with other antiepileptic drugs. Br J Clin Pharmacol. 1986 Jul;22(1):1003.
29. Blackford MG, Do ST, Enlow TC, Reed MD. Valproic Acid and Topiramate Induced Hyperammonemic Encephalopathy in a Patient With Normal Serum Carnitine. J Pediatr Pharmacol Ther JPPT. 2013;18(2):12836.
30. Fan CC, Huang MC, Liu HC. Lamotrigine might potentiate valproic acid-induced hyperammonemic encephalopathy. Prog Neuropsychopharmacol Biol Psychiatry. 2008 Oct

1;32(7):17478.

31. Halaby A, Haddad R, Naja WJ. Hyperammonemia induced by interaction of valproate and quetiapine. Curr Drug Saf. 2013 Sep;8(4):2846.
32. Chicharro AV, de Marinis AJ, Kanner AM. The measurement of ammonia blood levels in patients taking valproic acid: looking for problems where they do not exist? Epilepsy Behav EB. 2007 Nov;11(3):3616.
33. Wadzinski J, Franks R, Roane D, Bayard M. Valproate-associated hyperammonemic encephalopathy. J Am Board Fam Med JABFM. 2007 Oct;20(5):499502.
34. Mock CM, Schwetschenau KH. Levocarnitine for valproic-acid-induced hyperammonemic encephalopathy. Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm. 2012 Jan 1;69(1):359.
35. Stephens JR, Levy RH. Effects of valproate and citrulline on ammonium-induced encephalopathy. Epilepsia. 1994 Feb;35(1):16471.
36. Stewart JT, Fl T. Treatment of Valproate-Induced Hyperammonemia. J Am Geriatr Soc. 2005 Jun 1;53(6):10801080.
37. Daniotti M, la Marca G, Fiorini P, Filippi L. New developments in the treatment of hyperammonemia: emerging use of carglumic acid. Int J Gen Med. 2011;4:218.
38. Tsai M-F, Chen C-Y. Valproate-induced hyperammonemic encephalopathy treated by hemodialysis. Ren Fail. 2008;30(8):8224.

Table 1. Case histories of patients presenting with Valproate induced hyperammonemic Encephalopathy

Case No:	Age in years / Sex	Dosage of valproate in mg	Additional Medications	Day of Onset of VIHE	Serum Ammonia levels (mmol/L)	Symptoms	Action taken and time to recovery	Serum Ammonia levels on day of recovery (mmol/L)	Comments
1	46/ male	600 on day 1, 1000 on day 3, 1500 on day 10, 2000 on day 15	Lithium 900 mg, Risperidone 4mg	16	81	confusion, slurred speech, disorientation, memory impairment, hallucinatory behavior	Valproate reduced to 400mg, Day 21	14	Nil
2	56/male	600 on day 1, 1500 on day 2	Nil	3	174	Confusion	Valproate stopped, Day 11	25	Recent change to vegetarian diet
3	36/ male	1000 on day 1	Chlorpromazine 200mg, Lorazepam 2mg, Thiamine 200mg	2	160	Confusion, tremor, minimally response to stimuli, disorientation	Valproate stopped, day 5	18	Nil
4	36/ female	1500 on day 1	Olanzapine 10mg	1	68	Drowsy, confusion	Valproate stopped, day 4	32	History of harmful use of alcohol
5	53/ male	1000 on day 1 , 1500 on day 4	Olanzapine 10 mg, Lorazepam 2 mg	9	130	Confusion, cognitive impairment	Valproate stopped, day 16	29	Nil

Legal insanity some practical issues

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The interface between law and psychiatry is complex, and has potential for gross misunderstandings. Each discipline has its concern for the patient, but they speak different languages. The judicial language is binary the person is either competent or not competent, dangerous or not dangerous, criminally responsible or not responsible. On the other hand, psychiatry considers a continuum that ranges from the healthy to the very ill, there being different stages in between. Psychiatric concepts are relative, multifactorial, and far from absolute. A schizophrenia patient with persecutory delusions and some cognitive impairment still preserves most cognitive skills. Associated factors like alcohol or drug abuse and personality traits too play crucial roles in a person's behaviour. So the opinions regarding legal responsibility, fitness to stand trial, testamentary capacity, etc. become difficult, and the content is often "lost in translation".

Here, I deal with two main instances where psychiatrists are often called to court the insanity defence and the fitness to stand trial.

THE INSANITY DEFENSE

The insanity defence is a legal construct which excuses some mentally ill defendants from legal responsibility of their criminal behaviour. For an act to be criminal, there should be two components: *actus reus* (the harmful act) and *mens rea* (the evil intent or guilty mind). It was said from early times that "idiots, infants and the insane" are *non compos mentis* do not have control on the mind. Unsoundness of mind must be such as to make the offender incapable of knowing the nature of the act or not knowing that what he is doing is morally wrong or contrary to law.

EVOLUTION OF INSANITY DEFENSE

The circular evolution of the insanity defence from 19th century Britain through the famous McNaughton trial to the controversial acquittal in the US of John Hinckler Jr., who tried to assassinate Ronald Reagan, is interesting. 18th century Britain had the "Wild Beast Test" which said that if a defendant was so bereft of sanity that he understood the ramifications of his behaviour "no more than in an infant, a brute, or a wild beast", he would not be held responsible for his crimes.

Next was the Right or Wrong or the McNaughton Test. Guidelines for evaluating the criminal responsibility of defendants claiming to be insane were codified in the British courts in the case of Daniel McNaughton in 1843. McNaughton was a Scottish woodcutter who murdered the Secretary to the Prime Minister, Sir Robert Peel, in a botched attempt to assassinate the Prime Minister himself. McNaughton apparently believed that the Prime Minister was the architect of the myriad of personal and financial misfortunes that had befallen him. During his trial, nine witnesses testified to the fact that he was insane, and the jury acquitted him, finding him "not guilty by reason of insanity". Queen Victoria was not at all pleased with this outcome, and requested the House of Lords to review the verdict with a panel of judges. The judges reversed the jury verdict, and the formulation that emerged from their review that a defendant should not be held responsible for his actions if he could not tell that his actions were wrong at the time he committed them became the basis of the law governing legal responsibility in cases of insanity in England. The McNaughton rule was embraced with almost no modification by American courts and legislatures for more than 100 years, until the mid-20th century. In 1998, 25 states and the District of Columbia still used versions of the McNaughton rule to test for legal insanity.

One of the major criticisms of the McNaughton rule is that, in its focus on the cognitive ability to know right from wrong, it fails to consider the issue of control. Psychiatrists agree that it is possible to understand that one's behaviour is wrong, but still be unable to stop oneself. To address this, some states have modified the McNaughton test with an "irresistible impulse" provision, which absolves a defendant who can distinguish right from wrong but is nonetheless unable to stop himself from committing an act he knows to be wrong. The "Irresistible Impulse Test" is also known as the "policeman at the elbow" test: Would the defendant have committed the crime even if there were a policeman standing at his elbow?

Then came the "Durham Test", and its rise and fall. The 1950s saw a growing dissatisfaction with the McNaughton Test. It was criticized in both legal and psychiatric circles as rigid and antiquated. In 1954, an appellate court discarded the McNaughton rule and the "irresistible impulse" test in favour of a broader, medically based determination: In Durham v. United States, the U.S. Court of Appeals for the District of

Columbia ruled that a defendant could not be found criminally responsible "if his unlawful act was the product of mental disease or mental defect". The decision was hailed as revolutionary because it marked the replacement of moral considerations with more neutral scientific determinations that were reflective of advances in psychiatric and psychological research. It was the first major break from the "right/wrong" McNaughton rule in American jurisprudence.

The Durham rule proved vague and difficult to apply, however, and many were concerned that the broad definition would exonerate far more defendants than ever before. There was confusion over whether "mental disease or defect" should be interpreted to mean only psychosis, or any of the myriad of more minor disorders defined in the DSM. Critics worried that defendants would begin to use alcoholism, or other disorders whose only symptoms were antisocial behaviour, as excuses for crimes. It proved difficult to determine if the question of whether a defendant's actions were the product of his disease was a factual question for the jury or for expert psychiatric witnesses. And the rule was criticized for inadvertently granting psychiatrists and psychologists too much influence in the courtroom. 22 states explicitly rejected the Durham test.

In 1962, the American Law Institute (A.L.I.) set out a model insanity defence statute intended, like Durham, to soften the McNaughton standard and allow for the introduction of medical and psychiatric evidence. The standard in effect consolidates the principles of the McNaughton "right and wrong" rule and the "irresistible impulse" test. The A.L.I. formulation provides that a defendant will not be held criminally responsible if, at the time of the behaviour in question, "as a result of a mental disease or defect, he lacks substantial capacity either to appreciate the criminality of his conduct or to conform his conduct to the requirements of the law". The A.L.I. was a significant softening of the McNaughton standard. Instead of requiring a defendant to have no understanding whatsoever of the nature of his acts or the difference between right and wrong, the A.L.I. standard requires merely that he lack a "substantial capacity" to understand the right from wrong, and expands the McNaughton rule to include an "irresistible impulse" component.

The A.L.I. standard excludes those defendants whose mental illness or defect manifests itself only in criminal or antisocial conduct, thus addressing the conundrum of the serial killer whose only symptom of mental illness is the killing of his victims. As of 1998, the states were roughly split between the two standards: 22 states used some form of the A.L.I. rule, while 26 used a version of McNaughton with or without an irresistible impulse component.

Then came the infamous John Hinckley Jr case. In 1981, John Hinckley Jr. shot the then U.S. President Ronald Reagan, a secret service agent, a Washington police officer, and Reagan's Press Secretary James Brady. Hinckley claimed that he was trying to impress the actress Jodie Foster with whom he was infatuated. He later described the incident in a letter to The New York Times as "the greatest love offering in the history of the world At one time Miss Foster was a star and I was the insignificant fan. Now everything is changed. I am Napoleon and she is Josephine. I am Romeo and she is Juliet."

A jury acquitted Hinckley of 13 assault, murder and weapons counts, finding him not guilty by reason of insanity. There was an immediate public outcry against what many perceived to be a loophole in the justice system that allowed an obviously guilty man to escape punishment. There were widespread calls for the abolishment, or at least the substantial revision, of the insanity-plea laws.

THE INSANITY DEFENSE REFORM ACT OF 1984

After the Hinckley acquittal, members of Congress responded to the public outrage by introducing 26 separate pieces of legislation designed to abolish or modify the insanity defence. At the time of Hinckley's trial, all but one federal circuit had adopted the A.L.I. "substantial capacity" test, and all the new proposals were aimed at creating a stricter federal standard that would avoid acquittals like Hinckley's in the future. The debates on this legislation reflected the public's indignation over the Hinckley decision. Senator Strom Thurmond criticized the insanity defence for "exonerating a defendant who obviously planned and knew exactly what he was doing." Senator Dan Quayle claimed that the insanity defence "pampered criminals", allowing them to kill "with impunity".

This hyperbolic testimony was countered by psychiatric and legal professionals who called for the modification, rather than the total abolition, of the insanity defence. Ultimately, the resulting legislation the Insanity Defense Reform Act of 1984 was somewhat of a compromise. The insanity defence was not abolished, but the A.L.I. test was discarded in favour of a stricter version which more closely resembled McNaughton. In order to qualify, an insanity defendant must show that his mental disease or defect is "severe." The "volitional" prong of the test, which excused a defendant who lacked the capacity to control his behaviour, was eliminated. In effect, Congress returned to the 19th century "right/wrong" standard, echoing Queen Victoria's response to the McNaughton acquittal.

Congress also adopted a number of provisions that toughened procedural barriers to a successful insanity defence. Before Hinckley, the burden of proof in federal

cases was on the prosecution to prove beyond a reasonable doubt that a defendant was sane. The post-Hinckley reform legislation shifted the burden to the defendant to prove, with clear and convincing evidence, that he was legally insane at the time of the crime. The scope of expert psychiatric testimony was severely limited, and stricter procedures governing the hospitalization and release of insanity acquittees were adopted.

The introduction of the "guilty but mentally ill" (GBMI) verdict in many states was the biggest development in insanity defence law since the post-Hinckley reforms. A sort of hybrid alternative to an acquittal by reason of insanity, a defendant who receives a GBMI verdict is still considered legally guilty of the crime in question; but since he is mentally ill, he is entitled to receive mental health treatment while institutionalized. If his symptoms remit, however, he is required to serve out the remainder of his sentence in a regular correctional facility, unlike a defendant who was acquitted by reason of insanity who must be released if it is determined he is no longer on medication.

So many reforms have taken place in the US and parts of the Europe. In India insanity defence is still governed by Section 84, IPC, a direct descendant of McNaughton Rule. There is no reference to lack of control, irresistible impulse or diminished responsibility, and there have been no reforms.

