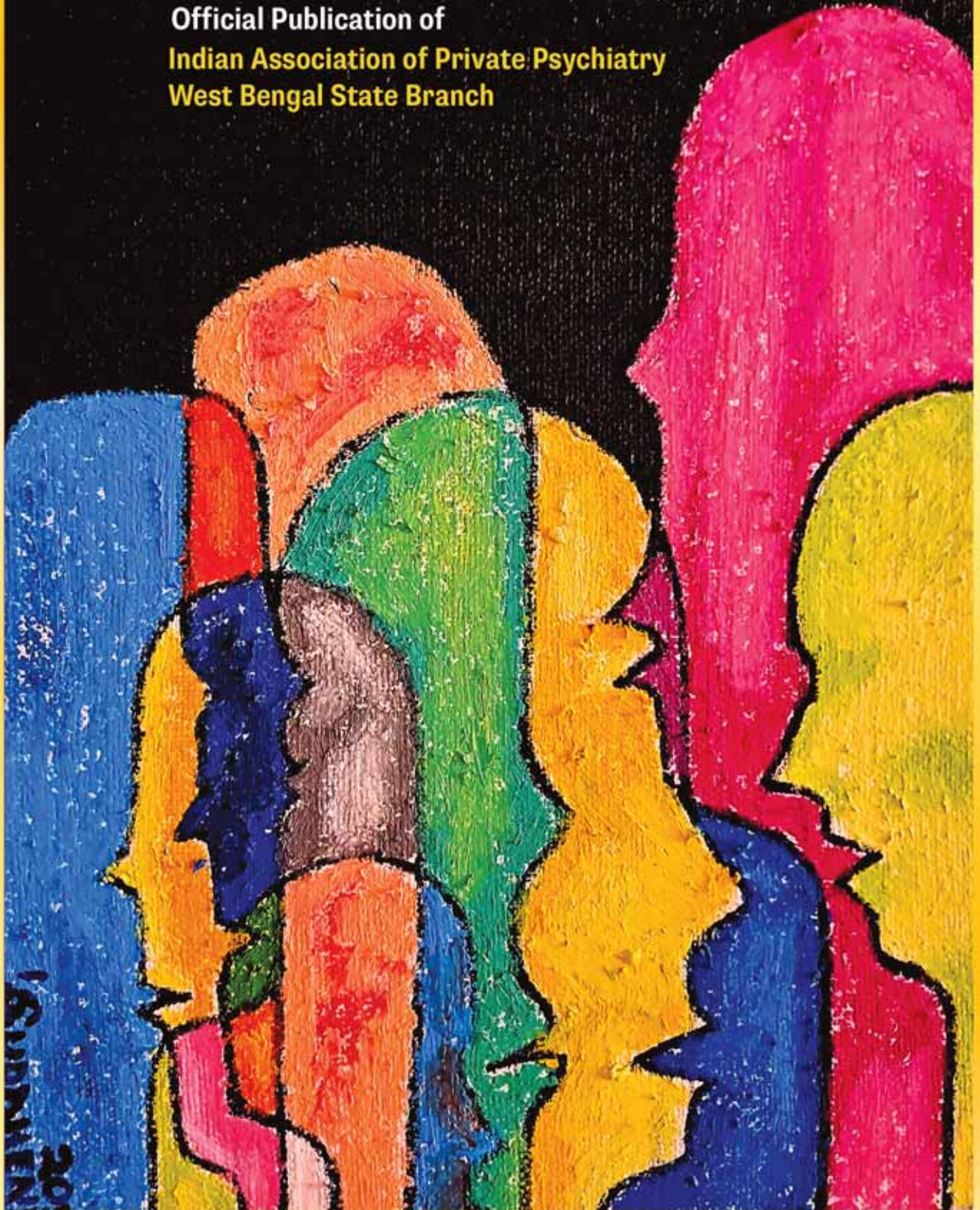


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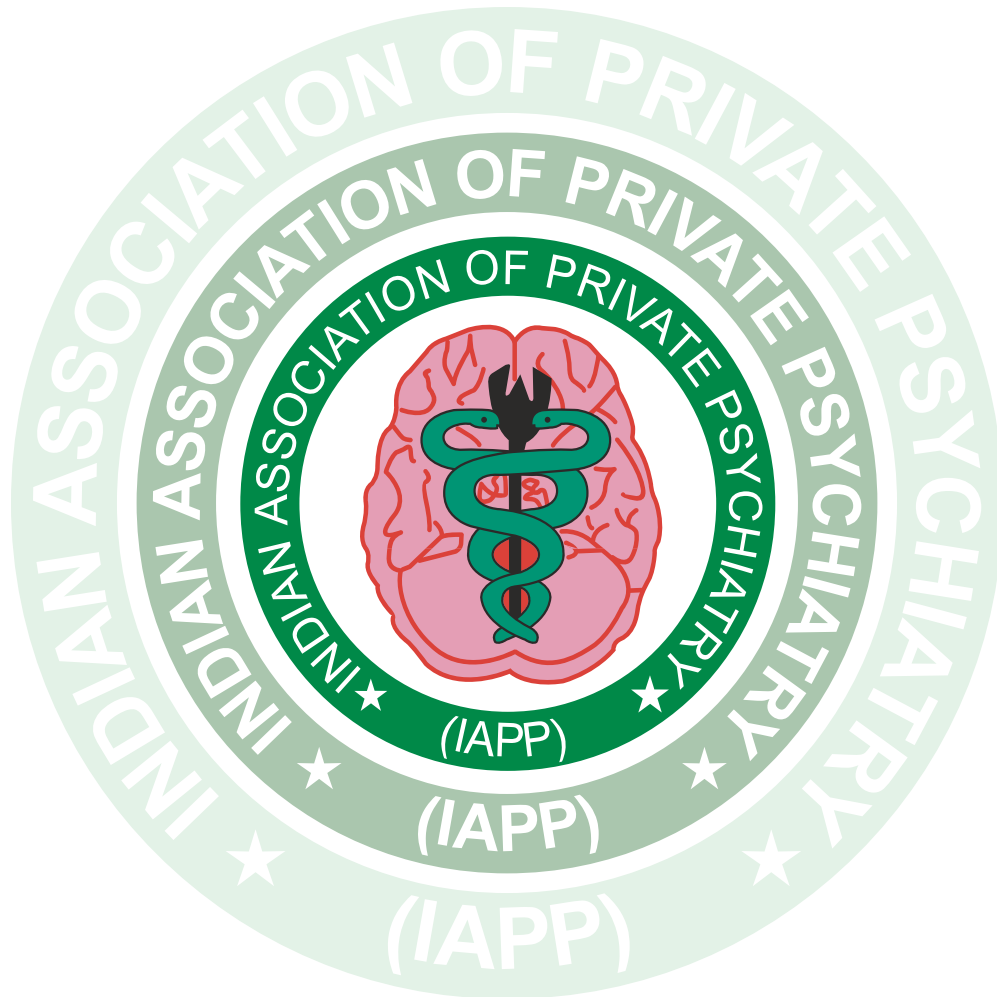
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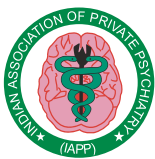


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Dr Ranjan Bhattacharyya

Hony Editor

Bengal Journal of Private Psychiatry

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It's my proud privilege to bring the volume 10, issue 1, September 2023 before the esteemed fellows and members of IAPP West Bengal State Branch as the Editor of Bengal Journal of Private Psychiatry.

The Government of India notified/gazetted the Mental Healthcare Act on 7th April 2017, the red-letter day. It was a much-needed step to provide a right-based approach for the persons with mental illnesses (PMI) and their caregivers but certain issues with this act should be amended to suit the Indian scenario as mentioned below.

1. The SMHA & MHRB should be formed in all states at the earliest and they should be empowered to treat persons with mental illnesses (PMI) mandatorily at the community level like that followed in US, UK, and Australia as it's the responsibility of Government to do so. The budgetary provision should be scaled properly covering rehabilitation centres, sheltered workshops, hostels, MHEs, etc and a concerted effort should be taken to remove the stigma.
2. While selecting Nominated Representatives (NR) responsibilities of family members can't be ignored (especially in the context of the Indian scenario) instead of protecting and honoring the human rights of PMI.
3. Emergency services for PMI and the coverage of mental illnesses to get reimbursed by Insurance companies (both in public and private sectors) including the 'Ayushman Bharat' scheme have ambiguity and discriminations despite IRDAI circulars.
4. Refusal to treat PMI comes from multiple levels including Doctors, Nursing and paramedical staff, Group D. Sweepers, Scavenging staff working in MHEs, police personnel, ambulance drivers etc, especially in emergencies who should be sensitized properly. The severity of mental illness has been equated with the purpose of involuntary admission which may delay the initiation of proper treatment in time.
5. Under MHCA, Government officials have been protected from legal proceedings in good faith but all stakeholders including caregivers, doctors, friends, and family members should get that legal safeguards.

Apart from treatment perspective, there's a gap with respect to fuelling careers and economy in Asia-Pacific region. To bridge this skill gap (upskilling and reskilling), digitalization, investment on mental health, leadership and clear communication are the need of the hour. Persons with Mental Illness (PMI) will lose 13 to 20 years of life due to early mortality in comparison to their non-psychiatric cohorts. PMI will be engaged in unhealthy lifestyle practices e.g lack of physical activities, poor nutrition, multiple physical comorbidities, smoking, overeating, lack of sleep, poor compliance of medicines and to get themselves checked up by qualified psychiatrists.

We need to spread self care for mental health, the 'ten commandments' are as follows

Self care in Mental Health

1. Regular Exercises-30 mins exercises, release Endorphin, a feel good substance which energizes to keep motivated throughout the day.
2. Diet -Healthy, nutritious and balanced diet with fresh seasonal fruits and vegetables rejuvenate nerve and lowers the risk of stress induced free radical damages.
3. Sleep- Adequate sleep for 6-8 hours a day without day time naps, blue light exposure (TV, Laptop, Computer, smartphone) just before sleep.

4. Meditation: Practicing Relaxation Exercises, Deep Breathing Exercises, Jacobson's Progressive Muscular Relaxations (JPMR) at a scheduled time regularly should be targeted.
5. Recreational Activities: Engaging in listening music, singing songs, sport activities etc.
6. Connectedness: Speaking with someone who can be trusted may be face to face or through audio-video calls, messaging apps.
7. Say No to Drugs and Psychoactive substances of abuse.
8. Focussing on the world around you (see, hear, taste, touch and smell).
9. Respect and Value yourself, avoid cynicism and self-criticism. Accept more, expect less.
10. Set your own limits and expectations. Don't rush or push yourself beyond the stretching point.

I am following the legacy of my predecessor, the immediate past editor of Bengal Journal of Private Psychiatry, my mentor and guide, Prof (Dr) Debasish Sanyal. I have been entrusted to take the good office of Hony Secretary, Indian Psychiatric Society, West Bengal State Branch (2016-2020). Thereafter, I have been given the charge of Editor of Bengal Journal of Private Psychiatry, an official publication of IAPP, West Bengal State Branch (2021-23).

I am indebted to IAPP National Office Bearers Dr Venu Gopal Jhanwar (President), Dr Avinash De Souza (Secretary), Dr Mrugesh Vaishnab (Vice President), Dr Vijay Nagecha (Hony Treasurer), Dr Prosenjit Ghosh (Hony Editor) and IAPP West Bengal State Branch Office Bearers Dr Dinen Banerjee (President), Dr Om Prakash Singh (Vice President cum President Elect), Dr Sanjay Garg (Hony Secretary), Dr Sanjay Saha (Hony Treasurer) and Executive members Dr Arnab Banerjee, Dr Sarmistha Chakraborty, Dr Sujit Sarkhel, Dr Soumya Chatterjee, Dr Kaustav Chakraborty, Dr Pinaki Sarkar and immediate past President & Secretary Dr Shyamal Chakraborty & Dr Hena Barat (Roy) for having faith on me and bestowing this responsibility.

The blessings from senior leaders, my mentors Dr R. R. Ghosh Roy, Dr Gautam Saha, Dr Asim Kumar Mallik, Dr Devashis Konar, Dr Jayaranjan Ram, Dr Rima Mukherjee, Dr Shyamal Chakraborty, Dr Abir Mukherjee, Dr Sabyasachi Mitra, Dr Sayandip Ghosh, Dr Indrajit Sengupta, Dr Amar Nath Mallick, Dr KMR Karim, Dr Benzarul Haque and others and support from my juniors always make me rejuvenated.

The current issue of BJPP has following contents

1. Cover page drawn by Dr Suddhendu Chakraborty.
2. List of names of IAPP National and State office Bearers.
3. Submission guidelines
4. Editor speaks (Editorial)
5. Leading the way by Dr Sanjay Garg
6. Neural Networks in Psychiatry by Dr Praveen Kumar Yadav & Dr Kumud Sahu
7. Pictorial CMEs by Dr Soumya Chatterjee, Dr Anweshak Das, Dr Gojendra Singh, Dr Archana Singh, Dr Sanjay Saha, Dr Mahesh Hembram and Dr Sanjay Saha.
8. Depression among medical students: time to come out and raise the curtain by Dr Ranjan Bhattacharyya
9. Ragging: its psychosocial effects and overview of the approach for mental health professionals by Dr Sayantan Chattopadhyay & Dr Pinaki Sarkar.
10. UG section: Case Presentation, Wilson's disease.
11. Mind It (Psychiatry Quiz) by Dr Tirthankar Dasgupta & Dr Ranjan Bhattacharyya (presented at Hopecon 2023).

Long live BJPP (Bengal Journal of Private Psychiatry)

Long live IAPP West Bengal State Branch.