Insanity defense can be raised in different ways

1. Not guilty by reason of insanity (NGRI)
2. Guilty but mentally ill (GBMI)
3. Diminished responsibility, automatism, amnesia

In the U.S., 26 states follow the "McNaughton" rule. 22 jurisdictions use some variation of the Model Standard set out by the American Law Institute (A.L.I.) in 1962. The A.L.I. rule is generally considered to be less restrictive than the McNaughton rule. Three states Montana, Idaho, and Utah do not allow the insanity defence at all. A major 1991 eight-state study commissioned by the National Institute of Mental Health found that less than 1 per cent of county court cases involved the insanity defence, and that of those, only around one in four were successful. 90% of the insanity defendants had been diagnosed with a mental illness. About a half of the cases had been indicted for violent crimes; 15 % were murder cases.

What is "Guilty but Mentally Ill (GBMI)"?

This does not eliminate the insanity defence; it is merely an alternative for defendants who are found to be mentally ill, but whose illness is not severe enough to relieve him of criminal responsibility. A defendant who receives a GBMI verdict is sentenced in the same way as if he were found guilty. The court then determines whether and to what extent he requires treatment for mental illness. When, and if, the defendant is deemed "cured" of his mental illness, he is required to serve out the rest of his sentence unlike an insanity-defence acquittee who would be released from psychiatric commitment once he is deemed to be no longer dangerous.

What happens to a mentally ill defendant who is acquitted of a violent crime?

Studies show that defendants acquitted by reason of insanity are likely to spend as much or more time confined in a psychiatric institution as they would have if convicted and sentenced to jail or prison for the same crime.

On *Mens Rea*

Few legal concepts are as complex as *mens rea*, and successful defences based on the claim that *mens rea* is lacking are uncommon. Every crime requires some degree of *mens rea*. It can be easier for a defendant to win a *mens rea* claim than an insanity defence. Lack of *mens rea* is easier to assert especially if expert testimony is permitted than insanity.

Very closely related to the insanity defence is the “Competency evaluation” or “Fitness to stand trial”. The two are closely related, but distinct.

Competency to trial / plead

Competency to stand trial hinges on a defendant's current mental state at the time of the trial. It is generally a low-level standard which merely requires that a defendant understands the proceedings against him that he is being tried for a crime; and the relative roles of prosecutor, defence attorney, and the judge and be able to assist his attorney in his defence. There is a common misperception that if an individual is found incompetent, it is the same as being found not guilty. In reality, if the defendant is deemed incompetent, there is no trial, and no conviction or acquittal.

One of the most widely used competency assessment instruments is the Mc Garry instrument which assesses 13 different areas of functioning. The clinician opines regarding competence; and the judge can honour, modify or disregard this opinion. A person is not incompetent until the judge says so.

What happens when a defendant is found incompetent to stand trial?

A finding of incompetence merely signals a hiatus in the criminal proceedings. In the majority of cases, a mentally ill defendant deemed incompetent receives treatment until he is deemed "restored to competence" and returns to court.

Until 1972, defendants found incompetent to stand trial often ended up being institutionalized automatically and indefinitely. In that year, the U.S. Supreme Court ruled that such institutionalization was unconstitutional, and that defendants deemed incompetent may not be held for a longer period than is reasonable to determine whether they will be able to attain competence in the foreseeable future. If the determination is made that he will not, commitment proceedings must be initiated or the defendant must be released.

The interaction between the psychiatric (or medical) discipline and the judicial discipline has inherent difficulties. The two disciplines use different languages which often can hardly merge into a common one. Each discipline has its own responsibility and part to play with regard to psychiatric patients. The psychiatrist's concern is to provide the best therapeutic intervention, while the court is concerned with the patient's rights, social justice, and protection of society. The two systems can be complementary only if both sides learn to understand and respect the principles and language of the other.

"From an umbrella to a canopy"- extension of community based rehabilitation through Occupational Therapy Units of DMHP Thiruvananthapuram

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Community - based occupational therapy involves working with people in their own environment than in a hospital setting. It enables the best use of one's residual abilities in order to function at as optimum a level as possible. District Mental Health Program (DMHP) Thiruvananthapuram shares National Mental Health Program (NMHP)'s vision to achieve decentralization of mental health care in the community, and has diversified into rehabilitation through establishment of Occupational Therapy Units in the community. From a pilot project of a cover-making Occupational Therapy Unit under the Santhwanam Occupational Therapy Program, the activities of **DMHP** Thiruvananthapuram has grown to three functioning occupational units, two daycare centers under the Comprehensive Mental Health Scheme 2014, and two more proposed Occupational Therapy Units in Panchayaths across Thiruvananthapuram district. This article outlines the growth of rehabilitation units in Thiruvanathapuram, projects the role of occupational therapy in community based psychiatric rehabilitation, details its evolving acceptance as one of the main stays of Comprehensive Mental Health Scheme (CMHS) as exemplified by the plans to bring all districts of Kerala under a unified rehabilitation canopy.

Background

Not more than 2-3% of the disabled in developing countries could benefit from rehabilitation services[1].In India, with the mental hospitals preferring an "asylum setting", rehabilitation had remained in dark ages. Deinstitutionalization envisaged by Phillipe Pinel can be attained in its whole sense only when rehabilitation services are strengthened in the community. From the 1960s and 1970s, because of deinstitutionalization, many more mentally ill were able to live in their communities rather than remaining confined to mental institutions. Medications and psychotherapies were the two major treatment approaches, and little attention was given to supporting and facilitating daily functioning and social interactions. Therapeutic interventions often had little impact on daily living, socialization or work opportunities. Barriers to social inclusion, like stigma and prejudice, are often present. Psychiatric rehabilitation emerged with the aims of helping community integration and independence of mentally ill. "Psychiatric rehabilitation" and "Psychosocial rehabilitation" are often used interchangeably to name this practice.

Rehabilitation is initiated when psychiatrically ill are unable to fully recover with the treatments administered so far and have high levels of disability owing to nature of their illness. The goal of psychiatric rehabilitation is to help disabled individuals to establish the emotional, social, and intellectual skills needed to live, learn, and work in the community with the least amount of professional support[2].The major objective of community-based rehabilitation (CBR) is to ensure that people with disabilities are able to maximize their physical and mental abilities, have access to regular services and opportunities, and achieve full social integration within their communities.[3]Occupational therapy promotes health by enabling people to perform meaningful and purposeful occupations. The primary goal of occupational therapy is to enable people to participate in activities of everyday life. Community based occupational therapy practice involves working with people in their own environment rather than in a hospital setting.

Role of DMHP

DMHP implements the aims and objectives of NMHP 1982 through decentralization of mental health care to the community using public health infrastructure and other resources. This model has been pilot-tested in Bellary district of Karnataka and was found very useful to address the basic mental health needs of the population[4]. By now this model has been implemented in all Indian states, and currently there are 125 DMHP sites in the country[5]. DMHP Thiruvananthapuram was launched in 1999.

The aim of DMHP Thiruvananthapuram, with respect to CBR, is to establish Occupational Therapy Units in various parts of Thiruvananthapuram district in a phased manner. The action plan was to have instructors for teaching and training the inmates in the necessary skills, five days per week. Those patients who are under the care of nearby DMHPs can also utilize these facilities.

"Opening the first umbrella"-A pilot program "Santhwanam" CBR center in Mangalapuram

First such initiative in the state was established by late

Dr. Suraj Mani on September 01, 1998, based on the State Mental Health Policy. The Inpatient Block of Mangalapuram PHC, which was not being used, was converted to a daycare center for the mentally ill. Initially it provided daycare facilities for 15 to 20 patients who were discharged from Mental Health Centre, Peroorkada, and provided them with food and medications. But subsequently the patient strength dwindled to 10 due to various financial and resources setbacks. It was at this juncture that DMHP Thiruvananthapuram extended its services to the unit and started a Medicine Cover Making Unit and a Tailoring Unit in 2008.The staff pattern included managerial supervision by PSW of DMHP, trained community health worker, a helper and a driver.

The daily schedule in the unit is as follows:

09.00 am	-Patients picked up by vehicle
10.00 am	-Tea and snacks
11.30am-01.30pm	-Occupational and recreational activities
01.30pm	-Lunch
02.00pm-03.30pm	-Occupational and recreational activities continued

Santhwanam functions under the supervision of Kerala State Mental Health Authority with financial assistance from the Kazhakuttam Block Panchayath and Primary Health Centre, Mangalapuram. Present infrastructure includes three functional rooms, three toilets, one kitchen and a spacious yard. The monitoring committee includes members of Kazhakuttam Block Panchayat and Mangalapuram Village Panchayat, State Mental Health Authority, Nodal Officer of DMHP Thiruvananthapuram, and the doctor of Mangalapuram Primary Health Centre. Inspections by DMHP team are done on a monthly basis. Medicine covers made at the center are bought by PHCs in Mangalapuram, Thonnakkal and Puthenthoppe. Incentives are given to the patients on the basis of number of covers made per month (Rs.10 for 100 covers). Paper needed to make the covers is provided by DMHP Thiruvananthapuram free of cost to the centre.

Santhwanam Cover-Making Unit in Snehasadanam Old Age Care Home,Kudappanakkunnu

Following a geriatric camp in December 2013, an Occupational Therapy Unit was established in January 2014. Currently, 17 inmates of the Home make medicine covers with paper provided by DMHP. The covers are purchased by PHC Chettivilakom under whose area the Home is situated. A qualitative and quasi-experimental evaluation has demonstrated many benefits to the inmates, like reductions in depression, anxiety and stress, improvements in interpersonal relations and generalized wellbeing, and a feeling of accomplishment upon being engaged. These were also noted to be of more importance to them than the nominal financial incentive.

Proposed Occupational Therapy Units

Following primary care integration and case detection campaigns in PHC Cherunniyoor and PHC Kuttichal, medical officers of these centers whom we trained and local self-governing bodies whom we sensitized have come forward with financial support and infrastructure provision for more Occupational Therapy Units proposed by DMHP Thiruvananthapuram. The centers will be active in the financial year 2014-15.

"Extension of the canopy"- Rehabilitation Centers under Comprehensive Mental Health Scheme 2014

CMHS 2014 brings all districts of Kerala under a common canopy. It has specific guidelines for establishment of separate Day Care Centers for males and females in the community under the supervision of DMHPs. The Centers are aimed to provide daycare facilities and occupational rehabilitation for 30 inmates each. The staff pattern comprises of a social worker, three staff nurses, three attendants and a driver, and will own a vehicle for the transportation of inmates.

OBJECTIVES OF THE VENTURE

1. Observe, identify, and assess the continuum of restrictions in activities, community participation and occupation due to illness and disability.
2. Identify and examine performance in areas other than occupation, like activities of daily living, instrumental activities of daily living, education, work, play, leisure, and social participation.
3. To rehabilitate those patients who have symptom control by providing training in various skills and assigning alternative activities to keep them engaged.
4. To allow patients from other DMHP clinics in parts of the district where rehabilitation facilities are scarce to be trained in the center.
5. To provide occupational opportunities so that the patients can be gainfully employed.
6. Helping the patients acquire specific skills to care for themselves and others, including keeping a schedule, medication management, education, employment, increasing community participation, community access (grocery store, library, bank, etc.), money management skills, routine building, engaging in productive activities to fill the day, coping skills, etc.
7. To impart basic skills so that dignity and self-worth of the individual can be sustained through the remuneration received.
8. Minimize caregiver burden by providing patients with alternative activities and with time spent constructively outside the family setting.

THE PLAN OF ACTION OF THE DAY CARE CENTRES

Staff for each center will be chosen through interview at Nodal Centers of DMHP in various districts. DMHP Thiruvananthapuram have interviewed and selected staff for the two day care centers which will be in the peripheral rural parts of Aryanadu and Chengal of Thiruvanathapuram district. In the two day care centers in Thiruvananthapuram, the Social Worker will monitor and supervise activities and directly report to the Nodal Officer, DMHP. The Staff Nurses will monitor transportation, provision of medications, and clinical care of the inmates with the help of attenders. Patients who have symptom control and are psychosocially disabled are being selected from nearby DMHP Clinics and PHC mental health clinics. To and fro transportation will be arranged in the Center's vehicle, and food will be provided through local Kudumbashree units.

PROPOSED ACTIVITIES

- Making paper covers for dispensing pharmaceutical drugs: Inmates will be trained to make paper covers. The covers will be sold to PHCs/CHCs and Taluk Hospitals in the district. (4000 covers can be made out of 20 kilograms of paper. The cost for 1 kilogram of paper is Rs.20. Covers will be made in small, medium and large sizes, with an incentive of Rs.10, Rs.12, Rs. 15 respectively for every 100covers made.)
- A tailoring unit: Four sewing machines were purchased and tailoring teachers will instruct the inmates on the basics of tailoring and sewing skills. This activity is mainly meant for women participants. The practice cloth will be bought at a subsidized rate.
- Candle making, Hortitherapy, Milieu therapy, etc.

Documentation, data management, maintenance of registers, and a reporting system to the Nodal Center will be established. The Center will be periodically evaluated by the DMHP team.

From Challenges and Road Blocks to Goals

Sustainability and effectiveness of these centers across the state depends on committed manpower, continuous financial support, and a dynamic intake and final community integration of the patients. Responsibilities and goals of these centers will include finding regular outlets to sell the products, and improving skills of the inmates sufficiently enough to enable them to work in any supported employment in the community. Ensuring a link with community, NGOs, local self-governing bodies, policy makers and stake holders will be the need of the future. Successful implementation in a unified manner, with practical adaptability, will be the norm for these centers for this scheme to put into action what it has envisaged. DMHP Thiruvananthapuram can be proud to be at the root of this implantation scheme, and being a forerunner in these endeavors in the state, has given its pioneering contributions for setting the path and establishing a workable protocol and implementation model for the other districts.