Leading the Way – Indian Association of Private Psychiatry West Bengal State Branch

Dr Sanjay Garg

Honorary Secretary, IAPP West Bengal State Branch

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IAPP West Bengal State Branch has always been at the pinnacle of activity amongst all branches of IAPP. Our dynamic team includes **Dr Dinen Banerjee** (President), **Dr O P Singh** (Vice President), **Dr Sanjay Saha** (Treasurer), **Dr Ranjan Bhattacharya** (Editor) and **Dr Arnab Banerjee**, **Dr Sarmishtha Chakraborty**, **Dr Sujit Sarkhel**, **Dr Soumya Chatterjee**, **Dr Kaustav Chakraborty**, **Dr Pinaki Sarkar** (EC Members) and myself **Dr Sanjay Garg** (Secretary). We are fortunate to have **Dr Shyamal Chakraborty** and **Dr Hena Barat Roy** (Ex Officio) and **Dr RR Ghosh Roy**, **Dr Amarnath Mallik**, **Dr Gautam Saha** and **Dr Arabinda Brahma** (Advisors).

Regular executive committee meetings were organized for running of the organization. The enthusiasm and participation of all members has facilitated in meeting able to organize these regular activities.

Our annual academic extravaganza, **PSYCON 2022**, was jointly organized with Indian Psychiatric Society West Bengal State Branch on the 10th & 11th of September, 2022 at **Ibiza, The Fern Resort & Spa**, Kolkata. The lavish academic feast at this Conference was enjoyed by one and all with delegates returning home more enlightened than ever before with fond memories of the unfailing hospitality offered by the Organizing Committee led by **Dr OP Singh**, (Organizing Chairperson), **Dr Sharmila Sarkar**, (Organizing Secretary), **Dr Sanjay Garg**, (Organizing Treasurer). The theme of the conference was **'Washers, Checkers and Beyond'**. Experts from local and national level shared their experience and expertise with **Dr Sujit Sarkhel** providing an engaging scientific program. **Dr Ranjan Bhattacharya** worked very hard to bring out the copy of our journal. The Annual General Body Meeting was also conducted during the conference.



We started a series based on the theme **'Mental Health - The Unmet Needs and Future'** - which has shown an overwhelming response. I am grateful to all the speakers, chairpersons and delegates who have helped me achieve this. The first program of this was held in November 2021 and we have managed to reach the 10th program now.

During this year, we began with the 6th program on 21st September 2022 to mark the occasion of **World Alzheimer's Day**. A panel discussion was held by esteemed members, **Dr Dinen Banerjee**, **Dr R R Ghosh Roy**, **Dr Amarnath Mallik**, **Dr Om Prakash Singh**, **Dr Arnab Banerjee**, **Dr Sanjay Saha**, **Dr Nilanjan Chandra** and **Dr Sanjay Garg**. The need to focus on Geriatric Care was highlighted along with awareness and sensitization of family members, care givers and personnel in general medical set up.

The 7th Program was organised on 16th December 2022 focusing on **Cognition in Mental Illnesses**. There were excellent



presentations by Dr Akhilesh Paland Dr Sanjay Garg with session being chaired by Dr Indrani Chatterjee & Dr Abhay De. Dr Sanjay Saha moderated the panel discussion on the role of L Carnosine in Cognition which was chaired by Dr Muktananda Kundu and Dr Saurabh Sankar Kundu. The panellists Dr Hena Barat Roy, Dr Shyamal Chakraborty and Dr Amarnath Mallik gave very relevant personal experience clinical tips.



On 18th January 2023 the 8th program was themed on **The role of Newer Antipsychotics**. Dr Sanjay Saha was the Master of Ceremonies. Dr Sujit Sarkhel introduced the theme followed by Dr Nilanjan Chandra enumerating upon the Newer Antipsychotics & their mechanisms of action. The session was chaired by Dr Debasish Bhattacharya and Dr Rita Roy. Dr Sharmila Sarkar highlighted the effectiveness of Cariprazine on various psychiatric disorders with chairing by Dr Debashish Bhattacharya and

Dr Amit Bhattacharya. Panel discussion on Experience sharing on Cariprazine was moderated by Dr J R Ram with participation of Dr Gautam Saha, Dr Abir Mukherjee, Dr Abhiruchi Mukherjee, Dr Subrata Naskar and Dr Soumya Chatterjee.

The 9th Program was held on the occasion of **World Schizophrenia Day** on 21st May 2023. Dr Gautam Bandyopadhyay spoke on Evolution of the concept of Schizophrenia with Dr Shyamal Chakraborty, Dr Amarnath Mallik and Dr Sujit Sarkhel as chairs. Dr Debasish Sanyal highlighted on Schizophrenia - Where have we failed? with chairpersons as Dr Prabir Paul, Dr Arabinda Brahma and Dr Sourav Das. Schizophrenia and New Psychopharmacology was deliberated by Dr Paramita Ray with Dr Dinan Banerjee, Dr Hena Barat Roy and Dr Akhilesh Pal as chairpersons. A debate on Schizophrenia as an illness does not exist moderated by Dr Sanjay Garg and chaired by Dr Indrani Chatterjee and Dr Payel Das had Dr Soumya Chatterjee, Dr Altaf Hossain for the motion and Dr Souvik Chakraborty, Dr Abhiruchi Chatterjee against the motion. Dr Abir Mukherjee moderated the Clinical Experience of using Cariprazine with Dr Sayandip Ghosh and Dr Arijit Bose as chairs. Dr PS Kundu, Dr Sharmila Sarkar, Dr Kaustav Chakraborty, Dr Debanjan Mondal and Dr Praveen Kumar expressed their clinical knowledge.



On 18th June 2023 the 10th program of the series was themed on **Pharmacology - The New Horizons**. Dr OP Singh provided the context. Dr Sanjay Saha and Dr Altaf Hossain spoke on L- Carnosine - The Enigmatic Molecule with Dr Hena Barat Roy, Dr Muktananda Kundu and Dr Pinaki Sarkar as chairs. Dr Saurabh Kundu and Dr Debanjan Mondal spoke on Vortioxetine - the new entrant with chairpersons as Dr Indrajit Sengupta, Dr KMR Karim and Dr Paramita Ray. Panel Discussion on L Carnosine - Clinical Applications was moderated by Dr Prabir Paul with panelists as Dr Amarnath Mallik, Dr Abir Mukherjee, Dr Payel Talukder, Dr Sharmistha Chakraborty, Dr Soumya Chatterjee, Dr Praveen Kumar and Dr Debanjan Banerjee. The second Panel Discussion on Vortioxetine - Clinical Pearls was moderated by Dr Angshuman Das with Panellists as Dr Shyamal Chakraborty, Dr Gautam Saha, Dr Padmakali Kar, Dr P S Kundu, Dr Kaustav Chakraborty, Dr Ranjan Bhattacharya and Dr Rajarshi Guha Thakurta.

World Sleep Day 2023 was jointly observed with World Sleep Society on 4th March 2023 with Dr Gautam Saha as inaugurator. Dr Debanjan Banerjee spoke on Why good sleep is needed for better cognition- in normal population and dementia with Dr Prabir Pal and Dr Shyamal Chakraborty as chairpersons. Dr Rima Mukherjee and Dr Satyajit Ash chaired the session by Dr Sourav Das on What are the common sleep disorders in the elderly?. Dr Uttam Agarwal, ENT Consultant spoke on What is Osa and where to suspect osa in geriatric age group with Dr Kaustav Chakraborty and Dr Ranjan Bhattacharya as chair. Debate on "Routine prescription of sleeping pills to the elderly is harmful"- was moderated by Dr J R Ram with Dr Ashim Mallick and Dr Sagar Basu as chairpersons. Dr Soumya Chatterjee and Dr Subrata Naskar provided for and against the motion. Panel discussion and experience sharing on "How to deal with common sleep issues in the elderly in routine psychiatry practice" was

moderated by Devashish Konar and Dr Sanjay Garg with Dr OP Singh, Dr Amit Bhattacharya, Dr Sharmistha Chakraborty and Dr Praveen Kumar as panellists. The whole program was brilliantly conceived by Dr Sourav Das.

Dr G S Bose Oration was organised in association with Indian Psychoanalytical Society on 30th January 2023. Dr Prabir Paul provided the introduction. Dr Arabinda Brahma, Honorary Secretary, IPS delivered the oration on the topic Psychoanalysis, Psychiatry, & Environment: How the Climate Change can lead to Mental Health Crisis. Dr Arnab Banerjee and Dr Sarala Kapoor chaired the session. Dr Hena Barat Roy gave the vote of thanks.



After a long gap due to COVID, we organised the **East Zone CME** of IAPP on 25th February 2023 with Dr Arabinda Brahma as the organising chairperson. We were fortunate to have Dr Venu Gopal Jhawar, President, IAPP and Dr Prosenjit Ghosh, Editor, IAPP. Dr Arabinda Brahma laid out the context with Dr OP Singh, Dr Gautam Saha and Dr Prosenjit Ghosh as chairpersons. Workshop on treatment issues in Bipolar Disorder had Dr Abir Mukherjee as moderator and Dr Arnab Banerjee, Dr Sayandip Ghosh and Dr Madhurima Ghosh as chairpersons and Dr Anweshak Das, Dr Archana Singh and Dr Tanmaini Das as speakers elucidating on Recent updates on pharmacological management of bipolar depression, Conventional mood stabilizers versus atypical antipsychotics in maintenance treatment: When to choose which agent? and How to choose mood stabilizers in women?. The next workshop on Treatment issues in schizophrenia spectrum disorders moderated by Dr Sujit Sarkhel was chaired by Dr Srikumar Mukherjee, Dr Santanu Goswami and Dr Praveen Kumar. Dr Udayan Majumder, Dr Rakesh Singh and Dr Gojendra Singh spoke on How effective are the newer molecules in acute phase?, What are the pharmacological options for negative symptoms? and When can typical antipsychotics still be used for effective outcome?. Dr Venu Gopal Jhawar spoke on Recovery in SMI - Targeting Reintegration with Dr Shyamal Chakraborty, Dr Hena Barat Roy and Dr Amit Bhattacharya chairing the session. Dr Gautam Banerjee moderated the workshop on Treatment issues in alcohol use disorders with chairing by Dr Uday Chaudhari, Dr KMR Karim and Dr Akhilesh Pal. Dr Sanjay Munda, Dr Nahid Islam and Dr Arijit Mondal spoke on Is Baclofen the answer where benzodiazepines are not suitable?, What are the latest pharmacological options available for relapse prevention?

and What are the effective detoxification protocols on outpatient settings?. Workshop on Treatment issues in depressive disorders was moderated by Dr Abhay De and Dr Dinen Banerjee, Dr Rita Roy and Dr Ranjan Bhattacharya were the chairpersons. Dr Dipayan Sarkar, Dr Sanjay Saha and Dr Soumya Chatterjee spoke on How to assess depression in comorbid medical disorders, What are the preferred pharmacological management options for treating depression in pregnancy? and In which situations tricyclic antidepressants are still the initial choice?. Dr Rajesh Nagpal, Guest Speaker elucidated the role of Biomarkers in Psychiatry with chairpersons as Dr Amarnath Mallik, Dr Prabir Paul and Dr Tirthankar Dasgupta. Workshop on Treatment issues in Obsessive compulsive and related disorders was moderated by Dr Sharmila Sarkar with Dr RR Ghosh Roy, Dr Indrajit Sengupta and Dr Muktananda Kundu as chairpersons. Dr Mahesh Hembram, Dr Samrat Singh Bhandari and Dr Utpal Bohra spoke on How long to continue maintenance pharmacotherapy?, Which augmentation agent should be chosen when? and Pharmacological management of body focused repetitive behaviours. The program was much appreciated and the clinical contents was praiseworthy.

As the Secretary of IAPP West Bengal State Branch, have represented the society in various programs, walks and fora to help raise awareness on mental health. On the occasion of **World Autism Month**, participated in a community awareness program to help integrate people suffering from ASD in the community. Discussed ways and means by which parents, teachers and general people may help such individuals to reach their maximum potential. On the occasion of **World Cancer Day** event organised to raise awareness and bring some cheer to patients. Outreach Program organised by **Dr P P Roy Foundation** in New Andul HC School. Parents and teachers showed keen interest with multiple queries and good interaction. Thanks to Dr Hena Barat Roy for her initiative. Privileged to be invited as a faculty at **Annual Conference of Association of Chest Physicians, BIMACON** and **IDEACON** to provide input on mental health. On the occasion of **World Kidney Day**, interacted with patients and family to raise awareness about challenges and difficulties faced by this vulnerable group. Collaborating with **Jadavpur University** to develop human resources and raise mental health awareness. Training of teachers, managers, paramedical staff, nurses, general public, etc to identify common mental illnesses, provide first aid and facilitate help seeking. Health Awareness at St Xavier's University to mark the **World Autism Day**. Heartening to see the interest shown by young people in mental health. On the occasion of **World Health Day**, considering the theme 'Health for All', elderly citizens of Kolkata had routine check-up and discussion about mental health concerns along with preventive strategies. Grateful to Health Point, NGO - The Bengal and Pronam for their support. On the occasion of **World Elder Abuse Awareness Day** an interactive awareness program for local elderly people along with some fun and games like antakshari, passing the parcel. Their enthusiasm was infectious with few of them being in their late 90s. On the occasion of **Pride Month**, an interactive workshop discussing the challenges and mental health issues faced by this community. It was heartening to see the parents opening up.





Neural Networks in Psychiatry

Dr Praveen Kumar Yadav, Senior Consultant Neurologist and Director, (Aarogyam Neuroclinic), Associate Professor(SRIMS), Durgapur

Dr Kumud Sahu DNB Resident, Department of General Medicine, DSP Main Hospital, Durgapur

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INTRODUCTION

Human Brain, the signature network system of nature, which controls the emotion and behaviour according to the crux of situation. Since ages, many scientist endeavoured to get the knowledge of human behaviour, emotion and its regulatory mechanism.

In 1878, Paul Pierre Broca, spoke about " the great limbic lobe" or "le grand lobe limbique" which means the border of cortex including cingulate, hippocampal gyri. The further accepted anatomical model of Limbic lobe was given by American physician, Jamez Papez, known as the famous "Papez Circuit", in 1937. He described the harmonious relation between the hypothalamus, anterior thalamic nucleus, the hippocampus cingulate gyrus and its interconnections in describing the role in emotions, memory, affect and goal directed behaviour.^[1] And in 1952, Paul D Maclean coined the term "limbic system" (limbic lobe and its subcortical structures along with their connections) which explains various brain functions.^[2] He also put forward the "Truine Brain theory" which says that, in reality, the human brain comprises of three brains in one: the R- complex (reptilian complex), the limbic system and the neocortex^[3].

Humans are different from other animals, by our ability to think. Human brain consist of frontal, parietal, temporal and occipital lobe, of which frontal lobe and its connections play a vital role in cognition, execution, personality, emotions, and motivation. The primary motor cortex (PMC), supplementary motor area(SMA), frontal eye field (FEF), orbitofrontal area (OFA), anterior cingulate gyrus are important areas of frontal lobe, connecting different parts of the brain via numerous circuits. Alexander et al. discovered five important frontal - subcortical circuits namely motor circuit; oculomotor circuit; lateral orbitofrontal circuit; dorsolateral prefrontal circuit and anterior cingulate circuit. Out of which two are motor circuits, rest are involved in psychosocial and executive functions[4](Fig:1).For orbitofrontal circuit, medial division also has been described.

Each pathway originates from pre- frontal cortex, projecting to striatum- globus pallidus complex , then to thalamus and ultimately ending back in frontal lobe, thus forming close loop. In addition to this, each loop have various afferent and efferent projections which form open loop(Table:1). All these loops have both direct and indirect pathway(Fig:2) which have respective stimulatory and inhibitory effect on thalamus, helps in balanced and organized action. Direct pathway connects striatum , globuspallidus internus/substantia nigra complex(GPi/SN) meanwhile indirect pathway links striatum to globuspallidusexterna(GPe)then subthalamic nucleus to GPi/SN complex, ultimately both pathways reach thalamus, and finally to the cortex.

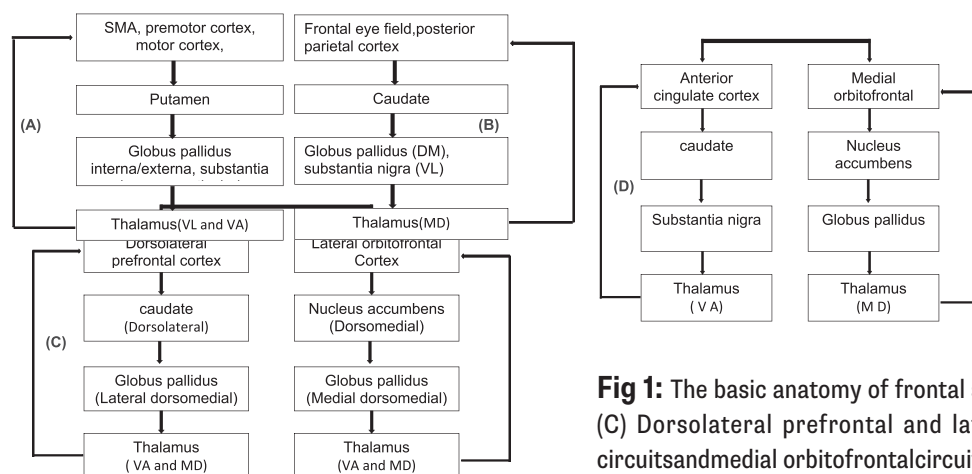


Fig 1: The basic anatomy of frontal subcortical circuits;(A)Motor(B)oculomotor (C) Dorsolateral prefrontal and lateral orbitofrontal(D) anterior cingulate circuits and medial orbitofrontal circuits. VA - ventral anterior; MD - mediodorsal

Circuits	Major open afferents	Major open efferents
Dorsolateral circuit	Dorsofrontal area 46 Parietal area 7a	Dorsofrontal area 46 Anterior frontal area 8
Orbitofrontal circuit	Superior temporal area 22 Orbitofrontal area 12	Orbitofrontal area 12 Mediofrontal area 25 and 32
Anterior cingulate circuit	Hippocampus Entorhinal area 28	Substantia nigra pars compacta Medial subthalamic nucleus Lateral hypothalamus

Table 1:Afferent and efferent projections[6]

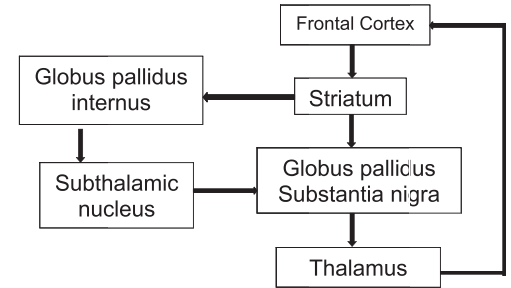


Fig:2-direct and indirect pathway of frontal subcortical circuit

NEURONS AND NEUROCHEMICALS:

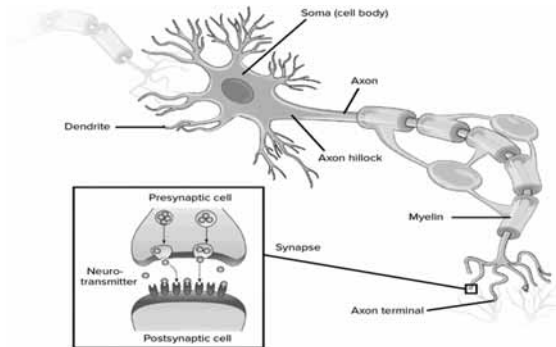


Fig 3:Neuron with synaptic cleft

Brain consists of billions of neurons. Any information in brain is transferred from one neuron to another neuron with a help of chemical messengers known as neurochemicals. The neuron comprises of cell body, axons, and dendrites and the gap between the two neurons is known as synaptic cleft. Neurochemicals are stored in the vesicle of pre-synaptic neuron terminal and release only when the dedicated neuron is activated. These are released and bind to the receptor on post-synaptic neuron/ cell (muscle), for its action (Fig 3). The remaining neurochemical is either destroyed by the enzymes or reuptake back.

Psychotic symptoms are strongly related with altered dopamine transmission. There are four dopaminergic pathways in the brain: nigrostriatal, meso-limbic, meso-cortical and tubero-infundibular, of which meso-cortical and meso-limbic pathways are more important in regulating emotions and behaviours. Excess dopamine in mesolimbic pathway causes positive symptoms of schizophrenia, while negative symptoms and cognitive deficits in schizophrenia are associated with low dopamine levels in meso-cortical pathway.[7] Nigrostriatal pathway consists of substantia nigra pars compacta (SNc) which sends dopamine input to striatum, having both D1 (spiny neurons) and D2 receptors. D1 activates thalamus at the same time D2 inhibits thalamus and dedicated cortical area for the particular action to occur, helping in coordination of that action and causing inhibition of any other extraneous movement/ action of body.

The Acetylcholine (ACh) in striatum sends input to the thalamus by pedunculo-pontine and lateral tegmentum, causing dopamine release via nicotinic and muscarinic receptors. Serotonin, the other important neurotransmitter in brain, is largely present in ventral striatum, hippocampus, amygdala and septal area, offering meso-cortical and mesolimbic dopamine pathway modulation, regulating executive function, sensory gating, and social behaviour. Schizophrenia, bipolar affective disorder (BPAD), and impulsive behaviour all share common defects in these functions. Glutamate, an excitatory neurotransmitter, acts through NMDA receptors to activate striatum to release dopamine and its antagonism inhibits ACh release via corticostriatal and thalamocortical projections. NMDA receptor hypofunction is known to cause schizophrenic symptoms. Nucleus Accumbens, present in caudate nucleus, receives excitatory input from frontal and limbic cortex, also modulating glutamate and dopamine action. GABA, an inhibitory neurotransmitter, predominant neurotransmitter in basal ganglia, enhances thalamo-cortical excitation and minimizes thalamic inhibition.

The following (Table:2) summarises the neurotransmitter involvement in mental disorder[8]

Neurotransmitters	Location/Function	Implications For Mental Illness
ACETYL CHOLINE was the first neurotransmitter discovered in 1921 by Ottolowei (German biologist)	ANS: sympathetic and parasympathetic nerve terminals, parasympathetic post synaptic nerve terminals CNS: Cerebral cortex, hippocampus, limbic structures and basal ganglia FUNCTIONS: Increased Levels-Huntington's disease, temporal lobe epilepsy, spinal cerebellar degeneration, cognition, memory and learning	Increased levels- Depression Decreased levels- Alzheimer disease, Huntington's disease and Parkinson's disease.

NOREPINEPHRINE Is strongly associated with bringing our nervous system into —high alert!	ANS: Sympathetic post synaptic nerve terminals CNS: Thalamus, hypothalamus, limbic system, hippocampus, cerebellum, cerebral cortex. FUNCTIONS: Mood, cognition, perception, locomotion, cardiovascular functioning, forming memories, sleep and arousal.	Decreased levels- Depression Increased levels- Mania, anxiety and schizophrenia.
DOPAMINE generally involved in regulatory motor activity in mood, motivation and attention	Frontal cortex, limbic system, basal ganglia, thalamus, posterior pituitary and spinal cord. FUNCTIONS- Movement and co-ordination, emotions, voluntary judgement and release of prolactin.	Decreased levels Parkinson's disease and depression Increased levels Mania and schizophrenia
SEROTONIN	Hypothalamus, thalamus, limbic system, cerebral cortex, cerebellum, spinal cord FUNCTIONS- Sleep and arousal, libido, appetite, mood aggression, pain perception, coordination, judgement.	Increased levels- Mania and schizophrenia and anxiety. Decreased levels- Depression and Parkinson's disease.
HISTAMINE	FUNCTIONS: Wakefulness, pain sensation and inflammatory response.	Decreased levels- Depression.
AMINO ACIDS A.GAMMA-AMINOBUTYRIC ACID (GABA)	Hypothalamus, hippocampus, cerebellum, basal ganglia, spinal cord. FUNCTIONS: Slowdown body activity.	Decreased levels- Huntington's disease, anxiety disorders, schizophrenia and various forms of epilepsy
GLYCINE	Spinal cord and brain stem FUNCTIONS: recurrent inhibition of motor neurons.	Toxic levels leads to glycine encephalopathy. Decreased Levels are correlated with spastic motor movements.
GLUTAMATE ASPARTATE It is an amino acid and mostly found as an excitatory neurotransmitter in brain	Pyramid cells of the cortex, cerebellum and the primary afferent systems: hippocampus, thalamus, hypothalamus and spinal cord.	Increased Levels- Huntington's disease, temporal lobe epilepsy, spinal cerebellar degeneration, cognition, memory and learning

Table:2- Neuro transmitters and their function and implication in mental illness.

Neuro-psychiatric illness is a heterogeneous group of disorder which can be due to macroscopic (structural changes- stroke, tumour) or microscopic brain changes; metabolism, blood flow, receptor-ligand binding. [4]. To identify these, there are modalities available like to CT, MRI, fMRI, FDG PET/ SPECT, EEG (Electroencephalogram), MEG (Magnetoencephalogram) [9]. MRI (sMRI) is used to rule out structural lesions of brain. Many studies done previously, showed decrease in Gray Matter Volume (GMV) of dorsal anterior cingulate gyrus and insula, by voxel based model, in illnesses like- schizophrenia, BPAD, elderly depressed patients and substance abuse while increased GMV of amygdala, hippocampus in major depressive disorder (MDD). [10-12] Different techniques of MRI are used 1) diffusion tensor imaging (DTI)- works on the principle of water diffusion in brain 2) magnetization transfer (MT). DTI measurement can be done by apparent diffusion coefficient (ADC) and fractional anisotropy (FA). ADC shows the amount of CSF as compared to FA, which shows the direction of flow, indirectly lining up with fibres. High FA when fibres are organized in particular direction and low when it is disorganized. MT helps in giving information about myelin sheath integrity. [13-15] As a result of this, it helps in giving information about gray and white matter of brain.

fMRI is the new springing up, non invasive, less radiation exposure causing tool, which works on the principle of BOLD- (blood oxygen level dependent) signal. It can be used to demonstrate the changes in neuronal activity with time and also the functional connectivity of neurons in particular disease. [5,6]. It works on the principle that when any cells is activated by any task, there is increase activity or oxygen demand or metabolism of that cell, causing increase in blood flow and decrease in deoxyhaemoglobin (Hbr), and thus increase BOLD signal and the second mechanism is due to the paramagnetic effect of deoxygenated blood [16,17]. Scientist found out that when patient is in resting states, there is still a persistent activity going on in brain, known as "Default mode". Therefore, to see the neuronal activity during any task and in resting state, the two types of fMRI (resting state MRI (rsMRI) and task specific MRI) were discovered to monitor therapy, to see differences

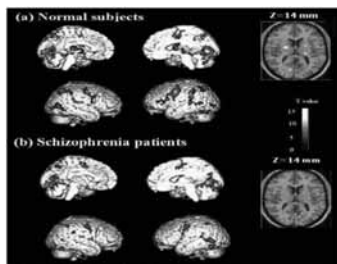


Fig 3: fMRI of a normal and schizophrenic person.