References

1. Training in the community for people with disabilities. The World Health Organization. Geneva: WHO; 1989.
2. Anthony, W. (1979). *The principles of psychiatric rehabilitation*. University Park Press, Baltimore, MD.
3. Sharma AK, Praveen V. Community based rehabilitation in primary health care system. Indian J Community Med. 2002;117:13942.
4. District Mental Health Programme: Editorial, Community Mental Health News, Issues no: 11-12,Apr-Sept 1988.
5. Implementaion of the National Mental Health Program during 11th Five Year Plan Guidelines. NO V-15011/6/2007-PH (Pt 2) New Delhi, Government of India, Nirman Bhavan.

Local Experience

"Thalir is budding"

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DMHP Thiruvananthapuram guidelines on School Mental Health implemented in Comprehensive Mental Health Scheme 2014-15

Abstract
The School Mental Health Program "Thalir (Bud)" of District Mental Health Program Thiruvananthapuram implements preventive, reconstructive and rehabilitative phases at schools of the district. The model is to be implemented statewide through Comprehensive Mental Health Scheme from the academic year 2014-15.The primary objective is to enhance awareness on common adolescent issues among teachers, parents and students, and to improve their management skills. Secondary objective is to provide counseling services to at-risk adolescents and to establish follow-ups with mental health services. Multilevel sensitization builds an effective network link between Integrated Child Development Scheme (ICDS) supervisors, Child Development Program Officers (CDPO) and school counselors of Social Welfare Department, and School Health Nurse of National Rural Health Mission and District Mental Health Program (DMHP). Classes on emotional and behavioral problems, substance use, suicide prevention, life skills and stress management for students from 5th to 12th standards (10-18 year olds), and on awareness and management skills for their parents and teachers, are taken by trained resource persons of DMHP using structured modules. Classes are followed by counseling camps in schools for the at-risk studentsby mental health professionals. Referral and follow-ups, with the guardians, are suggested to the nearest DMHP clinic or mental health clinics of Primary Health Centers. Post-intervention evaluation is done by teachers and monitored by DMHP. Building an effective interdisciplinary network can establish access for wider coverage of mental health needs of adolescentsthrough schools. Sensitization of teachers, parents and school students leads to early identification of psychological morbidities, timely interventions and easier access to health care services.

Introduction
The nation nurtures hopes for its future in its youth. Article 45 of the Indian Constitution states "The State shall strive to provide free and compulsory education to all citizens up to the age of 14."[1] Rights of the Child (UN Convention 1989) also have reiterated the need for education to go beyond providing knowledge.[2]In India we have National Policy for Children, Integrated Child Development Scheme (ICDS), National Mental Health Program (NMHP), National Policy on Mental Handicap, etc. to address the physical, psychological and social developmentsand rehabilitation of the needy through community participation.

District Mental Health Program (DMHP) has been functioning in Thiruvananthapuram district of Kerala since 1999.A targeted intervention for school children was launched in the district by 2011-12. The Comprehensive Mental Health Scheme (CMHS) 2014-15, to be implemented in all districts of Kerala, addresses the initiation of school mental health programs in the rest of the 13 districts. DMHP Thiruvananthapuramis the nodal center for training of other DMHPs.

Thalir
School Mental Health Program of DMHP Thiruvananthapuram, named ***Thalir,*** aims the empowerment of adolescents to overcomes tress, substance abuse and other emotional and behavioral problems, to prevent suicides, and to increase competence to cope with challenges of life using available resources. Objectives of the program are:

- Sensitization of teachers and parents
- Skill development of teachers, school counselors and school JPHN to form a link between the schools and DMHP andto identify and intervene in adolescent crises.
- Training of teams of resource persons and trainers, district and statewide,to conduct sessions related to emotional and behavioral problems of adolescence, substance use, suicide prevention, stress management, life skills, etc.
- Interventions for at-risk adolescents through counseling camps and referral to DMHP clinics.

METHODOLOGY AND MATERIALS
- Target population: Adolescents (10-19 years).
- The school intervention program concentrates on students of 5th to 12th standards.
- Educational materials and tools used:
  - "Thaliru'' booklet for parents, teachers and counsellors
  - Posters and leaflets on school mental health
  - Student evaluation forms

- Student reference forms
- Modules on teacher training and parenting skills

FUNCTIONAL LEVELS OF SCHOOL MENTAL HEALTH MODEL

Thalir aims holistic development of school children through the following phases:

1. Preventive:

- Sensitisation of parents to detect and manage behavioural and emotional problems through awareness classes at the school
- Mental health skill development classes for teachers
- Mental health training to school counsellors and School Health Nurse, Child Development Programme Officers(CDPOs) and ICDS supervisors

2. Reconstructive:

- Awareness programmes to school children through trained resource persons
- Counselling camps in schools for children in need
- Referring those requiring further management to nearby DMHP Clinics

3. Rehabilitative:

- Supervising the rehabilitation of special need children in Buds schools

4. Evaluation:

- Scrutinizing program model ,making timely changes in the guidelines, and rectifying errors

Fig 1

Sensitisation for link establishment

This phase involves training for School Health Nurses, school counsellors, ICDS supervisors and CDPOs. This improves links with the schools and brings down the stigma and resistance with respect to programme implementation. The trained School JPHN and counsellors further coordinate the conductance of classes and counselling camps in their respective schools by procuring requests for the same from the heads of institution and informing the DMHP team through emails and requests to coordinator of the programme in DMHP team.

Building a team of trainers

Dearth of manpower is the first roadblock to implementation of any program. This can be overcome only by building a team of quality and quantity. Human resources are built on the basis of presence of an aptitude for community social work and a basic training in health and psychology. The following resource persons are trained at DMHP Nodal Center:

- State level training of resource persons from other districts sent through concerned DMHP/CMHP.
- Interested teachers from High Schools (two from each school) of Thiruvananthapuram district.
- School Health Nurse in School Health Program and school councilors of Thiruvananthapuram district
- Psychology postgraduates
- Social Work postgraduates

GUIDELINES FOR SCHOOL MENTAL HEALTH IN OTHER DISTRICTS AS PER CMHS

- 4-6 resource persons (Psychology and Social Work postgraduates) should be selected by the Implementation Committee of concerned DMHP/CMHP in each district.
- Selected resource persons will be trained on early identification of common mental health problems in adolescents, stress management, and counseling skills by DMHP Thiruvananthapuram at Kerala State Health & Family Welfare, Thiruvananthapuram for three days**.**
- Training modules prepared by DMHP Thiruvananthapuram will be provided to resource persons from other districts.

Guidelines at school level

- Awareness classes by resource persons for parents, teachers and high school students
- Counseling camps
- Referral of at-risk adolescents who require further interventions to nearest DMHP Clinic
- Leaflets, brochures and posters provided for distribution among students and parents
- Evaluation forms provided to teachers, and they will submit them to DMHP
- School Health Nurse to liaise with school and DMHP/CMHP team

Fig 2

Common mental health problems addressed in adolescents

Fig 3

1. Topics covered

Topics covered by the awareness classes include emotional issues like love affairs & failures, family disharmony, financial problems, illnesses in family and alcoholism-related problems in family; behavioural issues like substance abuse, DSH (Deliberate Self Harm or suicide attempts), and conduct disorder; and other issues like suicide prevention, stress management, and life skill development.

Modules for presentation and training in schools are prepared by DMHP. Trainers take classes based on these guidelines.

2. Classes on exam stress

Time management, stress reduction,tips to improve attention, concentration and memory, etc. are a few areas. Module on exam stress is prepared by DMHP for use in the schools**.**

EXTENSION OF DMHP SERVICES THROUGH SMHP

- Anganwadis - Awareness classes are conducted for teachers and parents of preschool children. Awareness classes and workshops are conducted for adolescent groups.
- Camps in "Buds" school for management of autistic spectrum disorders, mental retardation, cerebral palsy, epilepsy, etc., and remedial education skills for parents.
- Mental health training for teachers of Buds school, social workers of NGOs, etc.

CONCLUSION

126schools have been covered in Thiruvananthapuram district through *Thalir* School Mental Health Program. Out of 25,413 adolescents brought under the program, 370 students with psychological morbidity were detected and mental health services were provided to them. Awareness classes for 503 parents and classes on skill enhancement for 428 teachers were also organized by DMHP Thiruvananthapuram (Data as of Feb 2014).

DMHP Thiruvananthapuram has been successfully implementing its School Mental Health Program since 2012 and has phased out into various areas with extension of its services. The program model has been approved and adopted in the CMHS 2014-15 implementation guidelines for all districts of the state. It will act as a forerunner for School Mental Health Programs to be implemented in other districts. The experience and successful implementation of the model and guidelines have enabled DMHP Thiruvananthapuram to take the role of the nodal training center for the other districts where these programs are yet to be born.

Early identification and interventions in child and adolescent mental health can lead to primordial as well as primary prevention of psychiatric morbidities. An effective network of school counselors, school JPHN and DMHP-trained resource persons can lead to wide coverage of mental health needs of children and adolescents in all districts through DMHP/CMHP supervision. An added attention to awareness of teachers and parents makes it an effective, non-restrictive and comprehensive mental health intervention.

REFERENCES

1. Constitution.org.India. Available from http://www.constitution.org/cons/india/const.html
2. Unicef.org.United Kingdom. UN Convention on the rights of children. Available from http://www.unicef.org.uk/UNICEFs-Work/Our-mission/UN-Convention/

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IMAGES

Fig 1

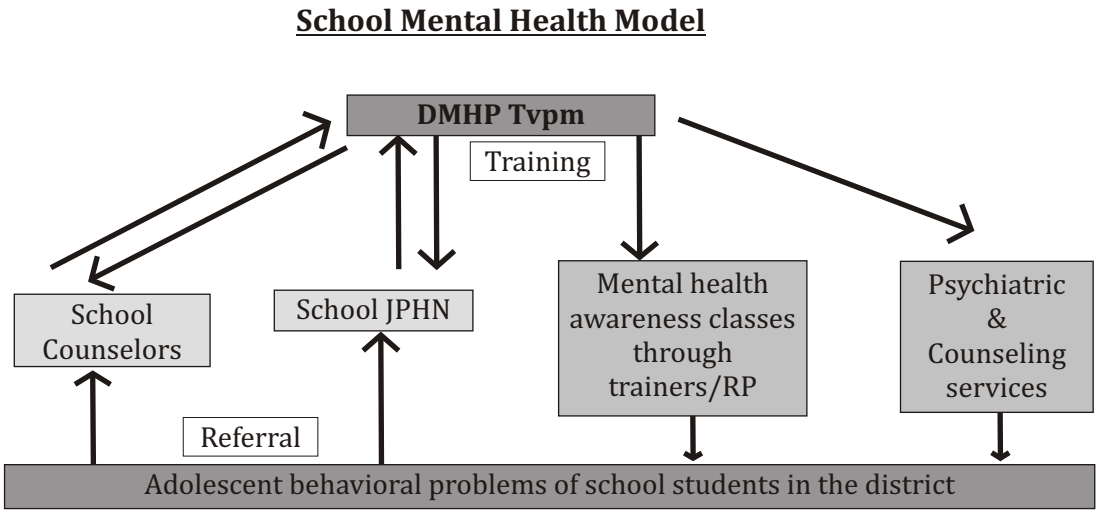

Fig 2

Fig 3

Review Article

Management of Illicit Drug Use - Part 1 Cannabis

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Abstract
Cannabis is the most common illicit drug abused across the world. The addictive potential and harmful effects of cannabis have been established. Anecdotal evidence suggests a recent spurt of its usage in Kerala, especially among adolescents and young adults. This selective review outlines the current clinical management strategies for cannabis use and related disorders. There is a lack of robust pharmacological trials, and most medications have been studied only in open-label trials. Currently there is better evidence base for psychosocial interventions. Many aspects of the management of cannabis dependence, including optimal duration of treatment, have not been studied. All of this is in spite of evidence that the number of people in the community who require treatment is large, and that only 20% users achieve long-term abstinence suggesting a need for a concerted effort to develop effective interventions.

(Key words Management, cannabis dependence, pharmacotherapy, psychosocial interventions)

Anecdotal evidence suggests that use, abuse and dependence of various substances have been increasing across our state in the last few decades. Though data is still preliminary with regards to the prevalence of use of various substances in our state, a large recent school and college survey in the District of Ernakulam has suggested that cannabis and solvents form the most prevalent illicit drug of use[1, 2]. It is in this background that this two-part article is being written, to selectively review recent publications on the current management strategies for cannabis and solvent use. (The second part, reviewing the management of solvent use, is to be published in the next issue of the journal).