Because imaging alone still doesn't provide the certain definitive data for diagnosis, the new popping up technology Artificial Intelligence, AI is one of the promising strategy for identifying the optimal use of different imaging metrics for diagnosing, for better treatment, therapeutic trial, to see treatment response, new drug trial or any research, to see the activities inside the brain and to differentiate it from normal person by searching for biomarkers causing mental illness. The theory put forward was "Graph Theory", which is not only used in rsMRI or task specific MRI, it is widely used to demonstrate the topography of brain network in AI. According to this, network is formed by nodes, edges, path, cluster, hub(Fig:4). Nodes which is a functional area (with single neuron) of the brain; edges i.e. connections via fibres (often white fibres); path is a connecting route, can be short path or long path, depending upon the nodes in between. Short path means efficient connection and strongly weighted (highly myelinated) and vice versa. Cluster is the density of connection between neighbouring nodes. Hub, having high number of edges connected to it, but low clustering.[22,23,24]

This graph theory is also used to study the surface area, cortical thickness, DWI data to know the complex brain structure, showed alteration in function and structure in ageing, mental illness, schizophrenia. AI technology is based upon the data fed to computer, processed by some pre-defined algorithm, known as Machine Learning(ML)(Fig:5). The subset of ML is Deep Learning(DL). The model class use for ML is by collection of artificially made neurons, or connected units, forming a network. This network is known by the name, Artificial Neural Network(ANN) as mentioned above in graph theory[25]. Machine learning works on two paradigms: supervised (SL) and unsupervised learning (USL) to analyse "big data".[26,27]

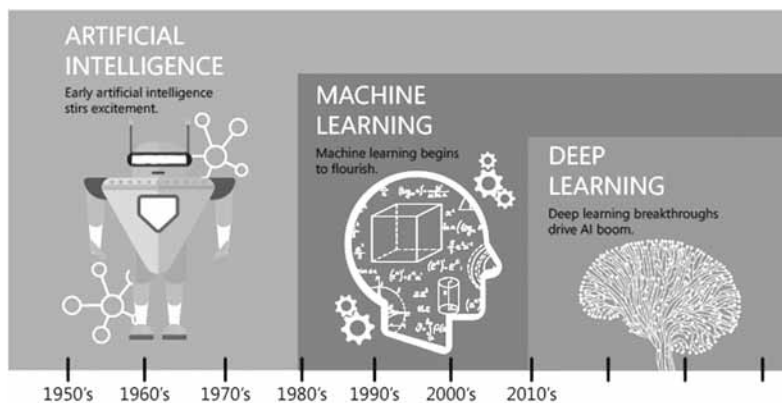


Fig:5-Machine learning.

and so on), the probability of patient committed suicide attempt is, "y". E.g.: x_1 = gender(if male=1, if female=0), age(continuous variable x), alcohol intake(if yes=1, no=0)[28]. In USL, no labelled outcome in contrast to SL. The machine, with the help of input data find the differences and similarities between the patients. The most common method used in USL is k-means clustering. The lack of labelled outcome make it more challenging and prevent bias. K means technique is used statistically to find the pattern of disease and its severity. Fuent-Tomas et al used cluster based Bipolar disorder classification, which helped psychiatrist for decisionmaking and personalised medicine.[29]

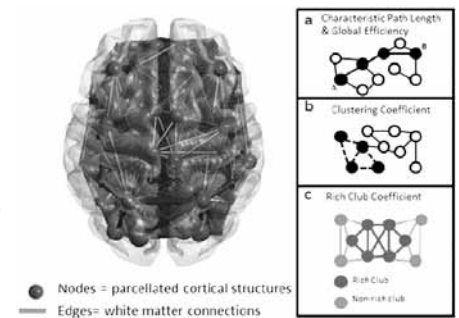


Figure 4 : graph representation of brain network

In supervised learning (SL), input and output set is to be given, accordingly we get the outcome after analysis. The purpose is to develop a model, for which predicted outcome can be formulated in the future based on the features given. It works on the basis of predefined output. For instance task is to find out that the particular person is schizophrenic or not, based on some factors of patients. SL method try to find the outcome(i.e. schizophrenic or not) and a series of features, such as age, gender, background etc. Commonly used SL algorithm are Logistic Regression(LR) and Support Vector Machine(SVM). Lee et al developed the LR model, found the probability of suicide attempt in adolescent, used binary numbers i.e. 0 and 1, for each variables(features) (x_1, x_2, x_3

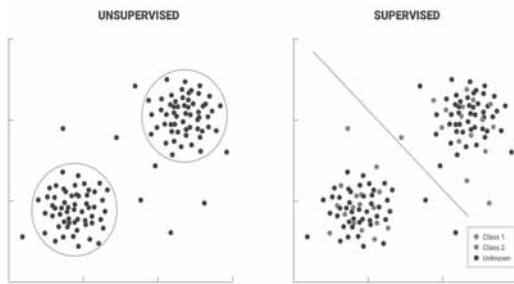


Fig:6-supervised learning and unsupervised learning

ARTIFICIAL NEURAL NETWORK AND DEEP NEURAL NETWORK

As described earlier, ANN is an artificial brain network. It was originated in 1940s, when search for language processing and vision started by a machine. The hallmark of NN based systems is that, they consist of network mimicking brain network, process information by "artificial neurons". It works on the basis of "training algorithm" and optimization function describes the goal of machine. NNs come in a variety of designs, derived from many principles or conceived for different use. Rosenblatt, an American psychologist, designed "PERCEPTRON" (Fig:7), which was a simple model of Feed Forward NN, helped in perception [30]. It comprises of layer of input, connected to output. He also formulated various algorithm based on the weight of input and output units. In

supplementary to this, there is "hidden layer" sandwiched between input and output layer, where all the processing of information were done, based on the algorithm.

Later, it was seen that adding one to many hidden layers increase the specificity of the machine programming [31]. In Feed Forward Model, the information goes unidirectional, to give the output, in contrast to the new Back-Propagation Model, in eighties, given by David Rumelhart et al, which enable information to go bidirectionally i.e. feedback connections is possible to give more relevant result and this marked the second wave of NN [32]. When the hidden layer is more than or equal to four, it is known as Deep Neural Network. Another, very commonly used model is CNN i.e. convoluted neural network or (ConvNet) for analysing image data, social gestures, speech and pattern recognition (Fig:8). It comprises of multiple hidden layers (filters), known as convoluted layer, processed by multiple feature maps. The result of the previous layer act as an element for further layer, i.e. non linear layer (rectified linear unit) to adjust the output, and then finally pass to the pooling layer, which reduces the dimension of inputs by down sampling [33,34].

The above three processing stages may be repeated multiple times.

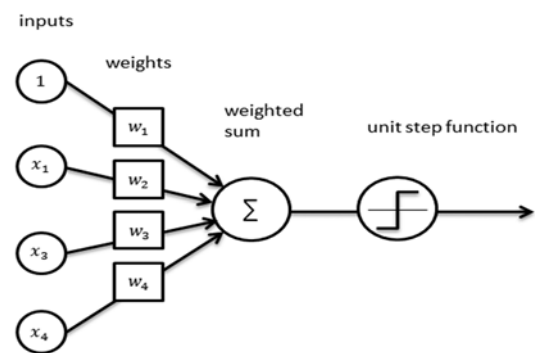


Fig:7-Perceptron

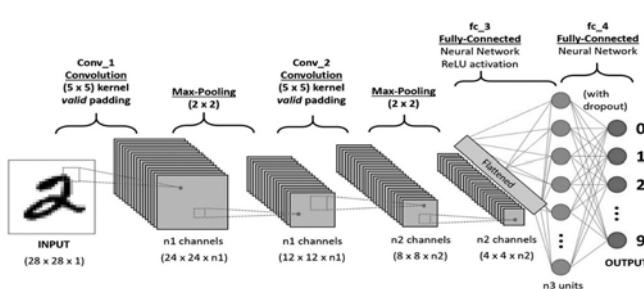


Figure:8-convoluted neural network

AI IN PSYCHIATRY

Many available AI based therapy in psychiatry used are Computer Assisted Therapy (CAT) (e-therapy/ Beating the Blues therapy for depression) for patients who need counselling and psychotherapy. This also provides support in the form of chat to highly skilled clinicians [35,36,37]. Moderate Online Social Therapy (MOST) - provide online peer support to depressive and psychotic patients [38]. AI based EEG model, depression patients were identified by 67% accuracy rates using linear discriminant analysis and 83.3% using logistic regression method [39,40]. Kinesics data aid in identifying-

schizophrenia by facial expression and depression by body movements and emotional changes. Many data obtained by investigations like imaging, genetics etc are combined to provide information on etiological mechanism. Khan et al proposed integrated mental-disorder Genome score or iMEGES to identify whole genome/exon sequencing data on personal genomes relating to psychiatric disorder [41,42]. DNNs are used in Electronic Health Recorder (EHR) and also incorporated with social media platforms like- Reddit and Twitter for mental illness [43,44]. Data obtained from wearable devices like- Health bands, sensors, mobile phones. Features like social interaction, changes in vitals, movement patterns, sleeping habit, stress can be extracted, which is also the source of prediction calculation of mental illness [46,47]. >90% were correctly detected by Hamilton Depression Rating Scale as depressed in bipolar patients by their typing speed, acceleration, and typing duration. Many people don't come out with their initial symptoms as they feel disgraceful, being treated by psychiatrist, especially in country like India, so for them AI removes stigma of this and also help to give unbiased individual treatment, cost effective, saves time and to prevent load of clinician, help in early identifying of disease, in research activities. But in spite of all the promising performances of AI, it is still lacking in human emotional behaviour, versatility to change according to the situation and decision making.

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Situations where TCA still the first choice

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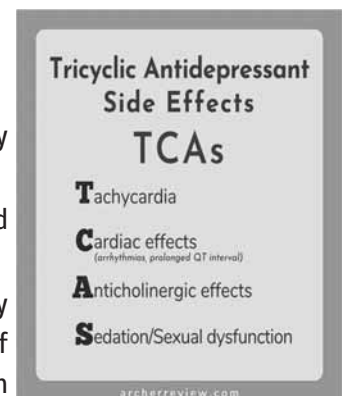
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That means usually TCAs are not considered as 1st option....why???

TRICYCLIC ANTIDEPRESSANTS (TCAs)

Adverse effects:

- Blockade of muscarinic receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, sinus tachycardia, constipation, and aggravation of narrow-angle glaucoma.
- The TCAs also block α -adrenergic receptors, causing orthostatic hypotension, dizziness, and reflex tachycardia.
- Weight gain is a common adverse effect of the TCAs. Sexual dysfunction, as evidenced by erectile dysfunction in men and anorgasmia in women, occurs in a significant minority of patients, but the incidence is still considered to be lower than the incidence of sexual dysfunction associated with the SSRIs.

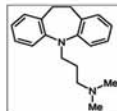


TRICYCLIC ANTIDEPRESSANTS (TCAs)

TCAs are the oldest class of antidepressant drugs

They have characteristic three-ring nucleus

- | | |
|-----------------|---------------|
| ■ Imipramine | Desipramine |
| ■ Clomipramine | Amitriptyline |
| ■ Nortriptyline | Doxepin |
| ■ Trimipramine | |



TETRACYCLIC ANTIDEPRESSANTS

- Maprotiline
- Amoxapine

Cost-effectiveness and cost-utility of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine

Adverse effects:

Randomised controlled trial

Published online by Cambridge University Press: 02 January 2018



- **No significant differences were found in effectiveness or cost-effectiveness.**
- The numbers of depression-free weeks over 12 months (on the Hospital Anxiety and Depression Scale) were 25.3 (95% CI 21.3-29.0) for TCAs, 28.3 (95% CI 24.3-32.2) for SSRIs and 24.6 (95% CI 20.6-28.9) for lofepramine.
- Mean health service costs per patient were \$762 (95% CI 553-1059) for TCAs, \$875 (95% CI 675-1355) for SSRIs and \$867 (95% CI 634-1521) for lofepramine.
- Cost-effectiveness acceptability curves suggested SSRIs were most cost-effective (with a probability of up to 0.6).

CLINICAL IMPLICATIONS

- Differences in antidepressant costs suggested that offering a tricyclic antidepressant might be the cheapest option, but differences in overall costs, cost-effectiveness and cost-utility were not significant.
- Most of the findings tend to support the National Institute for Clinical Excellence recommendations that SSRIs should be the first choice of antidepressant in primary care.

Is amitriptyline the strongest antidepressant?

- Amitriptyline does not work any better or worse than other antidepressants. However, for some people, the side effects are a problem and they may have fewer side effects with another antidepressant



Amitriptyline v. the rest: still the leading antidepressant after 40 years of randomised controlled trials Published online by Cambridge University Press: 02 January 2018

- Based on review of 186 RCTs.
- Recent systematic reviews indicate that low-dose TCAs are as effective as SSRIs in treating depression, and studies directly comparing low- and high-dose TCAs show only very modest benefits of high doses.
- The results from randomised trials suggest that amitriptyline probably has the edge in terms of efficacy over SSRIs.

Tricyclic antidepressants for preventing migraine in adults

Xiao-min Xu, Yang Liu, Mei-xue Dong, De-zhi Zou and You-dong Wei, Medicine (Baltimore). 2017 Jun; 96(22)

- Tricyclic antidepressants (TCAs) were the first agents shown to be effective in the prophylaxis of headaches in 1964 and have been one of the most commonly drugs for migraine prevention.
- TCAs were found to be more effective than placebo and SSRIs in achieving 50% reduction in migraine burden, but TCAs appeared to be less well tolerated.
- However, this analysis and another meta-analysis included studies recruiting patients with comorbidity of migraine and tension-type headache,

TCAs as Migraine Prophylaxis

- The most studied of the antidepressants for migraine prevention
- Amitriptyline may reduce number and intensity of attacks by 50 to 70% at daily doses of 10 to 100 mg
- Amitriptyline has shown similar efficacy to propranolol
- Proposed **mechanism of action**
 - Thought to involve inhibition of central cortical depression and sympathetic activity associated with migraine pathophysiology

TCAs are a first-line option for in patients without contraindications
May be excellent for patients who also suffer from depression, anxiety, or insomnia



Tension headache

- Usually bilateral
- Over temple, cranium or back of neck
- Described as tightness or pressure
- Gradual onset & progression
- Worsens over the day
- Asso. with depression or anxiety
- Relieved with NSAIDs, TCA, anxiolytics

prophylactic management of tension-type headache.

Acute management	Prophylactic management
Acetaminophen 1000 mg	Amitriptyline 10–75 mg/day
Ibuprofen 200–400 mg	Mirtazapine 30 mg/day
Naproxen sodium 375–550 mg	
Ketoprofen 25–50 mg	
Diclofenac potassium 50–100 mg	

Physicians should be aware of the risk of developing medication-overuse headache as a result of frequent and excessive use of analgesics in acute therapy. Dosages in prophylactic management with amitriptyline are increased until efficacy or side effects are reported.

Imipramine for therapy resistant enuresis: a retrospective evaluation

- There was evidence that TCA are effective at reducing the number of wet nights during treatment, but do not have a sustained effect after treatment stops, with most children relapsing.
- In contrast, there was evidence that alarm therapy has better short- and long-term outcomes.
- There was some evidence that tricyclics combined with anticholinergics may be more effective than tricyclic monotherapy.

TABLE 5

Comparison of Treatment Modalities for Nocturnal Enuresis

Treatment	Advantage	Disadvantage	Cost for brand name product (generic)*
Bed-wetting alarm	Effective, low relapse rate	Takes weeks for results; can be disruptive to family	\$50 to \$75, plus shipping and handling charges
Desmopressin (DDAVP)	Rapidly effective, few side effects	High-relapse rate with discontinuation	5-ml nasal spray: \$149 for 5-mL bottle 0.1-mg tablets: \$72 for 30 tablets 0.2-mg tablets: \$85 for 30 tablets
Imipramine (Tofranil)	Inexpensive, works quickly	High-relapse rate with discontinuation; side effects, including cardiotoxicity at high doses	25-mg tablets: \$28 (8) for 30 tablets

*—Prices for desmopressin and imipramine were obtained from www.drugstore.com (January 13, 2003) and reflect what patients' families are likely to pay.

- TCAs (especially doxepin, maprotiline, and amitriptyline) have been shown to be an effective treatment, with an 82% increase in somnolence compared with placebo, as well as measurably improved total sleep time, enhanced sleep efficiency, reduced latency to persistent sleep, and decreased wake times after sleep onset.
- Dosing should be kept at a minimum to minimize harsh anticholinergic effects and avoid daytime sedation.
- Patients should be advised to take new doses or dose escalations earlier in the night to ensure less hangover sedation the next morning.

Indications

Treatment of insomnia characterized by difficulties with sleep maintenance

Doxepin: antidepressant doses



Markov, D., & Daghramji, K. (2010). Low Dose Doxepin for Insomnia. In Drug Treatment of Sleep Disorders (pp. 111-118). Springer International Publishing.

Doxepin: hypnotic doses



Markov, D., & Daghramji, K. (2010). Low Dose Doxepin for Insomnia. In Drug Treatment of Sleep Disorders (pp. 111-118). Springer International Publishing.

Doxepin - Comments



- Originally approved in 1969
- Available in larger doses
 - Capsules: 10, 25, 50, 75 and 150 mg
 - Oral solution: 10 mg/ml
- Silenor more expensive than generic
- Doxepin 6 mg vs 10 mg?
 - No head-to-head clinical trials
- Oral solution can also be dosed at 6 mg

Markov, D., & Daghramji, K. (2010). Doxepin for insomnia. *Curr Psychiatry*, 9(10), 67-77.

PSYCHOPHARMACOLOGY INSTITUTE

Side effects

Side effects

- Somnolence/sedation
- Nausea

Free from

- Anticholinergic effects
- Withdrawal syndrome
- Rebound insomnia

Dosing

Dosage forms (Silenor)

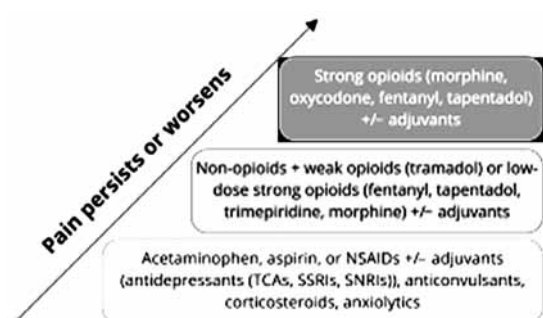
- Tablet
 - 3 mg
 - 6 mg

Dosing

- Adults: 6 mg
- Elderly: 3 mg

How to dose

- 30 minutes before bedtime



Pelvic and urogynecologic symptoms

- Chronic pelvic pain affects up to 24% of women and 5% to 10% of men.
- TCAs have shown efficacy in treating chronic pelvic pain with or without comorbid depression.
- Amitriptyline and to a lesser extent nortriptyline are the TCAs most often prescribed.
- Pain relief appears to be independent of antidepressant effects and may be achieved at low doses; initial dosing ranges from 10 to 25 mg at bedtime, which may be increased to 100 mg as tolerated.

Analgesic effects of TCAs:

- Occur more rapidly (a week or less after initiating TCA therapy),
- At lower serum blood levels
- At lower doses than those used for antidepressive effects.
- Pain-relieving properties can be observed at much lower doses, even 1/10th to 1/30th of their FDA-approved maximum.
- In small uncontrolled studies, about half of women with chronic pelvic pain became pain-free after 8 weeks of treatment with nortriptyline and imipramine.

Status of antidepressants in chronic pain management

- **Best evidence: TCAs**
 - Inhibit both NA and 5-HT reuptake
- TCAs are superior to SSRIs in pain management
- TCAs are superior to the anticonvulsant
- There is no consensus regarding which of the many TCA derivatives is most effective.
- The choice of TCA is therefore dictated largely by adverse effects

Antidepressant	Suggested Dose for Neuropathic Pain
Secondary-Amine TCAs	
Desipramine	10-25 mg/day; titrate up to 300 mg/day
Nortriptyline	10-150 mg/day
Tertiary-Amine TCAs	
Amitriptyline	10-25 mg/day; titrate up to 150 mg/day
Imipramine	10-150 mg/day
SNRIs	
Duloxetine	60-120 mg/day
Venlafaxine	Initially 37.5-75 mg/day; mean dose 225 mg/day; max 375 mg/day

max: maximum; SNRI: serotonin-norepinephrine reuptake inhibitor; TCA: tricyclic antidepressant.

Source: Reference 16.

- Based on a randomized, double-blind trial, amitriptyline was recommended as a treatment option for interstitial cystitis or bladder pain, with the greatest symptom improvement in patients tolerating a daily dose of 50 mg.
- Another study randomized 56 women with chronic pelvic pain to amitriptyline or gabapentin, or a combination of the drugs for 24 months. Although each regimen resulted in significant reduction in pain, fewer adverse effects occurred with gabapentin than amitriptyline. Poor compliance and early discontinuation of amitriptyline were common due to anticholinergic effects.
- TCAs have been used to treat chronic low back pain for decades and have been repeatedly shown to be more effective than placebo in reducing pain severity.
- A double-blind controlled trial from 1999 compared the effects of the TCA maprotiline (up to 150 mg daily), the SSRI paroxetine (up to 30 mg daily) and placebo and found a statistically significant reduction in back pain with maprotiline compared with paroxetine and placebo.
- However, a 2008 meta-analysis showed little evidence that TCAs were superior to placebo.

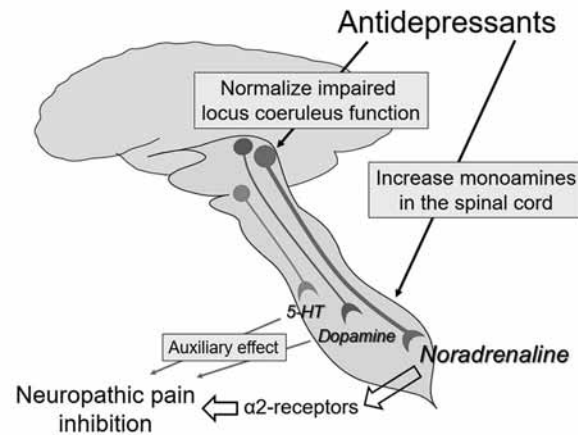
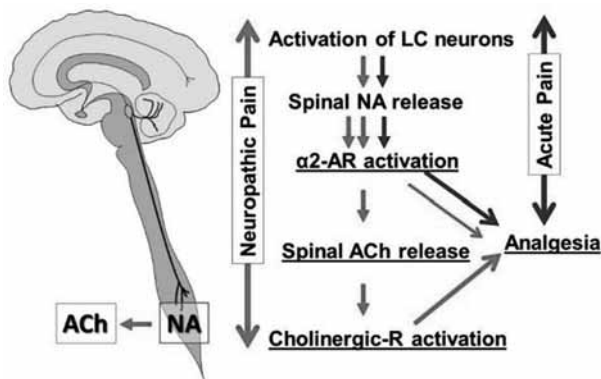
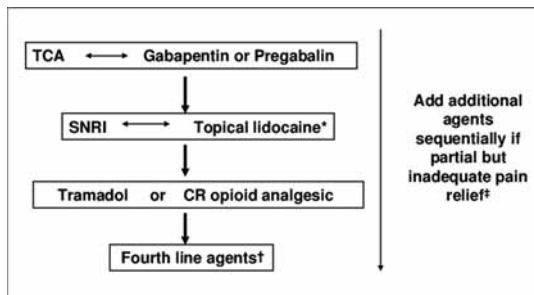
- Evidence of TCA efficacy for back pain was reported in 2018 with a well-designed six-month, double-blind, randomized controlled trial comparing low-dose amitriptyline (25 mg) with an active comparator (benztropine 1 mg).
- The authors reported that amitriptyline was effective in reducing pain and pain-related disability without incurring serious adverse effects.
- They suggested continued use of TCAs for chronic low back pain if complicated with pain-related disability, insomnia, depression or other comorbidity, although they called for further large-scale studies. They also cautioned that patients about the adverse effects of TCAs Need for monitoring of symptoms

Strategies to Treat Chronic Pain and Strengthen Impaired Descending

Noradrenergic Inhibitory System Ken-ichiro Hayashida and Hideaki Obata Int J Mol Sci. 2019 Feb; 20(4): 822

- Gabapentinoids (gabapentin and pregabalin) and antidepressants (TCA and SNRI) are often used to treat chronic pain.
- The descending noradrenergic inhibitory system from the locus coeruleus (LC) to the dorsal horn of the spinal cord plays an important role in the analgesic mechanisms of these drugs.
- Antidepressants increase noradrenaline levels in the spinal cord by inhibiting reuptake, and accumulating noradrenaline inhibits chronic pain through α_2 -adrenergic receptors in the spinal cord.

Stepwise pharmacological management of neuropathic pain.



- In a normal physiologic state (blue pathway), activation of LC neurons results in spinal noradrenaline (NA) release, which stimulates α_2 -adrenergic receptors (α_2 -AR) in the spinal cord to produce analgesia.
- In early-stage neuropathic pain following peripheral nerve injury (red pathway), noradrenergic axons sprout in the spinal cord, and the function of the α_2 -AR in the spinal cholinergic neurons changes from inhibition (Gi/o-coupling) to facilitation (Gs-coupling).
- Therefore, activation of LC neurons results not only in an increased release of NA but also the excitation of cholinergic interneurons to induce the release of acetylcholine (ACh) in the spinal cord, which is critical to the antihypersensitivity effect of spinal noradrenaline after nerve injury.
- The main pharmacologic mechanism of antidepressants involves binding with noradrenaline and serotonin (5-HT) transporters.Reuptake inhibition of these neurotransmitters leads to increased levels of noradrenaline and 5-HT in the synaptic cleft of the central nervous system.
- For patients with painful polyneuropathy, the NNT for noradrenaline reuptake inhibitors (e.g., nortriptyline, desipramine) is approximately 2.5 and that for SNRIs and selective 5-HT reuptake inhibitors (SSRIs) is 5.0 and 6.8, respectively.
- Based on these results, reuptake of noradrenaline plays a greater role than that of 5-HT in the analgesic action of antidepressants for neuropathic pain.
- Although clinical reviews show that gabapentinoids and antidepressants (TCA and SNRI) are first-line drugs for treating neuropathic pain..... strategies to select the first drug or to combine drugs are not well established.
- Therefore, gabapentinoids should be used for patients who can recruit descending inhibition (mostly early-stage neuropathic pain).

- If the effect of gabapentinoids is poor or inadequate, the medication should be changed to antidepressants or a combination of gabapentinoids and antidepressants.
- For late-stage neuropathic pain, the HDAC inhibitor valproate might be added.