General Considerations

Cannabis is obtained from the Indian hemp plant *Cannabis sativa*. Of the many psychoactive ingredients, delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) are of greatest interest. CBD is reported to have antipsychotic and anxiolytic properties and contributes significantly to the potential medical benefits of cannabis.[3] THC is present in all parts of the plant. Cut, dried and chopped parts of the plant are rolled into cigarettes and smoked, and are called as "joints". The dried exudate extracted from the top of the plant is hashish. The concentrate is referred to as hash oil, and is commonly inhaled as vapours. Sensimilla made from the seedless female flower is another potent form of the drug. Cannabis can also be prepared in food for oral consumption, most common being brewing it in tea leaves (referred to as 'bhang').

Cannabis is the most common illicit drug used across the world. Studies from various countries report that 20-40% have lifetime cannabis use and 3-5% have regular use, with most regular users being below the age of 25 years[3,4]. The Indian National Household survey reports that 3% of adults have used cannabis[5] According to a recent survey from Kerala, 1.7% of college students and 0.7% of school students have used cannabis in their lifetime[1, 2]. Addictive potential of cannabis has been established. The harmful effects of cannabis are summarized in Table 1

As with other substances of abuse, two major cannabis-related diagnoses have been described

1. Cannabis use disorders which include cannabis abuse and cannabis dependence
2. Cannabis induced disorders which include intoxication delirium, psychotic disorder and anxiety disorder.

With the recent publication of DSM V it is now officially recognised that long-term regular use leads to withdrawal [6], which though not life-threatening like alcohol, can be discomforting and can last up to 4 weeks in 50-95% of individuals (Table 2)

General Principles for Treatment

Very few subjects report for treatment of primary cannabis use. Most often in practise, subjects' cannabis use comes to attention when they are assessed for other mental health issues. It is important to note that a very high rate of drop outs are noted after initial assessment, especially in outpatient settings, which actually means a quick assessment should be immediately followed by brief intervention.

Assessment

A comprehensive assessment determines the management plan and the monitoring requirements of the patient.

Broad domains of assessment should include the following:

- Pattern of recent history of cannabis and other drug use, Quantity/Frequency of use, Indicators of severity of dependence/withdrawal symptoms/Periods of abstinence
- Past treatment & outcome, Presenting/ Predisposing/Precipitating/Perpetuating/Protective factors, other substance use
- Mental Health History: Present/Past-Psychiatric diagnosis if any, Current/Past suicide risk, Admissions/Treatment, Family history, Current mental state, Psychosocial Issues/supports
- Treatment Goals: Abstinence, Reduction in usage, Stabilisation of mental state (all patients)
- Motivation to change: Internal/External motivators, Barriers to change, Success of previous attempts Pros & cons of changing, Behavioural changes required

After assessment, clinicians need to deliver accurate feedback in an empathic, non-judgemental, and non-threatening manner. Patients need to envision the benefits of change. After feedback, patients may be allowed to develop their goal in a collaborative fashion. This improves the subjects' motivation to sustain the changes they have decided to make.

Biochemical screening for cannabis

Cannabis can be detected in both urine and saliva (Table-3). Dipstick techniques are best used for screening, though it is not possible to distinguish between current/previous use. Mass spectroscopy and gas chromatography techniques are used for confirmatory tests but they can be expensive.

Intoxication

Intoxication is usually mild and self-limiting, and do not require any pharmacological interventions [10, 11]. Severe effects like anxiety/panic disorder and transient psychosis are best treated with benzodiazepines or second generation antipsychotics as appropriate to acutely control symptoms.

Withdrawal symptoms

Cannabis withdrawal should be targeted because it commonly serves as negative reinforcement for relapse to cannabis use in individuals trying to abstain. Withdrawal symptoms emerge typically after 1-3 days of abstinence, peak between 2-6 days and last from 4-14 days (rarely up to 4 weeks) [11,12].

Withdrawal symptoms from cannabis are not life threatening, and if the patient is well motivated out-patient detoxification may be attempted.

Inpatient detoxification is considered if there are:

1. Multiple failed attempts at out-patient detoxification.
2. Poly-substance use
3. Comorbid medical or psychiatric conditions.
4. Aggressive behaviour or suicidal tendencies
5. Severe withdrawal symptoms that cannot be managed on an outpatient basis
6. History of poor treatment compliance

Psycho-education

Process and symptoms of cannabis withdrawal and approximate duration of the symptoms should be explained to all the patients. This is extremely useful for self-management of withdrawal symptoms that can be attempted. There is strong evidence for use of psychosocial interventions, like sleep hygiene, progressive muscle relaxation, exercise and social supports, especially for mild to moderate withdrawal.

Pharmacotherapy for detoxification

No medications are approved for treatment of cannabis withdrawal. Medications should be initiated for those with mild withdrawal only if absolutely required, and should be symptom focussed. A typical regime should be limited to not more than one week.

In patients experiencing severe withdrawal, a number of medications have been tried in small clinical trials. The results are summarized below:

- **Dronabinol:** (Synthetic THC) This is an anti-emetic used in cancer chemotherapy and HIV, and is currently unavailable in India, though it is expected to be licensed soon. In doses of 30mg tid, Dronabinol is reported to reduce cannabis withdrawal symptoms significantly [13].
- **Lithium:** Lithium reduces withdrawal symptoms in doses of 600-900mg/daily, and one study showed it has persisting effect in maintaining abstinence[13].

  Valproate and Bupropion have no effect, and might even worsen the withdrawal[13].

Appropriate treatment should be initiated if a diagnosable psychiatric condition emerges after the withdrawal period.

Pharmacotherapy for relapse prevention

No medication has been shown to be effective or licensed in cannabis dependence. Most studies to date are open label studies, which means most practice guidelines do not make an evidence based recommendations. The major strategy as of now is to substitute agonist with antagonist or Neuromodulation.

Substitution with cannabnoid (CB1) receptor agonistDronabinol: In doses 10-50mg/daily reduced

cannabis use and suppressed cannabis withdrawal. Rates of abstinence did not show much improvement [10, 14, 15].

Neuromodulation

- **Entacapone** This agent inhibits Catechol O Methyl Transferase, an enzyme which metabolises catecholamine neurotransmitters and thereby regulates the release of dopamine. Open label trials in 36 patients with a dose of up to 2000mg/day for 12 weeks had found reduced craving for cannabis [10, 14].
- **N Acetyl Cysteine** At a dose of 600mg/twice daily for 4 weeks, this agent decreased cannabis use and craving, and was well tolerated [15].
- **Atomoxetine:** At a dose of 40-80mg/day, Atomoxetine caused reduction in cannabis use and increase in abstinent days. It was more effective in patients with history of ADHD [14].
- **Buspirone:** At dose of 60mg/day over 12 weeks, Buspirone reduced cannabis craving and use [13,14].

Pharmacotherapy for Comorbid Psychiatric Conditions

Cannabis users frequently have comorbid mood symptoms, especially depression. Clinical trials have demonstrated the efficacy of fluoxetine at a dose of 20-40mg/day to reduce the cannabis use and to improve depressive features [13].

Cannabis use is more common in those with schizophrenia. It may contribute to increased relapse rate, noncompliance, poor social function, and exacerbation of positive symptoms. Hence its treatment is very important in this group. A retrospective study done to evaluate the efficacy of clozapine over risperidone showed that those on clozapine had greater chances of maintaining abstinence from cannabis [13,14].

Psychological Interventions

Brief Interventions

Brief Interventions are generally opportunistic interventions for clients who have presented for treatment of some other condition and detected to have risky levels of cannabis use.

"FRAMES" is one of the most widely used brief intervention strategy in substance use. "FRAMES" was initially formulated as a brief intervention strategy for alcohol use. Various trials have shown that the six components of "FRAMES" are effective in harmful use of various substances, including cannabis [12].

The components of "FRAMES" include:

Feedback: can be about the physical, psychological or social harm caused by cannabis.

Responsibility: Therapist should emphasise personal responsibility for change. Treatments are likely to be unsuccessful if the patient is coerced into treatment.

Advice: to either cut down or completely abstain. Total abstinence is often advisable for most people, especially those who have a history of mental illness or for whom there are significant psychosocial issues.

Menu: This is about discussing a menu (range) of options jointly with the patient, to cut down or abstain and set specific treatment goals.

Empathic interviewing: Clinician's empathy is at the heart of delivering brief interventions. Never confront the patient as it is always unhelpful. Instead, empathetically explore his reasons for change with him.

Self efficacy: is about empowering the patient or enhancing the patient's own belief that they can change.

Brief Intervention can be completed within 15-20 minutes, with success closely linked to ensuring of follow-ups.

Psychotherapy for cannabis

Three major psychotherapies described below have the best evidence in cannabis related disorders. Most therapies have a mean duration of six weekly sessions [13, 14].

Motivational Interviewing, Cognitive Behaviour Therapy, Contingency Management

Motivational Interviewing

Motivational Interviewing (MI) is a clinical strategy designed to enhance client motivation for change. MI is supported by over 60 trials [13, 14] which have shown its effectiveness in a range of behaviours, including substance use, health promotion behaviours, medication adherence etc.

There are four basic principles underlying MI

Principle 1: Express Empathy

Expressing empathy towards the patient shows acceptance and increases the chance of a good rapport.

- Acceptance enhances self-esteem and facilitates change.
- Skilful reflective listening is fundamental.
- Participant ambivalence is normal

Principle 2: Develop Discrepancy

Developing discrepancy enables the patient to see that the present situation does not necessarily fit into his values and what he would like in the future.

- A participant is encouraged to present the arguments for change.
- Change is motivated by a perceived discrepancy between present behaviour and important personal goals and values.

Principle 3: Roll with Resistance

One view of resistance is that the client is behaving defiantly. Another is that resistance is a signal that the client views the situation differently. This requires that the therapist understand the client's perspective. This is usually a signal for the therapist to change direction or to listen more carefully. Rolling with resistance prevents a breakdown in communication between participant and therapist and allows the subject to explore his views.

- Avoid arguing for change.
- Do not directly oppose resistance.
- New perspectives are offered but not imposed.
- The participant is a primary resource in finding answers and solutions.
- Resistance is a signal for the therapist to respond differently.

Principle 4: Support Self-efficacy

Self-efficacy is a crucial component to facilitating change. If a participant believes that he has the ability to change, the likelihood of change is greatly increased.

- A person's belief in the possibility of change is an important motivator.
- The participant, not the therapist, is responsible for choosing and carrying out change.
- The therapist's own belief in the participant's ability to change becomes a self-fulfilling prophecy.

Cognitive Behaviour Therapy (CBT)

CBT works on the principle that for many patients with drug use it is the primary mechanism to cope with a range of situations, both negative (distressing) and positive (celebrations). CBT works on helping subjects to develop a range of techniques for overcoming habitual reliance on drugs as a coping mechanism [15].

The following coping skills are enhanced:

- Managing urges and cravings
- Recognising triggers of drug use
- Developing personal strategies to avoid or deal with such triggers
- Managing negative emotions
- Stress management skills
- Assertiveness training
- Relaxation skills

Contingency Management (CM)

CM involves the systematic use of positive and negative consequences (reward and punishment) following target behaviour[15]. CM considers drugs as operant behaviour, i.e. behaviour that is maintained partly by biochemical effects of the substance and partly by reinforcing environmental influences. CM seeks to provide alternative incentives contingent upon abstinence from a particular target drug. CM has been found to assist cannabis users to achieve extended periods of continuous cannabis abstinence [15].

Before initiating CM the following need to be agreed upon:

- The target behaviour
- The type of reward
- Principles of application

Family Interventions

Family Interventions are especially effective in adolescents. Family therapy takes a family systems approach to resolve problems by enhancing intra-family communication, improving parental limit setting, and facilitating collaborative recovery work [15]. Empirical support for the efficacy of family based treatments has emerged across multiple randomized trials[16]. In adolescents, family based interventions have definite advantage when combined with other forms of psychotherapy.

12-Step Facilitation Programs

Twelve step programs are an integral part of substance use disorders. In 2008, the Marijuana Anonymous World Service published a 12 step workbook [16]. But the extent to which these 12 step programs are utilized, their long-term efficacy, and their potential role as an integral component of psycho-social interventions for cannabis dependence have not been examined.

To conclude, many aspects of management of cannabis dependence are still unclear. Optimal duration of treatment has not been studied. There is significant lack of pharmacological trials and many of the drugs mentioned above have been studied only in open-label trials. Evidence is more robust for psycho-social interventions. In spite of this, the number of people who require treatment in the community remain large and few people actually receive any intervention. Studies suggest that long term abstinence is achieved by only 20%, suggesting a need for a concerted effort to develop effective interventions for the betterment of patients, families and the society at large.

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References

1. Psychological Profile of School Going Adolescents in the District of Ernakulam, Kerala NRHM Report 2013
2. Psychological Profile of College students in the District of Ernakulam, Kerala NRHM Report - 2013
3. Shoyama Y, Tamada T, Kurihara K, Takeuchi A, Taura F, Arai S, etal. Structure and function of d1-tetrahydrocannabinolicacid (THCA) synthase, the enzyme controlling the psychoactivity of *Cannabissativa*: *Journal of Molecular Biology* 2009; *423:96-105.*

4. Copeland, J. & Swift, W. Cannabis use disorder: Epidemiology and management: *International Review of Psychiatry 2009; 21*(2); 96103.
5. Ministry of Health and Family Welfare Government of India. India: National Family Health Survey (NFHS-3) 2005-06 Key Findings. From: www.measuredhs.com/pubs/pdf/SR128/SR128.pdf Accessed May 2014
6. APA: *Diagnostic and Statistical Manual*. 5th edition. Arlington: American Psychiatric Association; 2013.
7. Budney AJ, Moore BA, Vandrey RG, Hughes JR. The time, course and significance of cannabis withdrawal. *Journal of Abnormal Psychology 2003;112*, 393402.
8. Budney AJ, et al. Review of the validity and significance of cannabis withdrawal syndrome. Am J Psychiatry 2004; 161(11):19671977.
9. Copersino, M.L., Boyd, S.J., Tashkin, D.P., Huestis,M.A., Heishman, S.J., Dermand et al Cannabis withdrawal among non-treatment-seeking adult cannabis users. *American Journal on Addiction.2006; 15*(1):814.
10. Danovitch Itai, Gorelick A. State of the Art Treatments for Cannabis Dependance: Psychiatr Clin North Am.2012;35(2):309-326.
11. Budney AJ, Roffmann R, Stephens RS, Walker D. Marijuana dependence and its treatment Addict Sci Clin Pract.2007; 4(1):4-16.
12. Budney AJ, Moore. BA,Sigmon S, Higgins ST. Contingency management interventions for cannabis dependence. Roffmann R, Stephens R, editors. Cannabis dependence: its nature, consequences and treatment. Cambridge University Press 2006: 155-176.
13. Copeland J. Developments in the treatment of cannabis use disorder. Curr Opin Psychiatry.2004; 17:161-168.
14. McRae AL, Budney AJ, Brady KT. Treatment of marijuana dependence**:** a review of the literature. J Subst Abuse Treat. 2003; 24(4): 369-376.
15. Budney .J, Vandrey G, Stanger Catherine: Pharmacological and psychosocial interventions for Cannabis use disorders: NIH-PA Manuscript 2010; 32(01):546-S55.
16. Stephens RS, Roffman RA, Simpson EE. Treating adult marijuana dependence: a test of the relapse prevention model. J Consult Clin Psychol. 1994; 62(1): 92-99.

Table 1 Harmful effects of cannabis

Risks of acute intoxication	• Impaired attention, memory, and psychomotor performance while intoxicated • Cannabis-induced psychosis • Increased risk of motor-vehicle accidents
Most probable chronic effects	• Subtle cognitive impairment in attention, memory, and the organisation and integration of complex information • increased risk of developing a dependence syndrome • adverse respiratory effects and increased risk of lung cancer
Probable risks among special populations	Adolescent cannabis use: • Poorer school performance and outcomes • Lower levels of degree attainment by age 25 • Higher unemployment • Lower levels of life satisfaction • Leaving the family home • Early sexual activity and teenage pregnancy • Other illicit drug use and dependence Pregnant Women • Low birth weight baby (which can lead to mortality, morbidity, and disability) • exacerbation of some mental health conditions such as depression , anxiety, and schizophrenia

Table 2 Symptoms of cannabis withdrawal

SYMPTOM	DURATION	PREVALENCE
Anger, aggression, irritability	Few days to 3 weeks	Highly prevalent
Anxiety/ nervousness	Few days to 3 weeks	Highly prevalent
Restlessness	Few days to 3 weeks	Highly prevalent
Sleep difficulties	Few days to 4 weeks	Highly prevalent
Craving	Few days	Common
Weight change/ decreased appetite	First week	Common
Depressed mood	Lasting upto 4 weeks	Less common

Table 3 Cannabis Detection Times

Amount	Urine	Oral fluid
Single use	3-4 days	4-14 hours
Oral ingestion	1-5 days	Unknown
Daily use/ chronic use	10-36 days	4-30 hours

Review Article

Living to eat: Understanding Food Addiction

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Abstract
In the recent years, in an attempt to understand obesity, the food addiction model has been proposed. Using animal models of addiction, behaviour patterns similar to drug dependence have been seen for sugars and fats. Dopamine and opiod receptors along with dopamine circuit involvement similar to drug dependence have been implicated in food addiction. Studies in human populations have shown food addiction to be present only in a group of obese and binge eating disorder individuals and also present in those who are not obese. The food addiction model can have implication in treatment of individuals with maladaptive eating patterns and in food policies.

Key words: Food addiction, obesity, binge eating disorder, food policy

The world is fighting an obesity epidemic. The National Family Health Survey -3, 2005-06 showed that more than 13% of women and 9 % of men in India are overweight or obese.(1). In the past few years researchers have found patterns similar to drug dependence and obesity (2), including compulsive (3) and binge eating patterns (4). This has led to the concept of food addiction. Much evidence in based on hyperpalatable foods(5), though hypotheses on addiction potential of refined food(6) and salt(7) has also been made. This article briefly illustrates the current evidence on the concept of food addiction and its possible implications.

ANIMAL MODELS OF FOOD ADDICTION

Recent attempts have been tried to explain food addiction based on animal models and similarities with drug dependence behavior. It was the pioneering works of late Bartley G. Hoebel (1935- 2011) whose efforts on understanding hunger and satiety brought about the evidence for addiction for sugars (8) . By placing rats in alternating 12 hours schedules of starvation and feeding with sucrose solution and chow, Hoebel along with his team were able to demonstrate binging behavior among rats. These rats were also sensitive to amphetamine , and this led to a hypothesis of possible involvement of the dopamine system (9). With this study as his foundation, he was able to show that after abstinence, rats would show enhanced intake of sugar similar to craving (10), withdrawal symptoms including anxiety (11), and signs similar to opiate withdrawal (12). He also showed that rats feeding on a combination of sweet-fat diet did not show the addiction symptoms when compared to rats fed on sugar alone (13). This suggested the possibility that food addiction could also be nutrient-specific.

Animal studies have also shown increased motivation to work for sugar (14), and aggressive behavior when sugar is removed (15). Intermittent access to high fat and sweet fluid has also been shown to increase motivation in binge-eating rats(16). Cross sensitization with cocaine(17) and amphetamine(9) and cross tolerance with morphine (18) have also been noted.

Stress and calorie restriction in rats has been found to promote binge eating (19). Food seeking has also been noticed in rats under the setting for aversive stimulus (20). Rats have even shown preference for sugar solutions over cocaine (21).

Binging behavior has also being noticed in rats feeding on high fat diet (22), but studies have not able to reproduce the same results on addictive behavior as that of rats addicted on sugar. Hoebel et al reviewed studies on addictive type behaviors of rats on different nutrients and proposed that sugar might be the cause of addictive behavior in obese patients where fats induced weight gain.

NEUROBIOLOGICAL CORRELATES

Dopamine, the main chemical mediator for reward, has been implicated in food addiction. Wang et. al., by imaging studies, has found dopamine to be decreased in obese individuals in proportion to their Body Mass Index, causing increasing food consumption to compensate for decreased activation of dopamine circuits (23). Imaging studies have shown the involvement of overlapping of dopamine circuits for reward, motivation, learning and emotions involved in drug addiction and obesity (24). With regards to sugar addiction, animal studies have found increased D1 receptor and decreased D2 receptor binding in nucleus accumbens and striatum respectively. Opioid mu receptor binding (25) and opioid-like withdrawal symptoms have also been found to be high in rats which consume excess sugar.

With relation to neuroanatomical areas, certain similarities have been noted with obesity and drug dependence, leading to the possibility of food addiction in obese individuals. Similar to drug addiction, craving related activation of hippocampus, insula and caudate nucleus have been noted in obese individuals (26). The same areas, along with medial and lateral orbitofrontal cortex, amygdala, nucleus accumbens/ventral striatum, medial prefrontal cortex, anterior cingulate cortex, ventral pallidum, caudate, and putamen has also been noted be activated in food related cues (27), and the situation is similar to cues related to smoking (28). Reward deficiency syndrome has also been described in obese individuals following the finding of downregulation of D2 receptors in the striatum and hypersensitivity of reward circuits to hyperpalatable food cues (29)

YALE FOOD ADDICTION SCALE

Yale Food Addiction Scale (YFAS) was developed by Gearhardt et al (30) with questions based on substance dependence criteria of Diagnostic and Statistical Manual- IV, and has been validated as a tool for diagnosis of food addiction (31)(32). This questionnaire consists of 27 items that assess eating patterns over the past 12 months. The YFAS scoring is by a combination of Likert scale ranging from 0-7 and a dichotomous scoring. When three or more symptoms are present within the past 12 months and clinically significant impairment or distress is present, the criteria for food addiction is said to be met.

FOOD ADDICTION IN HUMAN POPULATION

Using the YFAS, the concept of food addiction as phenotype of obesity has been proven by Davis et al (32). Pedram et. al found the prevalence of food addiction to be 5.4 % in Newfoundland and Labrador province, Canada, with 62.1 % of the population being obese(33). The study also found a higher rate of food addiction in women than men, and a positive correlation between food addiction and severity of obesity.

A study showed obese patients not seeking weight loss treatment having a 25% prevalence of food addiction(32), and another study showed 15% prevalence of food addiction among obese patients seeking weight loss treatment (31). A cohort study of individuals with normal Body Mass Index (BMI) showed a prevalence of 8.8 % of food addiction with negligible correlation between food addiction and BMI(34). Obese patients having binge eating disorders were found to have a prevalence 56.2% of food addiction(35). Meule has proposed a non-linear relationship between food addiction and BMI (36)

Food addicts have also shown proneness to mood disorders, emotion dysregulation, stress, and lower self-esteem(32) (35). Impulsivity was found to have positive association with food addiction and BMI (37).

IMPLICATIONS

From the above mentioned studies, we have to accept that, the food addiction concept, even if valid, need not have to be a casual explanation for obesity or binge eating disorder. With the evidence of food addiction present in a population with normal BMI (as described earlier), the concept of food addiction could explain maladaptive eating patterns.

Nevertheless, the concept of food addiction can have implications in treatment in a subset of obese and binge eating population meeting the criteria for food addiction. For example, Baclofen, raclopride and naltrexone have been shown to affect the intake of fat and sugar in rats (38). Overeaters Anonymous, a 12 step peer programme for people with food-related problems, has been formed, but evidence into its efficacy has been lacking. Other psychotherapies like Motivational Enhancement Therapy, Cognitive Behaviour Therapy, and Dialetical Behaviour Therapy will have to be studied for its usefulness for patients diagnosed with food addiction.

The concept of food addiction will have significant implications in food policies when more evidence becomes available in the future. Regulations on sugar and fat content can be expected, similar to the ones of alcohol and tobacco. This can bring upon changes in the eating patterns of humans.

CONCLUSION

Food addiction is in its growing stages with growing evidence of involvement of sugar and fat, presence in obese, non-obese and binge eating disorder individuals. Further research will help us in better understanding and validity of this concept and also in our fight against the obesity epidemic.

REFERENCES

1. Press Information Bureau English Releases [Internet]. [cited 2014 Jul 12]. Available from: http://pib.nic.in/newsite/ erelease.aspx?relid=31835
2. Fortuna JL. The obesity epidemic and food addiction: clinical similarities to drug dependence. J Psychoactive Drugs. 2012 Mar;44(1):5663.
3. Davis C, Carter JC. Compulsive overeating as an addiction disorder. A review of theory and evidence. Appetite. 2009 Aug;53(1):18.
4. Smith DG, Robbins TW. The neurobiological underpinnings of obesity and binge eating: a rationale for adopting the food addiction model. Biol Psychiatry. 2013 May 1;73(9):80410.
5. Gearhardt AN, Davis C, Kuschner R, Brownell KD. The addiction potential of hyperpalatable foods. Curr Drug Abuse Rev. 2011 Sep;4(3):1405.
6. Ifland JR, Preuss HG, Marcus MT, Rourke KM, Taylor WC, Burau K, et al. Refined food addiction: a classic substance use disorder. Med Hypotheses. 2009 May;72(5):51826.