TABLE 2

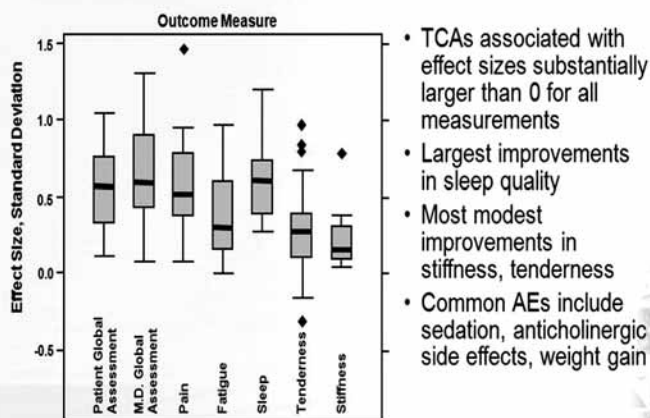
Dosing guide for tricyclic antidepressants in conditions other than depression

Indication	Medications	Initial/ maximum dosing	Dose escalation	Adverse effect management
Headache or migraine	Amitriptyline	10–25 mg/ 100 mg nightly	Individualized: Increase by 10–25 mg every 5–14 days, assess for tolerability and adverse effects	Dry mouth and secretions: Pilocarpine 5 mg 2–3/day
Neuropathic pain	Amitriptyline	25–50 mg/ 150 mg nightly (or divided into twice-daily doses if frequent pain or symptom flares)	Amitriptyline side effects (dry mouth, orthostasis) often limit dose escalation above 100 mg; nortriptyline or maprotiline may be considered (better tolerated at higher doses)	Constipation: Stool softeners, eg, docusate sodium, senna glycoside Weight gain: Consider augmenting with metformin 500–1,000 mg/day or topiramate 50–100 mg/day
Chronic low back pain	Amitriptyline, maprotiline	25–50 mg/ 150 mg nightly		Seizures, QT interval prolongation, active suicidal risk, orthostasis, or falls: Discontinue the agent
Fibromyalgia or chronic widespread pain	Amitriptyline, nortriptyline, maprotiline	25–50 mg/ 150 mg nightly (or divided into twice-daily doses if frequent pain or symptom flares)		
Irritable bowel syndrome	Amitriptyline, nortriptyline	10–25 mg/ 100 mg nightly		
Cyclic vomiting syndrome	Amitriptyline, nortriptyline	25–50 mg/ 100 mg nightly		
Chronic pelvic pain, interstitial cystitis, nocturia	Amitriptyline, nortriptyline, imipramine	10–25 mg/ 100 mg nightly		
Insomnia	Amitriptyline, maprotiline, doxepin	25–50 mg/ 150 mg nightly		

Fibromyalgia

Dual-Uptake Inhibitors: TCAs

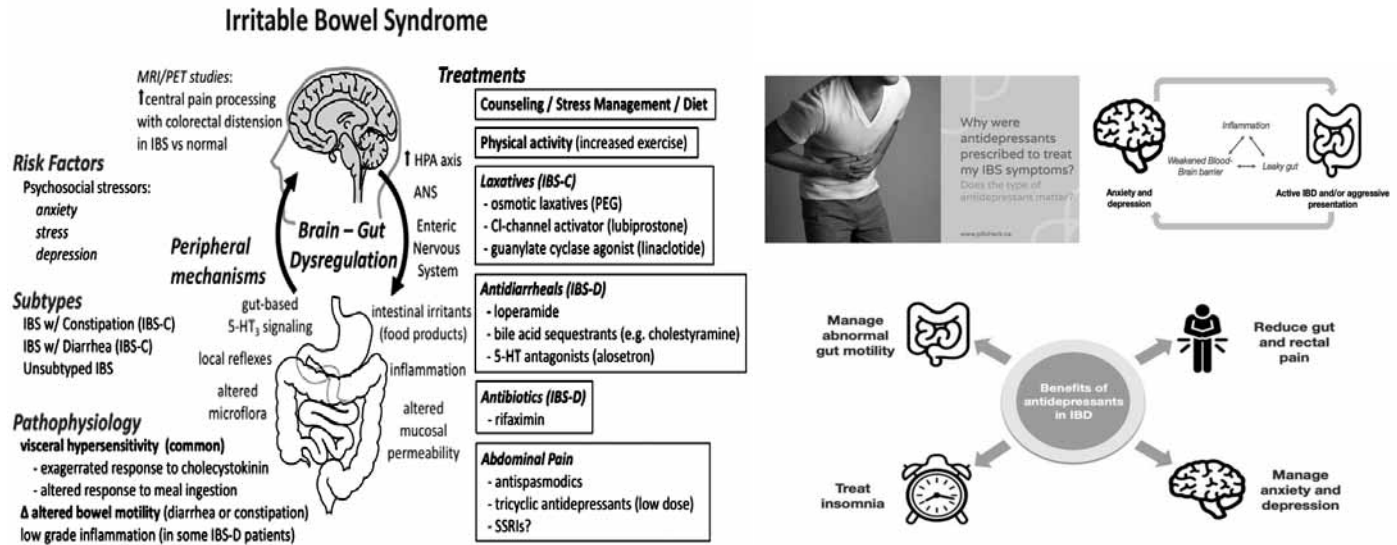
29



AE, adverse event.
Box plot of effect size in 9 controlled studies of TCA treatment of fibromyalgia.
♦ Observations lying beyond the 5th and 95th percentiles.
Arnold LM, et al. *Psychosomatics*. 2000;41:104-113.

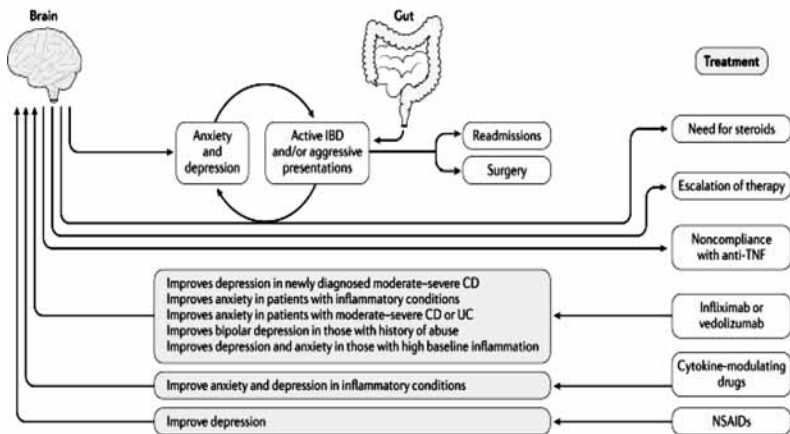
- A meta-analysis of nine placebo-controlled TCA trials showed large effect sizes for pain reduction, fatigue reduction, improved sleep quality and reduced stiffness and tenderness, with the most significant of these improvements being for sleep.
- A separate meta-analysis calculated that the number needed to treat with amitriptyline for a positive outcome is 4.9.
- Recent systematic reviews have supported these findings, listing TCAs as second-line agents after pregabalin, duloxetine and milnacipran.

- Of note, TCA monotherapy rarely produces a complete response in patients with moderate to severe fibromyalgia, chronic widespread pain or significant comorbidities (depression, anxiety).
- Supplementation with cognitive-behavioral therapy, physical therapy, functional restoration and other modalities is strongly recommended.



Antidepressants in inflammatory bowel disease

nature reviews gastroenterology & hepatology
18 February 2020



- Gut-brain dysregulation has been recognized by the scientific community as being crucial to the understanding of chronic gastrointestinal conditions, and this has translated into the practice of a newly established discipline, psychogastroenterology.
- Although there is no substantial evidence that TCAs are useful in reducing active inflammation in inflammatory bowel disease, a study involving 81 patients found that residual noninflammatory gastrointestinal symptoms (such as diarrhea and pain) responded to TCAs, including nortriptyline and amitriptyline, with greater benefit for ulcerative colitis than for Crohn disease.



- TCAs have also shown prophylactic benefit in cyclic vomiting syndrome, with a clinical response in over 75% of patients in controlled cohort studies.

Cyclic Vomiting Syndrome - Treatment

Acute Treatment

Abortive Therapy

- Sumatriptan (5-HT / serotonin agonist)
- Aprepitant (neurokinin 1 antagonist)
- Benzodiazepines

Supportive Care

- IV hydration & electrolyte repletion
- Minimal stimulation
- Antiemetics (e.g. ondansetron)
- Pain control (e.g. IV ketorolac)

Chronic Treatment

Non-Pharmacologic Therapy

- Avoiding triggers (e.g. fasting, cannabis)
- Good sleep hygiene
- Consider psychology and/or psychiatry referral

Prophylactic Therapy

- Tricyclic antidepressants (e.g. amitriptyline)
- Anticonvulsants (e.g. topiramate, levetiracetam)

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Efficacy of Tricyclic Antidepressant Therapy in Adults With Cyclic Vomiting Syndrome: A Two-year Follow-up Study

Reza A. Hejazi, MD, Savio C. Reddymanu, MD, Farid Namin, MD, Teri Lavenburg, ARNP, Pernilla Foran, LPN, and Richard W. McCullum, MD, FACP, FRACP (Aust), FACP

	Male	Female	Total (%)
No. patients	22	19	41
Irritable bowel syndrome	3	5	8 (19)
Diabetes mellitus	3	2	5 (12)
Hx of migraine headache	7	5	12 (29)
Family hx of migraine headache	2	1	3 (7)
Marijuana use	16	6	22 (53)
Medication			
Amitriptyline	21	17	38 (93)
Nortriptyline	1	1	2 (5)
Doxepine	0	1	1 (2)
L-carnitin or coenzyme Q10 in addition to TCAs	5	2	7 (17)
Topiramate in addition to TCAs	2	1	3 (7)

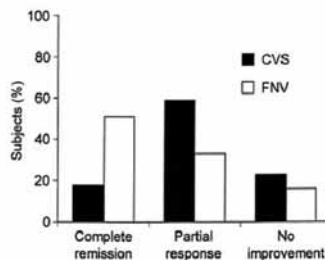
Outcome Measures	Baseline Mean ± SD (95% Confidence Levels)	After First Year of Tricyclic Antidepressant Therapy, Mean ± SD (95% Confidence Levels)	After Second Year of Tricyclic Antidepressant Therapy, Mean ± SD (95% Confidence Levels)	P, First Year	P, Second Year
Frequency of CVS episodes/yr	17.8 ± 8.3 (4.5-180)	5.4 ± 3.8 (1-54)	3.3 ± 2.8 (1-42)	0.003	0.002
Duration of CVS episodes (d)	6.7 ± 6.1 (0.2-30)	2.5 ± 2.7 (0-14)	2.2 ± 2.4 (0-10)	0.0009	0.0008
No. ED visits and Hospitalizations/yr	15 ± 13.4 (1-27)	4.2 ± 5 (0-20)	3.3 ± 3.6 (0-14)	0.009	0.007

Cyclic Vomiting Syndrome in Adults: Clinical Features and Response to Tricyclic Antidepressants

Chandra Prakash, M.D., M.R.C.P., and Ray E. Clouse, M.D.

- Open-label trial: 17 adult CVS patients response to TCA tx
- Complete remission in 17.6%; partial response in 58.8%

Tricyclic Antidepressant	Number of Uses*	Partial Response or Remission, N†	Median Dose to Response, mg/day (Range)
Amitriptyline	7	6	50 (25-50)
Doxepin	7	6	50 (25-150)
Nortriptyline	4	4	50 (10-75)
Desipramine	3	0	
Imipramine	1	0	



- Tricyclic antidepressants (TCAs) positive in more than 80% of CVS patients.
- TCAs are thought to alter the afferent pathways involved in central regulation of the vomiting process.
- Side effects seen in one-third of CVS patients.

Trigeminal Neuralgia - Treatment

- Carbamazepine
- Gabapentin
- Baclofen
- Phenytoin
- Valproate
- Chlorphenesin
- Adjuvant
 - TCAs
 - NSAIDs
 - Surgery for refractory cases

Pharmacological management of neuropathic pain in patients with vestibular schwannomas: Experience of the Atlantic Lateral Skull Base clinic



Typical history of prodrome & rash in a dermatomal distribution
Shooting/burning pain in the same area as the rash? Allodynia?

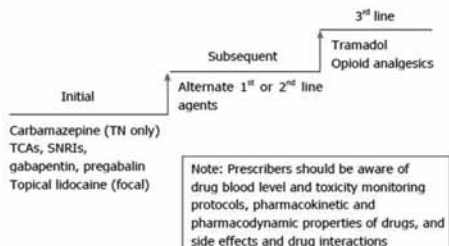
YES

Drugs used in the treatment plan may include the following, based on preference for patient's condition and physician's preference:

- Gabapentin
- Pregabalin
- Duloxetine
- TCA, e.g. amitriptyline, nortriptyline
- Lidocaine cream
- Capsaicin cream*

*use if available

Refer to pain service if drug treatment is ineffective



Primary care remains responsible for the diagnosis, treatment, prescribing of medication, and monitoring of the patient

The preference for these medications is based upon the patient's condition and the physician's choice

Clomipramine and sexual function in men with premature ejaculation and controls

S M Haensel, D L Rowland, K T Kallan J Urol 1996 Oct;156(4):1310-5

- Clomipramine significantly increased the latency to ejaculation during sexual activity (coitus or masturbation) from approximately 2 to 8 minutes in men with primary premature ejaculation.
- Laboratory assessment indicated that men with primary premature ejaculation were better able to control ejaculatory response with clomipramine therapy.
- In these men clomipramine also resulted in increased satisfaction with sex life and relationship.

On-demand use of clomipramine effective, safe in men with premature ejaculation

- Clomipramine inhibited nocturnal penile tumescence in all subjects.
- low doses of clomipramine in the treatment of premature ejaculation, specifically when taken on an as-needed basis as little as 4 hours prior to sexual activity.
- beneficial effects of the drug were not uniform across clinical subjects.

Last but not the least.....