7. Cocores JA, Gold MS. The Salted Food Addiction Hypothesis may explain overeating and the obesity epidemic. Med Hypotheses. 2009 Dec;73(6):8929.
8. Avena NM, Rada P, Hoebel BG. Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav Rev. 2008;32(1):2039.
9. Avena NM, Hoebel BG. A diet promoting sugar dependency causes behavioral cross-sensitization to a low dose of amphetamine. Neuroscience. 2003;122(1):1720.
10. Avena NM, Long KA, Hoebel BG. Sugar-dependent rats show enhanced responding for sugar after abstinence: evidence of a sugar deprivation effect. Physiol Behav. 2005 Mar 16;84(3):35962.
11. Avena NM, Bocarsly ME, Rada P, Kim A, Hoebel BG. After daily bingeing on a sucrose solution, food deprivation induces anxiety and accumbens dopamine/acetylcholine imbalance. Physiol Behav. 2008 Jun 9;94(3):30915.
12. Colantuoni C, Rada P, McCarthy J, Patten C, Avena NM, Chadeayne A, et al. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. Obes Res. 2002 Jun;10(6):47888.
13. Bocarsly ME, Berner LA, Hoebel BG, Avena NM. Rats that binge eat fat-rich food do not show somatic signs or anxiety associated with opiate-like withdrawal: implications for nutrient-specific food addiction behaviors. Physiol Behav. 2011 Oct 24;104(5):86572.
14. La Fleur SE, Vanderschuren LJMJ, Luijendijk MC, Kloeze BM, Tiesjema B, Adan R a. H. A reciprocal interaction between food-motivated behavior and diet-induced obesity. Int J Obes 2005. 2007 Aug;31(8):128694.
15. Galic MA, Persinger MA. Voluminous sucrose consumption in female rats: increased "nippiness" during periods of sucrose removal and possible oestrus periodicity. Psychol Rep. 2002 Feb;90(1):5860.
16. Lardeux S, Kim JJ, Nicola SM. Intermittent access to sweet high-fat liquid induces increased palatability and motivation to consume in a rat model of binge consumption. Physiol Behav. 2013 Apr 10;0:2131.
17. Gosnell BA. Sucrose intake enhances behavioral sensitization produced by cocaine. Brain Res. 2005 Jan 21;1031(2):194201.
18. Lieblich I, Cohen E, Ganchrow JR, Blass EM, Bergmann F. Morphine tolerance in genetically selected rats induced by chronically elevated saccharin intake. Science. 1983 Aug 26;221(4613):8713.
19. Hagan MM, Wauford PK, Chandler PC, Jarrett LA, Rybak RJ, Blackburn K. A new animal model of binge eating: key synergistic role of past caloric restriction and stress. Physiol Behav. 2002 Sep;77(1):4554.
20. Latagliata EC, Patrono E, Puglisi-Allegra S, Ventura R. Food seeking in spite of harmful consequences is under prefrontal cortical noradrenergic control. BMC Neurosci. 2010 Feb 8;11(1):15.
21. Lenoir M, Serre F, Cantin L, Ahmed SH. Intense Sweetness Surpasses Cocaine Reward. PLoS ONE [Internet]. 2007 Aug 1 [cited 2014 Jul 13];2(8). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1931610/
22. Corwin RL, Wojnicki FH, Fisher JO, Dimitriou SG, Rice HB, Young MA. Limited access to a dietary fat option affects Ingestive behavior but not body composition in male rats. Physiol Behav. 1998 Dec 1;65(3):54553.
23. Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, et al. Brain dopamine and obesity. Lancet. 2001 Feb 3;357(9253):3547.
24. Volkow ND, Wang G-J, Fowler JS, Telang F. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. Philos Trans R Soc B Biol Sci. 2008 Oct 12;363(1507):3191200.
25. Colantuoni C, Schwenker J, McCarthy J, Rada P, Ladenheim B, Cadet JL, et al. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. Neuroreport. 2001 Nov 16;12(16):354952.
26. Pelchat ML, Johnson A, Chan R, Valdez J, Ragland JD. Images of desire: food-craving activation during fMRI. NeuroImage. 2004 Dec;23(4):148693.
27. Stoeckel LE, Weller RE, Cook EW, Twieg DB, Knowlton RC, Cox JE. Widespread reward-system activation in obese women in response to pictures of high-calorie foods. NeuroImage. 2008 Jun;41(2):63647.
28. McBride D, Barrett SP, Kelly JT, Aw A, Dagher A. Effects of expectancy and abstinence on the neural response to smoking cues in cigarette smokers: an fMRI study. Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol. 2006 Dec;31(12):272838.
29. Kenny PJ. Reward mechanisms in obesity: new insights and future directions. Neuron. 2011 Feb 24;69(4):66479.
30. Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale. Appetite. 2009 Apr;52(2):4306.
31. Clark SM, Saules KK. Validation of the Yale Food Addiction Scale among a weight-loss surgery population. Eat Behav. 2013 Apr;14(2):2169.
32. Davis C, Curtis C, Levitan RD, Carter JC, Kaplan AS, Kennedy JL. Evidence that "food addiction" is a valid phenotype of obesity. Appetite. 2011 Dec;57(3):7117.
33. Pedram P, Wadden D, Amini P, Gulliver W, Randell E, Cahill F, et al. Food Addiction: Its Prevalence and Significant Association with Obesity in the General Population. PLoS ONE [Internet]. 2013 Sep 4 [cited 2014 Jul 13];8(9). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3762779/
34. Meule A, Vögele C, Kübler A. Deutsche Übersetzung und Validierung der Yale Food Addiction Scale. Diagnostica. 2012 Jan 1;58(3):11526.
35. Gearhardt AN, White MA, Masheb RM, Morgan PT, Crosby RD, Grilo CM. An examination of the food addiction construct in obese patients with binge eating disorder. Int J Eat Disord. 2012 Jul;45(5):65763.
36. Meule A. Food addiction and body-mass-index: a non-linear relationship. Med Hypotheses. 2012 Oct;79(4):50811.
37. Murphy CM, Stojek MK, MacKillop J. Interrelationships among impulsive personality traits, food addiction, and Body Mass Index. Appetite. 2014 Feb 1;73:4550.
38. Corwin RL, Wojnicki FH. Baclofen, raclopride, and naltrexone differentially affect intake of fat and sucrose under limited access conditions. Behav Pharmacol. 2009 Sep;20(5-6):53748.

Review Article

Pursuit of Happiness - The Ketamine Version

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Abstract

Major depressive disorder is an extremely debilitating condition affecting millions of people worldwide and results in high public health costs. Although over the past half century better treatment strategies were evolved, delayed onset of antidepressant action remains one of the major limitations in the management of major depressive disorder. Recent research shows low dose ketamine, an NMDA receptor antagonist, emerging as a novel rapid acting antidepressant. This review examines the literature on ketamine and its antidepressant properties. The pharmacological properties, including the chirality of ketamine, are reviewed along with the preclinical and clinical data on ketamine's use as a rapidly acting antidepressant. Literature on various routes of administration, side effects, safety and abuse potential and ongoing research on neurocognitive effects and mechanism of action of ketamine are also examined. There is paucity of controlled trials and data on the biomarkers, mechanism of action underlying the rapid action, and measures to sustain the antidepressant action of ketamine. Understanding the molecular pathways through which ketamine exerts its antidepressant effects would help in developing novel antidepressant agents that do not evoke the same negative side effects of this drug.

Ketamine was first synthesized by Calvin Stevens at the Parke-Davis Laboratories in 1962[1].The pharmacological use of Ketamine, a chiral arylcyclohexy lamine (RS)-2-(2-chlorophenyl)-2-methylaminocyclohexanone, began when it was patented in Belgium in 1963 as a veterinary anesthetic. In 1965 it was determined that Ketamine could be a safer anesthetic alternative to phencyclidine (PCP) with fewer propensities for side effects. The same year itself the first known account of ketamine's recreational use was noted by Professor Edward Domino. He described it as a potent psychedelic drug and for which it was termed as a "dissociative anesthetic". After being patented for human use in 1966 by Parke-Davis Laboratories, ketamine became available, by prescription, in 1969, in the form of Ketamine Hydrochloride under the name of Ketalar. Ketamine was approved by the FDA in 1970 as an anesthetic agent[2].It was administered to the injured soldiers during the Viet Nam War as a field anesthetic.

Pharmacology

Ketamine is classified as an NMDA receptor antagonist with high-affinity for PCP site.It has a complex pharmacological profile and shows affinity for numerous other receptors, effects on which may also contribute to the impact of ketamine on mood and cognition. Racemic Ketamine hydrochloride has an elimination half-life of 22.5 hours and distribution half-life of 1015 minutes. Its bioavailability is 93% in intramuscular, 2550% in intranasal, and 1620% in oral routes. It undergoes hepatic metabolism involving Cytochrome system CYP2B6, CYP3A4 and CYP2C9.Ketamine is metabolized into norketamine and dehydronorketamine[3].

Ketamine Antidepressant Effects

The recent clinical research demonstrates evidence to support ketamine's use as an antidepressant[4-8].Ketamine was first reported to have therapeutic effects in a study on eight patients with major depressive disorder(MDD)in 2000 which showed that an intravenous ketamine infusion (0.5 mg/kg) resulted in significant and rapid but short-lived antidepressant effects[4].In a randomized controlled trail(RCT), Zarate et al[5] confirmed the findings of Berman et al[4].Response rates of ketamine in treatment resistant depression (TRD) in the open-label and controlled trials have ranged from 25% to 85% at 24 hours post infusion and from 14% to 70% at 72 hours post infusion[7].Murrough et al. compared IV ketamine with midazalom[9].The ketamine group had better MADRS score than the midazolam group 24 hours after treatment. Unlike traditional antidepressants, a sub anesthetic dose of ketamine does not induce an affective switch in TRD[10].

Following on from the initial trials of ketamine in MDD, others have looked at ketamine in bipolar depression[6,8] and have shown it to be rapidly effective but not long lasting. Patients were maintained on lithium or valproate during the study time frame.

Ketamine and Suicidality

Ketamine showed rapid reduction in suicidal ideation scores on the depression rating scales used in the pioneer trials[4,5]. This has since been replicated in two open-label investigations of MDD patients and in one RCT on bipolar patients[6,8,11]. They demonstrated that ketamine was associated with robust and rapid

antisuicidal effects[8,11]. Rapid reductions in explicit and implicit suicidal cognitions were noted within a day of treatment which persisted if received additional infusions. Researchers considered that the attenuation of suicidality was likely to be the result of the antidepressant effect of the treatment than a specific antisuicidal effect[12]. Studies in the emergency room a well as palliative care setting found that a single IV bolus of ketamine rapidly improving suicidal ideation[13,14].

Sustaining the Antidepressant Effects of Ketamine

Preclinical trials attempted to sustain the response to ketamine have largely centered on repeated infusions. Parise and collegues[15] found that ketamine reversed the chronic unpredictable stress-induced depression-like behaviours in mice in the Forced swim test. They also indicated that repeated ketamine exposure induces enduring resilient-like responses regardless of age of exposure. Results with repeated infusions clinically[16-18] have been less positive than the preclinical trials. Aan hetRot et al suggested that the most practical use of repeated ketamine infusions might be on a short-term basis to elicit rapid relief until a more sustainable treatment and relapse prevention strategy could be demonstrated[16].Efforts to maintain ketamine's antidepressant effects using other pharmacological agents were also disappointing. Riluzole failed to provide any benefit over placebo in maintaining the response whereas Memantine gave variable results[19-22].

Ketamine and ECT

ECT is the most rapid of the accepted treatments for TRD, yet there remains a delay in the antidepressant effect. Ketamine is used as the anesthetic agent in ECT, usually when it is not possible to adequately induce seizures with barbiturates.[23] Two case studies report synergistic antidepressant effects of ketamine anesthesia in ECT.[24,25] Ostroff et al.[26] reported rapid response in depressive symptoms in a patient receiving ketamine anesthesia for ECT but not achieving an adequate seizure. Findings from an open-label trial suggested that ketamine anesthesia has an early antidepressant effect during ECT than propofol anesthesia. As the pychomimetic side effects are dose-related, subanesthetic doses of ketamine with alternate anesthetic agents is an effective augmentation strategy for TRD[22].A report on the use of sub anesthetic dose ketamine augmentation with ECT shows that it speeds the response rate[27].

Routes of Administration

The IV route of administration (ROA) was used in the first clinical report on MDD[4].Subsequent replications have used the same ROA and dosing strategy (0.5 mg/kg slow infusion over 40 minutes). Intramuscular ketamine in the dose of 0.25 mg/kg was also found as effective and safe as 0.5 mg/kg I.M.or I.V, substantially alleviating depressive symptoms within a few hours and sustained for 3 days.[28]McNulty et al[29] reported the effectiveness of a single low-dose (0.5 mg/kg) subcutaneous ketamine in hospice patients with symptoms of TRD and anxiety and it was sustained with a compounded flavored oral ketamine solution (40 mg/5 mL) that is not commercially available. De Gioannis A et al[30] suggested oral ketamine augmentation for chronic suicidality in TRD. In a trial among hospice care patients who received daily oral ketamine experienced a robust antidepressant and anxiolytic response with few adverse events and a response rate similar to IV ketamine. But the time to response was more protracted[31]. Intranasal ketamine trails report rapid effects and minimal adverse effects[32]. Lara etal. demonstrated clear and sustained antidepressant effects of sublingual ketamine on mood, cognition and sleep[33].

Chirality

Ketamine is a chiral drug with R and S enantiomers. Although commonly administered as a 1:1 racemic mixture of (S) and (R) ketamine, S-ketamine(S-K) is available for medical use in several European countries. S-K has 34 times higher affinity to the phencyclidine binding site of the NMDA receptor than R-ketamine(R-K).[34]Other pharmacological differences are that the S-K is 12 times more potent as an ACh antagonist,[35] and has a 2- to 3-fold higher potency for opiate receptors than the R-K.[36] S-K is also three times more potent as anesthetic and two times more potent as analgesic than R-K[37].In equianalgesic doses, R-K is more psychotomimetic than S-K[38,39].Therefore, S-K is safer and more effective than R-K in TRD. Paul *et al.*[40] reported that S-K (0.25 mg/kg) may be as effective as an antidepressant as racemic ketamine (0.5 mg/ kg) and may not induce perceptual or mood disturbances as does racemic ketamine. The enhanced pharmacological potency of S-K suggests that use of this isomer may reduce undesirable adverse effects without altering its clinical benefit[40].S-K has potentially important tolerability advantages over its racemic mixture. After a subanaesthetic dose of R-K fifty percent of subjects experienced anterograde amnesia while only 8% experienced this side effect with S-K[41].Neuroimaging studies have shown rapid recovery of cerebral functions and increases in cerebral blood flow with S-K[42, 43]. S-K showed better neuroprotective functions than its racemic mixture in animal models of ischaemia and in human cognitive laboratory experiments[44,45].