Clomipramine (ANAFRANIL)



FDA-approved for:

- ❖ Obsessive-compulsive disorder (OCD)

Used off-label for:

- ❖ Cataplexy (in narcolepsy)
- ❖ Confusional arousals
- ❖ Sleep terrors
- ❖ Sleepwalking

Dynamic interactions:

- ❖ Serotonergic (very strong)
- ❖ Sedation/CNS depression
- ❖ Weight gain (moderate)
- ❖ QT prolongation (mild)
- ❖ Anticholinergic (strong)
- ❖ Lowers seizure threshold (strong)
- ❖ Hyponatremia (5-HT)
- ❖ Antiplatelet effects (5-HT)

Kinetic interactions:

- Multi-CYP
- ❖ 2C19 substrate
- ❖ 2D6 substrate
- ❖ 1A2 substrate
- ❖ 3A4 substrate

Multi-CYP substrates are less likely to be involved in clinically significant interactions.



All TCAs are 2D6 substrates.



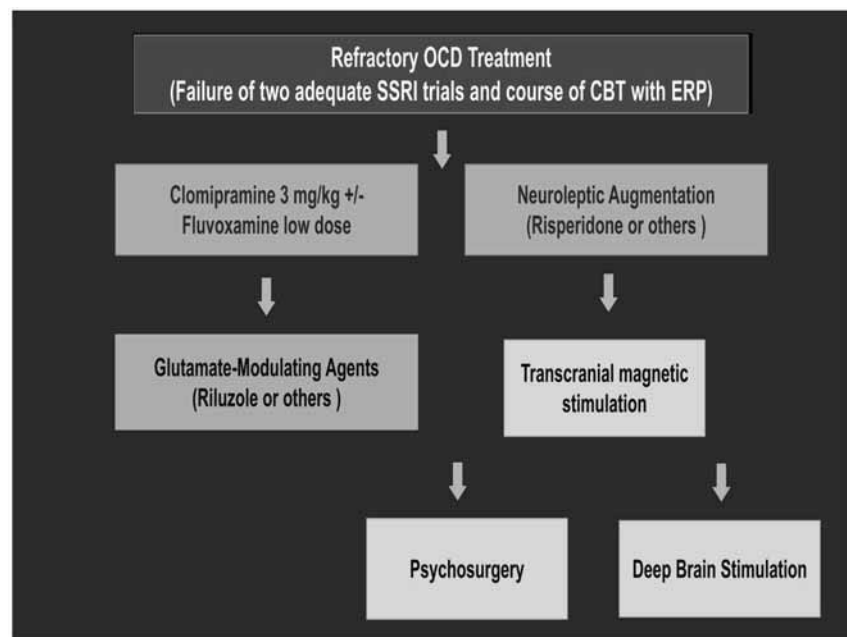
2C19 substrate

It is unclear whether clomipramine is more efficacious than SSRIs

- Clinical trials that directly ("head-to-head") compare clomipramine to an SSRI generally do not find clomipramine to be more efficacious (American Psychiatric Association, 2007).
- However, when these data were combined in meta-analyses, some of them found clomipramine may be more efficacious than SSRIs.
- The most recent meta-analysis (Skapinakis et al., 2016), however, did not find clomipramine to be more efficacious than SSRIs.
- The combination of these observations suggests that the difference in efficacy, if any, is probably not large.

Clomipramine is associated with more adverse effects than are the SSRIs

- Clomipramine is associated with some troublesome adverse effects like dry mouth, dizziness, etc., and also with potential cardiovascular adverse effects. At higher doses, it usually requires doing periodic ECGs and measurements of serum level.
- Notably, clomipramine is associated with significantly more weight gain than SSRIs, even more than paroxetine, the SSRI that is associated with the greatest weight gain.
- In a 2.5-year follow-up study, clomipramine was associated with the greatest increase in weight increase and fluoxetine and sertraline with the least (Maina et al., 2004).
- The percentage of patients who gained 7% or more of their baseline weight were: clomipramine 35%, fluoxetine 9%, sertraline 5%.



BIPOLAR DEPRESSION: recent updates on pharmacological management

Dr Anweshak Das

Consultant Psychiatrist
Guwahati, Assam

How to cite this article: Das A. Bipolar depression: recent updates on pharmacological management. Beng J Priv Psychiatry 2023; 10 (1): 30-36

Global Scenario

Prevalence - 39.5 million in 2019

Male : Female ? 1:1

Lifetime prevalence of bipolar disorder - 2.4%

Average age of onset - 25 years old

Burden: India

Prevalence - 7.6 million (0.6%)

6.9% of DALYs

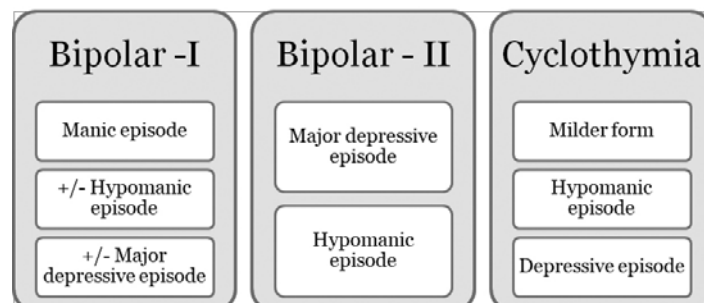
High SDI (Socio-demographic Index) states - Highest prevalence

Goa, Kerala, Sikkim and Himachal Pradesh

No difference between genders

Highest - Adolescence

Types of Bipolar Disorders



Other specified bipolar & related disorders

Challenges in diagnosing Bipolar Disorder

- Most frequent misdiagnosis is that of MDD, as patients may not recall periods of hypomania or mania
- Patients with bipolar II disorder were usually misdiagnosed as having unipolar depression
- Second most common Schizophrenia and other psychotic disorders in 30% of patients
- Symptoms of borderline personality disorder(BPD), substance use disorder (SUD) and attention deficit hyperactivity disorder (ADHD) overlap significantly those of hypomania/mania

Bipolar depression accounts for most symptomatic periods in bipolar disorder (BD) and is associated with elevated suicide risk and high morbidity and mortality rates.

On average, the ratio of major depressive to manic/hypomanic episodes is 3:1 for bipolar I disorder Ratio of major depressive to hypomanic episodes is 39:1 for bipolar II disorder

Need gap in Diagnosis

- Hypomanic episodes are unreported as they have a milder presentation than mania with no functional impairment
- Predominance of depressive symptoms were even greater compared to mood elevation in patients with bipolar II disorder

60% Initial misdiagnosis of bipolar depression as unipolar depression >> Bipolar depression

Misdiagnosis – Unipolar depression

- Most frequent misdiagnosis in patients with bipolar disorder, especially in BPD II, because patients with this illness, by definition, never experience an episode of full-blown mania
- Another reason for misdiagnosis is the prevalence of depressive symptoms is higher than that of hypomanic or manic symptoms during bipolar disorder type I or II, and these disorders often start with a depressive episode.

Misdiagnosis

Indeed, subthreshold hypomanic symptoms can occur in as many as 40% of patients with major depressive disorder Episodes of bipolar depression and unipolar major depression have the same general diagnostic criteria. However, a history of manic or hypomanic episodes distinguishes bipolar depression from unipolar depression.

Consequences of Misdiagnosis

- Initial misdiagnosis results in delay of appropriate treatment, thereby increasing recurrence and chronicity of episodes
- Inappropriate treatment with antidepressants result in manic episodes and trigger rapid cycling
- Delay in start of mood stabilizers in bipolar disorder, also increased treatment time and health costs that resulted in increased mortality

Avoiding Misdiagnosis

- It is important to differentiate bipolar depression from unipolar depression
- Evaluating a patient for bipolarity
- Presence of hypersomnia and motor retardation during depression as symptoms suggestive of bipolar depression
- Multiple failed antidepressant trials, rapidly occurring episodes of recurrent depression suggest bipolarity

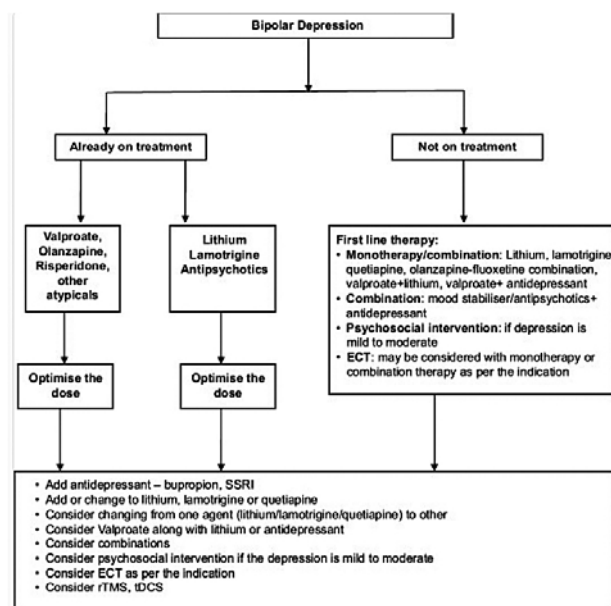
According to the International Society of Bipolar Disorders Working Group on Bipolar Depression

A probable diagnosis of bipolar depression should be considered if ≥5 of the following characteristics are present*	A probable diagnosis of unipolar depression should be considered if ≥4 of the following characteristics are present*
Family history	
Positive for bipolar disorder	Negative for bipolar disorder
Course of illness	
Early onset of first depression (<25 years)*	Later onset of first depression (>25 years)*
Multiple prior episodes of depression (≥5 episodes)*	Long duration of current episode (>6 months)*
Symptomatology	
Hypersomnia and/or increased daytime napping	Initial insomnia/reduced sleep
Hyperphagia and/or increased weight	Appetite loss/weight loss
Atypical depressive symptoms such as leaden paralysis	
Psychomotor retardation	Higher activity levels
Psychotic features and/or pathological guilt	Somatic complaints
Lability of mood	

Guidelines

- Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders guidelines (2018) recommend quetiapine, lurasidone + lithium/valproic acid, lithium, lamotrigine, lurasidone and adjunctive lamotrigine.
 - British Association for Psychopharmacology guidelines (2016) endorse quetiapine, lurasidone or olanzapine as first-line treatments for acute bipolar depression.
 - On the other hand, National Institute for Health and Care Excellence guidelines (2018) recommend olanzapine + fluoxetine, or quetiapine
-
- World Federation of Societies of Biological Psychiatry and German (2012) guidelines only include quetiapine as a first-line agent for the acute treatment of bipolar depression.
 - Swiss Society for Bipolar Disorder (2015) recommends monotherapy with lithium (as well as quetiapine/quetiapine XR and lamotrigine)
 - Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines (2015) classify quetiapine, lurasidone, olanzapine, lithium, lamotrigine and valproate as first-line therapies for the treatment of bipolar depression

Dr Nilesh Shah, Dr Sandeep Grover and Dr G. Prasad Rao. Clinical Practice Guidelines for Management of Bipolar Disorder. 2017



- The main goal of management is to achieve euthymia, normal level of functioning and to avoid switching to hypomanic/manic episode.
- Among the various mood stabilizers, there is ample evidence to suggest that lithium and lamotrigine may be used as the first line medications in the management of bipolar depression.
- If the patient presents with a breakthrough episode, the initial strategy is to check the medication compliance and ensure adequate compliance.

REVIEW



The Diagnosis and Management of Bipolar I and II Disorders: Clinical Practice Update

William V. Bobo, MD, MPH

Medication name	Starting dose	Effective dose (drug level)	Treatment priority and comments
Monotherapy, mood stabilizers			
Lamotrigine	Variable ^c	Variable ^c	Second line; but takes several weeks ^d to achieve target doses
Lithium	150-300 mg bid	900-1800 mg/d (0.6-1.2 mEq/L)	Second line; may be higher priority in patients at high risk for suicidal behavior ^e
Divalproex	250 mg bid	750-2500 mg	Second line; usually avoided in women of reproductive age
Carbamazepine	100 mg bid	800-1600 mg (4-12 µg/mL) ^f	Third line ^e
Monotherapy, antipsychotic drugs—generally higher priority than mood stabilizer monotherapy for patients with psychotic symptoms; medications with established maintenance-phase efficacy (Table 5) are preferred, whenever possible			
Quetiapine	50 mg at bedtime	300 mg at bedtime	First line
Lurasidone	20 mg/d	20-120 mg/d	First line; all doses must be taken with food
Olanzapine	5 mg at bedtime	5-12.5 mg at bedtime	Second line ^g
Cariprazine	1.5 mg/d on day 1 3 mg/d on day 2	1.5-3 mg/d	Third line monotherapy
Combination therapy—generally preferred if monotherapy is ineffective or “breakthrough” depressive episodes occur despite ongoing treatment; combinations that include ≥1 agent with established maintenance-phase efficacy (Table 5) are preferred, if possible			
Lithium + lamotrigine	See above guidelines regarding dosing	See above guidelines regarding dosing	First line
Lithium or divalproex + an atypical antipsychotic	See above guidelines regarding dosing	See above guidelines regarding dosing	First line; lithium or divalproex plus either quetiapine or lurasidone
Olanzapine + fluoxetine	3 mg/25 mg-6 mg/25 mg at bedtime	6 mg/25 mg-12 mg/50 mg at bedtime	Second line; lithium or divalproex + olanzapine ^g
Lithium + divalproex	See above guidelines regarding dosing	See above guidelines regarding dosing	Second line ^h
Lithium or divalproex + an antidepressant ⁱ	See above guidelines regarding dosing	See above guidelines regarding dosing	Second line; higher priority in patients with a history of good response to antidepressants taken with mood-stabilizing medications
Atypical antipsychotic + an antidepressant ⁱ	See above guidelines regarding dosing	See above guidelines regarding dosing	Second line; antipsychotics include quetiapine, lurasidone, and olanzapine Higher priority in patients with a history of good response to antidepressants taken with mood-stabilizing medications
Lithium + carbamazepine	See above guidelines regarding dosing	See above guidelines regarding dosing	Third line
Lamotrigine + quetiapine	See above guidelines regarding dosing	See above guidelines regarding dosing	Third line

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SPECIAL ARTICLE

Treatment-resistant bipolar depression: concepts and challenges for novel interventions

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Jair C. Soares^{1,3}

consensus of internationally recognized experts, which defined TRBD as “failure to reach sustained symptomatic remission for 8 consecutive weeks after two different treatment trials, at adequate therapeutic doses, with at least two recommended monotherapy treatments or at least one monotherapy treatment and another combination treatment.”