Mechanism of Action

Ketamine's antidepressant effects have mostly been explained in terms of its effects on the glutamate system. There is a large body of preclinical literature on brain glutamate function and depression [4648]. MDD has been associated with low BDNF levels as well as with low mammalian target of rapamycin (mTOR) expression [49,50]. Ketamine has been found to increase mTOR

phosphorylation but not BDNF levels[51,52]. Synaptogenesis in response to mTOR activation is hypothesized to contribute to ketamine's acute and sustained antidepressant effects [53]. Duman et al [54]suggested that the ketamine at low doses increases glutamate neurotransmission by both increased glutamate release and increased AMPA receptor expression and insertion into the synaptic plate. This causes secondary increase in BDNF release, and hence activation of extracellular signal-regulated kinases (ERK) signalling which then stimulates mTOR a kinase that controls protein translation and thus via a complex signaling path, leads to increased synaptic protein expression (GluR1) and increased insertion and density of synapses leading to increased structural connectivity between neurons, particularly in the pre-frontal cortex. However, in healthy volunteers, ketamine does not appear to affect brain glutamate levels even during IV infusion [55]. In mice, ketamine does not appear to activate mTOR signaling [56]. Clearly more work is needed to delineate the biological mechanism underlying ketamine's antidepressant effects.

Another suggested mechanism is immunomodulation. Ketamine is able to reduce inflammation, an effect that could occur via inhibition of NF-kB or by preventing IDO activation and the possible concomitant shift of tryptophan metabolism toward neurodegenerative metabolites[57].

The role of glycogen synthase kinase-3 (GSK-3)[57], a kinase that, interestingly, is also a target of mood-stabilising agents, in the antidepressant effect of ketamine is far from clear and more work needs to be done in this area.

Of interest, recent evidence has shown that the antidepressant effects of ketamine were completely abolished when female rats were ovariectomized, and restored upon oestrogen and progesterone supplementation, suggesting a critical role for gonadal hormones.[58] This may be clinically relevant, as ketamine has already shown sex-specific differences, both in rat models of analgesia and catalepsy[59] and in human studies looking at amnestic effects.[60]

Side Effects, Abuse Potential and Safety of Ketamine

Ketamine also known as "Special K" is one of several "club drugs" that is abused to induce a dissociative state. Adverse effects of sub anesthetic ketamine infusion include confusion, dizziness, euphoria, perceptual disturbances, increased libido and elevated blood pressure; these usually last for not more than 1-2 hours[61]. Berman et al. found transient cognitive deficits and euphoria which returned to baseline within 2h following the infusion[4]. Zarate et al. demonstrated perceptual disturbances, confusion, elevations in blood pressure, euphoria, dizziness and increased libido, majority of which were ceased within 80 min after the infusion[5].Euphoria or derealisation/depersonalization never persisted beyond 110 minutes. Murrough et al reported significant dissociative symptoms and elevated blood pressure in the ketamine group[9].

Not much is known about ketamine's safety when given repeatedly at sub-anesthetic doses in depressed patients.Chronic ketamine abuse has been associated with cystitis[62]and bilary dilatation[63]. However ,Krystal etal. commented that such findings in ketamine abusers may overestimate the clinical risks of long-term treatment[63].Ketamine abusers often take multiple substances, administer more frequent and higher doses than needed to treat depression,[64].Nonetheless, the development of long-term ketamine treatment for TRD would need to be accompanied by careful studies of its safety.

Ketamine results in up-regulation of mTOR[65] in patients with cancer and this may cause the acceleration of tumor growth[66]. Further research addressing the safety of ketamine in cancer patients with TRD is mandatory.

Despite the fact that most of the studies demonstrate that the psychotomimetic effects of ketamine appear transient, concerns regarding abuse could lead to the therapeutic benefits being overlooked. These side-effects when compared with those of monoaminergic antidepressants may represent some advantage for ketamine over existing therapies. Zarate et al. commented that the misuse of therapeutically relevant agents is not a new phenomenon in psychiatry and should not preclude the trials as putative treatments [67].

Neurocognitive Effects of Ketamine

The short-term effects of ketamine on neurocognition in healthy volunteers have been studied extensively[68-74]. Ketamine appears to disrupt information en coding that occurs during drug administration but does not impair recall for previously learned information[70,71,73]. Some studies have found evidence for selective impairments in executive functioning related to ketamine[68,69] while other studies have found no impairments[71,72]. A large review of possible untoward or prolonged events associated with ketamine use in healthy volunteers found ketamine to carry a very low risk of adverse events [74].

A critical initial observation regarding the antidepressant effect of ketamine was the temporal discordance between acute dissociative and neurocognitive effects and improvements in core symptoms of depression[4,5,19]. Lower levels of baseline neurocognitive performance, particularly processing speed in TRD are associated with an increased response rate to ketamine[75].

This is potentially consistent with a model relating BDNF or neuroplasticity to cognition and antidepressant response to ketamine as the BDNF functioning is linked to cognition[76] and there is association between a common single nucleotide polymorphism in the gene coding for BDNF and antidepressant response to ketamine as reported by Laje et al[77]. Ketamine results in selective disruption of delayed recall for information learned directly after administration of the drug. Acute reductions in cognitive performance following ketamine carries negative prognostic significance[75]. The influence of the glutamate release inhibitor lamotrigine on the cognitive side effects of ketamine was found to be non significant [75].

Biomarkers and Clinical Predictors of Response to Ketamine

Ongoing research is exploring the identification of the biomarkers and clinical predictors of positive response to ketamine[78].Some significant findings are listed below.

Genetics

The 'Val66Met SNP' has been linked to impaired trafficking/regulation of BDNF .Animal studies found that Val/Val mice exhibited increased pre frontal cortex synaptogenesis and antidepressant response to ketamine. A recent study among TRD patients found that the Val/Val BDNF allele were more likely to have an increased antidepressant response to ketamine than Met carriers.

Functional Neuroimaging

Salvadore et al using magnetoencephalography (MEG) demonstrated that higher pretreatment levels of rACC activity correlated positively with the magnitude of subsequent antidepressant response to ketamine[79]. Studies suggest that high pgACC response to emotionally salient stimuli, but low pgACC response to increased cognitive demands, predicts antidepressant response to ketamine. Pretreatment ACC activity may be a putative biomarker of treatment response.

Pretreatment Glx/glutamate ratio in the dorsomedial/ dorsal anterolateral PFC negatively correlate with the improvement with ketamine. MDD patients who show the greatest clinical improvement with ketamine may be characterized by larger reductions in glial concentrations. This hypothesis is supported by post-mortem studies that found prominent reductions in glial pathology in MDD patients. Thus, glial cellular deficits may serve as unique targets for novel strategies in the treatment of MDD.

Sleep Architecture

Decreased slow wave sleep is a prominent feature of depression. Slow wave activity (SWA) and individual slow wave parameters are sensitive markers of cortical synaptic strength, thus serving as surrogate markers of central synaptic plasticity. A recent study of patients with TRD investigated the acute effects of ketamine on depressive symptoms relative to EEG SWA, individual slow wave parameters, and plasma BDNF. In this study, early sleep SWA and BDNF levels increased compared to baseline. Those patients that responded to ketamine had changes in BDNF proportional to changes in EEG parameters[80]

A significant positive correlation was found between baseline delta sleep ratios (DSR) and reduced MADRS score post-ketamine infusion[81].Low baseline DSR scores also predicted an improved response the following week. These effects are similar to those seen following antidepressant treatment in general, which normalizes slow wave sleep and DSR suggesting that DSR may reflect a biomarker of response to ketamine[81].

Clinical Predictors

Krystal et al pointed out that subjects with alcohol dependence (ADS) had fewer perceptual alterations and decreased dysphoric mood during ketamine infusion[82]. Same was also observed in healthy individuals with family history of ADS. Also the MDD patients with family history of ADS had a better short term outcome after ketamine infusion. Genetic variation in the NMDA receptor 2Agene has been associated with ADS, may be potential genetic mechanism.

Future Directions

The clinical variables predicting good response, maintenance of the good response and quick relapse should be the focus of future studies. Trials with bigger sample size, using active placebos, stereo isomers, alternative doses and routes of administration, examining the mechanism of action, biomarkers, adverse effects, abuse potential of ketamine will give more insight about the status of ketamine as an antidepressant. Understanding the molecular pathways through which ketamine exerts its antidepressant effects would help in the development of novel antidepressant agents that do not evoke the same negative side effects of ketamine.

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References

1. ReichDL, SilvayG.Ketamine: an update on the first twenty five years of clinical experience. Can J Anaesth 1989; 36 (2): 186-97)
2. Ketalar_ (ketamine) hydrochloride injection [package insert]. Rochester (MI): JHP Pharmaceuticals, LLC, 2009 Feb]
3. Sanjay J. Mathew, Asim Shah, Kyle Lapidus, Crystal Clark, Noor Jarun, Britta Ostermeyer and James W. Murrough

Ketamine for Treatment-Resistant Unipolar Depression Current Evidence CNS Drugs 2012; 26 (3): 189-204

4. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000; 47 (4): 351-4
5. Zarate CAJr,SinghJB,CarlsonPJ,etal:A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression.ArchGen Psychiatry2006;63(8):856864
6. ZarateCAJr,BrutscheNE,IbrahimL,etal:Replicationof ketamine's antidepressantefficacy inbipolardepression:a randomized controlledadd-ontrial.BiolPsychiatry2012; 71(11):939946
7. Aan HetRotM,ZarateCAJr,CharneyDS,MathewSJ: Ketamine for depression: where do we go from here? Biol Psychiatry 2012;72(7):537547
8. Diazgranados N,IbrahimL,BrutscheNE,etal:A randomized add-ontrialofan N-methyl-D-aspartate antag- onist intreatment-resistant bipolardepression.ArchGen Psychiatry 2010;67(8):793802
9. Murrough JW,IosifescuDV,ChangLC,etal:Antide- pressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial.AmJ Psychiatry 2013;170(10):11341142
10. Niciu, M.J.,Luckenbaugh,D.A.,Ionescu,D.F.,etal.,2013. Subanestheticdose ketamine does not induce an affective switch in three independent samples of treatment-resistant major depression.Biol.Psychiatry74(10), e23e24.
11. Price RB, Nock MT, Charney DS, et al. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol Psychiatry 2009; 66 (5): 522-6
12. Diaz Granados N, Ibrahim LA, Brutsche NE, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment- resistant major depressive disorder. J Clin Psychiatry 2010; 71 (12): 1605-11
13. Larkin GL, Beautrais AL. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. Int Neuropsychopharm 2011; 14 (8): 1127-31
14. Thangathurai D, Mogos M. Ketamine alleviates fear, depression, and suicidal ideation in terminally ill patients [letter]. J Palliat Med 2011; 14 (4): 389
15. Parise,E.M., Alcantara, L.F., Warren,B.L., 2013. Repeated ketamine exposure induces an enduring resilient phenotypeinadoles centandadultrats. Biol.Psychiatry74 (10),750759.
16. Aan hetRot,M.,Collins,K.A,Murrough,J.W,etal.,2010. Safety and efficacy of repeated dose intravenous ketamine for treatment resistant depression.Biol. Psychiatry 67,139145.
17. Murrough, J.W.,Perez,A.M.,Stern,J.,etal.,2013b. Rapidandlonger-term antidepressant effects of repeated ketamine infusions in treatment-resistant depression. Biol. Psychiatry 74,250256.
18. Segmiller, F.,Rüther,T.,Linhardt,A.,etal.,2013.Repeated S-ketamineinfusionsin therapyresistantdepression: acaseseries.J.Clin.Pharmacol.53(9),996998.
19. Mathew, S.J.,Murrough,J.W.,AanhetRot,M.,etal.,2010. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: a pilot randomised,placebo-controlled continuation trial.Int.J.Neuropsychopharmacol. 13,7182.
20. Ibrahim, L.,DiazGranados,N.,Franco-Chaves,J.,etal., 2012.Course ofimprovement in depressivesymptomstoa single intravenous infusion of ketaminevs.add-on riluzole: resultsfroma4-week,doubleblind,placebo-controlled study. Neuropsychopharmaclogy 37, 15261533.
21. Kollmar, R., Markovic, K., Thurauf, N., et al., 2008. Ketamine followed by memantine for the treatment of major depression. Aust. N.Z. J. Psychiatry 42, 170.
22. Zarate,C.A.,Singh,J.,Quiroz,J.A.,etal.,2006b.Adouble-blind, placebo-controlled study of memantine in the treatment of major depression.Am.J. Psychiatry 163,153155
23. Loo C, SimpsonB, MacPhersonR: Augmentation strategies in electroconvulsive therapy. JECT2010;26(3): 202207
24. Goforth HW, HolsingerT: Rapid relief of severe major depressive disorder by use of preoperative ketamine and electroconvulsive therapy.JECT2007;23(1):2325
25. McDaniel WW, SahotaAK, VyasBV, LaguertaN, Hategan L, OswaldJ: Ketamine appears associated with better word recall than etomidate after a course of 6 electroconvulsive therapies.JECT2006;22(2):103106
26. Ostroff R, GonzalesM, SanacoraG: Antidepressant effect of ketamine during ECT.AmJPsychiatry2005;162 (7):13851386
27. Ryan Sultan,M.D.,PatricioRiva-Posse, M.D., StevenJ. Garlow, M.D.,Ph.D., Ann C.Schwartz,M.D. Beneficial Pre-ECT Ketamine Infusion in a Patient with Treatment Resistant Depression Psychosomatics2014:55:396399
28. Chilukuri H, Reddy NP, Pathapati RM, Manu AN, Jollu S, ShaikABAcute antidepressant effects of intramuscular versus intravenous ketamine. Indian J Psychol Med. 2014 Jan;36(1):71-6. doi: 10.4103/0253-7176.127258.
29. McNulty JP(1), Hahn K. Compounded oral ketamine. Int J Pharm Compd. 2012 Sep-Oct;16(5):364-8
30. De Gioannis A(1), De Leo D(2). Oral ketamine augmentation for chronic suicidality in treatment-resistant depression. Aust N Z J Psychiatry. 2014 Jan 22;48(7):686. [Epub ahead of print]
31. Irwin SA(1), Iglewicz A, Nelesen RA, Lo JY, Carr CH, Romero SD, Lloyd LS. Daily oral ketamine for the treatment of depression and anxiety in patientsreceiving hospice care: a 28-day open-label proof-of-concept trial. J Palliat Med. 2013 Aug;16(8):958-65. doi: 10.1089/jpm.2012.0617. Epub 2013 Jun
32. Lapidus KA, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, Feder A, Iosifescu DV, Charney DS, Murrough JW. A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder Biol Psychiatry. 2014 Apr 3. pii: S0006-3223(14)00227-3. doi:10.1016/j.biopsych.2014.03.026. [Epub ahead of print]
33. Lara, D.R.,Bisol, L.W.,Munari, L.R.,2013. Anti depressant, mood stabilizing and precognitive effects of very low dose sublingual lketamine in refractory unipolar and bipolar depression.Int.J. Neuropsychopharmacol. 16(9), 21112117.
34. Vollenweider FX, Leenders KL, Oye I, et al. Differential Psychopathology and patterns of cerebral glucose

utilization produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). Eur Neuropsychopharmacol 1997; 7 (1): 25-38

35. Lodge D, Anis NA, Burton NR. Effects of optical isomers of ketamine on excitation of cat and rat spinal neurons by amino acids and acetylcholine. Neurosci Lett 1982;29 (3): 281-6
36. Finck AD, Ngai SH. Opiate receptor mediation of ketamine analgesia. Anesthesiology 1982; 56 (4): 291-715.
37. Kohrs R, Durieux ME. Ketamine: Teaching an old drug new tricks. Anesth Analg 1998;87:1186-93.
38. Raeder JC, Stenseth LB. Ketamine: A new look at an old drug. Curr Opin Anaesthesiol 2000;13:463-8.
39. Liu J, Ji XQ, Zhu XZ. Comparison of psychic emergence reactions after (+/-)-ketamine and (+)-ketamine in mice. Life Sci 2006;78:1839-44.
40. Paul R, Schaaff N, Padberg F, Möller HJ, Frodl T. Comparison of racemic ketamine and S-ketamine in treatment-resistant major depression: Report of two cases. World J Biol Psychiatry 2009;10:241-4.
41. Pfenninger E, Baier C, Claus S, et al. Psychometric changes as well as analgesic action and cardiovascular adverse effects of ketamine racemate versus s-(+)-ketamine in subanesthetic doses [in German]. Anaesthesist 1994; 43 (2): 68-75
42. Himmelseher S, Pfenninger E. The clinical use of S-(+)-ketamine: a determination of its place. Anasthesiol Intensivmed Notfallmed Schmerzther 1998; 33 (12): 764-70
43. Langsjo J, Maksimow A, Salmi E, et al. S-ketamine anesthesia increases cerebral blood flow in excess of the metabolic needs in humans. Anesthesiology 2005; 103: 258-68
44. Proescholdt M, Heimann A, Kempski O. Neuroprotection of S(+) ketamine isomer in global forebrain ischemia. Brain Res 2001; 904: 245-51
45. Pfenninger E, Durieux M, Himmelseher S. Cognitive impairment after small-dose ketamine isomers in comparison to equianalgesic racemic ketamine in human volunteers. Anesthesiology 2002; 96 (2): 357-66
46. Hashimoto K (2009): Emerging role of glutamate in the pathophysiology of major depressive disorder. Brain Res Rev 61:105123.
47. Machado-Vieira R, Manji HK, Zarate CA (2009): The role of the tripartite glutamatergic synapse in the pathophysiology and therapeutics of mood disorders. Neuroscientist 15:525539.
48. Skolnick P, Popik P, Trullas R (2009): Glutamate-based antidepressants:20 years on. Trends Pharmacol Sci 30:563569.
49. Post RM (2007): Role of BDNF in bipolar and unipolar disorder: Clinical and theoretical implications. J Psychiatr Res 41:979 990.
50. Jernigan CS, Goswami DB, Austin MC, Iyo AH, Chandran A, Stockmeier CA, et al. (2011): The mTOR signaling pathway in the prefrontal cortex is compromised in major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry 35:1774 1779.
51. Denk MC, Rewerts C, Holsboer F, Erhardt-Lehmann A, Turck CW (2011): Monitoring ketamine treatment response in a depressed patient via peripheral mammalian target of rapamycin activation. Am J Psychiatry 168:751752.
52. Machado-Vieira R, Yuan P, Brutsche N, DiazGranados N, Luckenbaugh D, Manji HK, et al. (2009): Brain-derived neurotrophic factor and initial antidepressant response to an N-methyl-D-aspartate antagonist. J Clin Psychiatry 70:16621666.
53. Li N, Lee B, Liu R-J, Banasr M, Dwyer JM, Iwata M, et al. (2010): mTORDependent synapse formation underlies the rapid antidepressant effectsof NMDA antagonists. Science 329:959 964.
54. Duman RS, Li N, Liu RJ, Duric V, Aghajanian G. Signaling pathways underlying the rapid antidepressant actions of ketamine. Neuropharmacology 2012;62(1): 35e41. Epub 2011/09/13.
55. Taylor MJ, Tiangga ER, NÃ Mhuircheartaigh Ri, Cowen P (2012): Lack of effect of ketamine on cortical glutamate and glutamine in healthy volunteers: A proton magnetic resonance spectroscopy study. J Psychopharmacol 26:733737.
56. Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, et al. (2011): NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 475:9195.
57. PA Zunszain, MA Horowitz, A Cattaneo, MM Lupi and CM Pariante Ketamine: synaptogenesis, immunomodulation and glycogen synthase kinase-3 as underlying mechanisms of its antidepressant properties Molecular Psychiatry(2013) 18,1236-121
58. Carrier N, Kabbaj M. Sex differences in the antidepressant-like effects of ketamine. Neuropharmacology 2013; 70C: 2734.
59. Winters WD, Hance AJ, Cadd GC, Lakin ML. Seasonal and sex influences on ketamine-induced analgesia and catalepsy in the rata possible role for melatonin. Neuropharmacology 1986; 25: 10951101.
60 Morgan CJA, Perry EB, Cho HS, Krystal JH, D'Souza DC. Greater vulnerability to the amnestic effects of ketamine in males. Psychopharmacology 2006; 187:405414
61. Innovative approaches to treatment - refractory depression: The ketamine Story T. S. Sathyanarayana Rao, Chittaranjan Andrade Indian J Psychiatry 52(2), Apr-Jun 2010
62. Chen, L.Y., Chen, K.P., Huang, M.C., 2009. Cystitis associated with chronic ketamine abuse. Psychiatr. Clin. Neurosci. 63, 591.
63. Krystal, J.H.,Sanacora,G.,Duman,R.S.,2013.Rapid-actingglutamatergicantide- pressants:the path toketamineandbeyond.Biol.Psychiatry73,11331141.
64. Morgan, C.J., Curran,H.V.,2012.Ketamine use:a review.Addiction107,2738.
65. Yang, C., Zhou, Z., Yang, J., 2011. Be prudent of ketamine in treating resistant depression in patients with cancer. J. Palliat. Med. 14 (5), 537.)
66. Shor, B., Gibbons,J.J.,Abraham,R.T.,2009.Targeting mTOR globally in cancer: thinking beyond rapamycin. CellCycle8,38313837.
67. ZarateJr,C.A.,Machado-Viera,R., Henter,I.,etal., 2010. Glutamatergicmodulators: the future for treating mooddisorders?Harv.Rev.Psychiatry18(5),293303.

68. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS (1994) Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199214

69. Krystal JH, D'Souza DC, Karper LP, Bennett A, Abi-Dargham A, Abi-Saab Cassello K, Bowers MB Jr, Vegso S, Heninger GR, Charney DS (1999) Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. Psychopharmacology (Berl) 145:193204

70. Krystal JH, Perry EB Jr, Gueorguieva R, Belger A, Madonick SH, Abi-Dargham A, Cooper TB, Macdougall L, Abi-Saab W, D'Souza DC (2005) Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. Arch Gen Psychiatry 62:985994. doi:10.1001/archpsyc.62.9.985

71. Morgan CJ,MofeezA, Brandner B, Bromley L, Curran HV(2004) Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. Neuropsychopharmacology 29:208218. doi: 10.1038/sj.npp.1300342

72. Parwani A, Weiler MA, Blaxton TA,Warfel D, Hardin M, Frey K, Lahti AC (2005) The effects of a subanesthetic dose of ketamine on verbal memory in normal volunteers. Psychopharmacology (Berl) 183: 265274. Doi:10.1007/s00213-005-0177-2

73. Rowland LM, Astur RS, Jung RE, Bustillo JR, Lauriello J, Yeo RA (2005) Selective cognitive impairments associated with NMDA receptor blockade in humans. Neuropsychopharmacology 30:633 639. Doi:10.1038/sj.npp.1300642

74. Perry EB Jr, Cramer JA, Cho HS, Petrakis IL, Karper LP, Genovese A, O'Donnell E, Krystal JH, D'Souza DC, Yale Ketamine Study Group (2007) Psychiatric safety of ketamine in psychopharmacology research. Psychopharmacology (Berl) 192:253260. Doi:10.1007/s00213-007-0706-2

75. James W. Murrough & Le-Ben Wan & Brian Iacoviello & Katherine A. Collins & Carly Solon & Benjamin Glicksberg & Andrew M. Perez & Sanjay J. Mathew & Dennis S. Charney & Dan V. Iosifescu & Katherine E. Burdick Neurocognitive effects of ketamine in treatment-resistant major depression: association with antidepressant response Psychopharmacology (2014) 231:481488

76. Swardfager W, Herrmann N, Marzolini S, Saleem M, Shammi P, Oh PI, Albert PR, Daigle M, Kiss A, Lanctot KL (2011) Brain derived neurotrophic factor, cardiopulmonary fitness and cognition in patients with coronary artery disease. Brain Behav Immun 25:12641271.

77. Laje G, Lally N, Mathews D, Brutsche N, Chemerinski A, Akula N, Kelmendi B, Simen A, McMahon FJ, Sanacora G, Zarate C Jr (2012) Brain-derived neurotrophic factor Val66Met polymorphism and antidepressant efficacy of ketamine in depressed patients. Biol Psychiatry 72:e27e28.

78. Carlos A. Zarate Jr., M.D., Daniel C. Mathews, M.D. And Maura L. Furey, Ph.D. Human biomarkers of rapid antidepressant effectsExperimental Therapeutics & Pathophysiology Branch, Division of Intramural Research Program,National Institute of Mental Health, National Institutes of Health, and Department of Health and Human Services, Bethesda, Maryland

79. 80Salvadore G, Cornwell BR, Colon-Rosario V, Coppola R, Grillon C, Zarate CA Jr, et al. Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. Biol Psychiatry. 2009; 65:289295.

80. 87Duncan WC, Sarasso S, Ferrarelli F, Selter J, Riedner BA, Hejazi NS, et al. Concomitant BDNF and sleep slow wave changes indicate ketamine-induced plasticity in major depressive disorder. Int J Neuropsychopharmacol. 2012; 7:111.

81. 88Duncan WC Jr, Selter J, Brutsche N, Sarasso S, Zarate CA Jr. Baseline delta sleep ratio predicts acute ketamine mood response in major depressive disorder. J Affect Disord. 2012 Aug 4. [Epubahead of print].

82. 91Krystal, J.H., Petrakis, I.L., Krupitsky, E., Etal., 2003. NMDA receptor antagonism and the ethanol intoxication signal:form alcoholism risk to pharmacotherapy.Ann. N.Y.Acad.Sci.1003,176184.