Novel/Newer Agents

Agent	Pharmacological Details	Summary of Evidence in Bipolar Depression
Ketamine	- NMDA receptor antagonist; dissociative anesthetic agent⁷² - Thought to exert antidepressant effects via NMDA receptor antagonism and possible inhibitory effects on norepinephrine and serotonin transporter function⁶²	- Several RCTs and open-label retrospective studies have demonstrated rapid improvement of depression, suicidal ideation and anhedonia following single low (subanesthetic) intravenous doses, compared with placebo⁷³⁻⁷⁸ - Response rate for depression was statistically significant versus placebo for up to approximately 3 days^{74,75} - Some evidence of improvement in fatigue for up to 2 weeks following single intravenous dosing⁷⁹ - AEs include dizziness, blurred vision, restlessness, nausea/vomiting and headache; AEs are usually transient and mild; no serious AEs reported^{73,77,80} - Use may be limited by need for administration by an anesthesiologist and hospitalization post-administration⁸¹ - Potential use as a longer-term treatment is currently unclear⁸¹
Modafinil/ armodafinil	- Wakefulness-promoting, low-affinity dopamine transport inhibitor⁶⁸ - Armodafinil is the active R-enantiomer of modafinil⁶⁸	- A 6-week placebo-controlled study demonstrated that modafinil added to a mood stabilizer ± an antidepressant resulted in significantly greater response and remission rates than placebo⁶⁹ - Incidence of treatment-emergent hypomania/mania was similar between groups⁶⁹ - Three 8-week studies of armodafinil as an adjunctive treatment in bipolar depression have been inconsistent in their findings^{68,82,83} - In a 6-month, open-label extension study of patients completing these trials, armodafinil improved depressive symptoms and patient functioning and was generally well tolerated⁸⁴ - Most frequently reported AEs were headache, insomnia and anxiety
Pramipexole	D₂/D₃ receptor agonist⁷⁰	- Two small, 6-week RCTs have investigated the effectiveness of pramipexole as an adjunct to mood stabilizers in bipolar depression (n=22; n=21)^{70,85} - In one, improvements from baseline in HAM-D score and CGI severity were significantly greater with pramipexole versus placebo, as was HAM-D responder rate⁷⁰ - In the other, ANOVA for MADRS total score showed a significant treatment effect, and MADRS responder rate was significantly higher with pramipexole versus placebo⁸⁵ - In both trials, pramipexole was well tolerated and not associated with an increased incidence of hypomania/mania^{70,85} - Additional limited evidence supporting the use of adjunctive pramipexole for bipolar depression from open studies^{86,87}
Riluzole	- Inhibits glutamate release and enhances glutamate reuptake and AMPA trafficking⁶³ - Inhibits voltage-dependent sodium channels⁸⁸	- In an 8-week, open-label study conducted in 14 acutely depressed bipolar patients (MADRS ≥20), riluzole added to existing lithium treatment resulted in significant improvement in MADRS total score and no switch to hypomania/mania was observed⁸⁹ - Interim analysis of an 8-week, placebo-controlled RCT of riluzole monotherapy, conducted in 19 patients with bipolar depression, demonstrated that there were no significant differences on MADRS or HAM-D scores for riluzole versus placebo, and anxiety scores (HAM-A) were significantly lower for placebo versus riluzole⁹⁰ - The trial was subsequently stopped⁹⁰
N-acetyl cysteine	- Acetyl derivative of the amino acid cysteine⁹¹ - Increases glutathione levels in the brain, which may decrease oxidative stress and inflammation⁹¹	- In a 24-week, multicenter RCT, conducted in patients with bipolar disorder in the maintenance phase, N-acetyl cysteine (as an adjunct to usual treatment) resulted in significant improvements on MADRS versus placebo⁹² - A subsequent RCT of N-acetyl cysteine as an adjunctive maintenance treatment for bipolar disorder yielded inconclusive results due to low event rates⁹³ - A 20-week placebo-controlled RCT will assess the effects of adjunctive N-acetyl cysteine treatment on depressive symptoms in patients diagnosed with bipolar depression⁹⁴ - Primary outcome will be mean change from baseline on MADRS

Agent	Pharmacological Details	Summary of Evidence in Bipolar Depression
Other anti-inflammatory agents	Bipolar disorder has been proposed to be a multisystemic inflammatory disease due to high levels of comorbid medical conditions and adjunctive anti-inflammatory medication may, therefore, be a rationale therapeutic strategy⁶⁴	- A systematic review and meta-analysis of 10 RCTs assessing treatment with adjunctive non-steroidal anti-inflammatory drugs, omega-3 polyunsaturated fatty acids, N-acetylcysteine and pioglitazone demonstrated a moderate and statistically significant antidepressant effect⁶⁵ - No switching to hypomania/mania or clinically significant AEs were reported⁶⁵ - In an 8-week, open-label pilot study of adjuvant therapy with the antibiotic, minocycline, conducted in 20 patients with bipolar disorder experiencing acute depressive symptoms, 50% were MADRS responders and 40% were MADRS remitters⁶⁶ - Higher baseline glutathione levels were associated with significantly greater improvement in MADRS score⁶⁶ - In another 8-week, open-label pilot study, conducted in 29 patients with bipolar I/II depression, adjunctive minocycline resulted in significant reductions on MADRS, HAMD-17 and CGI-severity⁹⁵ - A Phase IIa, 2x2, placebo-controlled RCT evaluated augmentation therapy with minocycline and/or aspirin for bipolar depression⁹⁶ - MADRS responder rates were significantly higher for aspirin + minocycline versus placebo + placebo, and for aspirin + minocycline and aspirin + placebo versus minocycline + placebo and placebo + placebo⁹⁶ - Patients with higher baseline levels of IL-6 responded better to minocycline than those with lower levels⁹⁶ - An 8-week, placebo-controlled RCT demonstrated that addition of the cyclooxygenase-2 inhibitor, celecoxib, to escitalopram therapy in patients with bipolar depression resulted in significantly greater improvements on HAMD-17 than placebo⁹⁷ - CRP levels decreased significantly more with celecoxib versus placebo⁹⁷ - Baseline CRP levels were significantly higher in patients with bipolar depression versus healthy controls, indicating that CRP may be a useful biomarker for bipolar depression⁹⁷ - A multicenter, 3-month, placebo-controlled RCT with factorial design will investigate the effectiveness of minocycline and/or celecoxib added to usual therapy for the treatment of depressive symptoms in patients experiencing a DSM-5 bipolar I or II disorder and a current major depressive episode⁹⁸ - Primary outcome will be mean change from baseline to Week 12 on HAM-D⁹⁸ - CRP levels will be measured at baseline and end of treatment⁹⁸

Minocycline
Aspirin
Pioglitazone
Celecoxib

Brexipiprazole	- Serotonin and dopamine receptor modulator¹⁰¹ - Sub-nanomolar potency as an antagonist at serotonin 5-HT_{2A} and adrenergic α1A receptors⁷¹ - A partial agonist at serotonin 5-HT_{1A} and dopamine D₂ receptors⁷¹	- In an open-label study, treatment with brexpiprazole 4 mg/day for 8 weeks resulted in decreases in MADRS total and Inventory of Depressive Symptomatology Self-report scores at Weeks 4 and 8 in 21 patients with bipolar depression⁷¹ - An increase in Quality of Life in Bipolar Disorder score from baseline to Week 8, with no significant changes in Young Mania Rating Scale and cognitive scores were also reported⁷¹
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Pharmacologically similar agents like ketamine NMDA-glutamate receptor antagonist and newer e.g., apimostinel, rapastinel Neurosteroids that interact with GABAA receptors and found effective for postpartum depression (e.g., brexanolone)

Pharmacologically similar agents like ketamine NMDA-glutamate receptor antagonist and newer e.g., apimostinel, rapastinel Neurosteroids that interact with GABAA receptors and found effective for postpartum depression (e.g., brexanolone)

Depression in bipolar disorder (BD) is the major residual psychiatric morbidity with available treatments, accounting for three-quarters of the 40–50% long-term time-ill

Unresolved morbidity, and especially depression, is associated with excess medical morbidity, including metabolic syndrome and cardiovascular disease, with increased mortality

Suicide risk in BD is similar in types I and II BD, greater than in most other psychiatric disorders, ca. 20-times above general population rates, and strongly associated with depression, especially with agitation (mixed-dysphoric states), and in the days–weeks following hospital discharge

Predicting suicide in BD clinically is limited regarding individuals and timing

Treatments proposed to prevent suicidal behavior in BD include lithium, clozapine, and possibly ketamine and psychotherapies, which all require further study

Therapeutics of bipolar depression is far less well developed than for nonbipolar major depression, probably reflecting lack of recognition of differences between bipolar and unipolar depression

The short-term value and safety of antidepressant treatment for bipolar depression remains controversial, and long-term value remains virtually untested; it is best avoided with ongoing dysphoric agitation or mixed features

Some modern antipsychotics are effective in bipolar depression short-term; lithium and lamotrigine have modest prophylactic value long-term but are not adequately tested short-term; other anticonvulsant mood-stabilizers have very limited evidence of short- or long-term efficacy in bipolar depression

All available treatments for bipolar depression have risks of adverse metabolic or neurological effects; valproate and carbamazepine are also highly teratogenic

Depression among medical students: time to come out and raise curtain

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Medical students face huge stress throughout their curriculum. This may lead to burnout and depression which runs in a continuum. The transition period from pre-clinical to clinical stage has been considered as significant stressful phase in the life of Indian Medical Student. The burnout in students depends on several factors. The perceived stress, general psychopathology, type of coping and duration of this stressful period are key attributing factors. The perceived stress can be reduced by positive reframing, acceptance, applying mature defence mechanism like humour, active coping strategies, meticulous planning etc.

It's important to remember that depression is a medical condition and seeking professional help from mental health experts is essential for proper diagnosis and treatment.¹ Findings of research works on Depression in Medical students suggested four major causes as mentioned in Table 1.

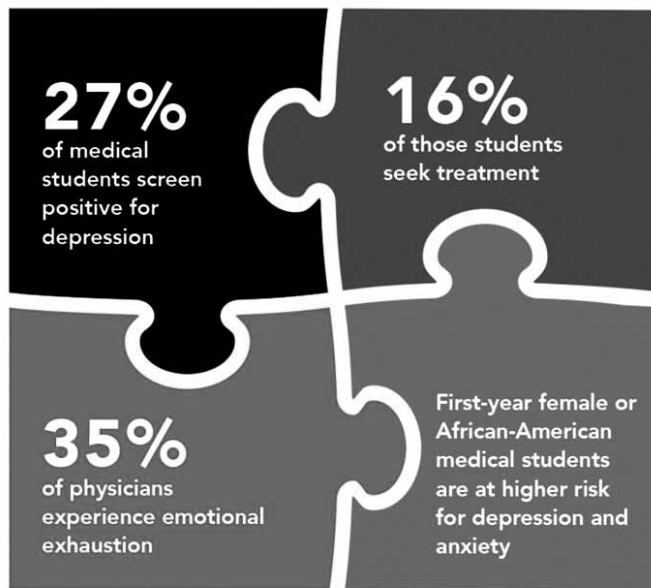
Table 1: Factors attributing to depression among medical students.

1. Significant stress during training will lead to depression and burnouts which in turn attribute to poor academic performances and quality of patient care in future.
2. Perceived stress is attributed to general psychopathology and depressive-anxiety factors of burnout parameters.
3. Medical students doesn't seek treatment for their own which s/he'll provide or seek otherwise for their patients and relatives.
4. Break in relationship and failure in examinations often acts as a trigger compounded by adopting maladaptive coping strategies like psychoactive substance abuse.

A recent meta-analysis showed that depression affects approximately one third of medical students worldwide, and it is also likely that the overall prevalence of depressive symptoms among medical students is higher than that reported in the general population. Students with depressive symptoms also suffer from other psychological difficulties, such as anxiety, burnout, suicidal thoughts, and substance abuse.²

Another study showed that students are more likely to engage in active coping by their final year of medical school than they were in their earlier years. It is hard to discern if students learn these skills as they progress due to their medical school experiences, their training, or simply by maturing, but the evidence suggests that junior medical students are more at risk of suicidal thoughts or attempts. This underscores the importance of learning and applying healthy coping mechanisms early on in medical training. Research has shown that active coping strategies, such as positive framing, talking to family and friends, leisure activities, and exercising, can reduce the level of perceived stress among college students.

In a JAMA review some alarming findings have emerged up which are mentioned in Figure 1 below. In the Figure 2 it has been summarized in a flow diagram how a medical students face burnout and eventually depression.



Source: "Prevalence of Depression, Depressive Symptoms, and Suicidal Ideation Among Medical Students: A Systematic Review and Meta-Analysis," *JAMA*, Dec. 6, 2016.

Fig 1: Depression in Medical students.

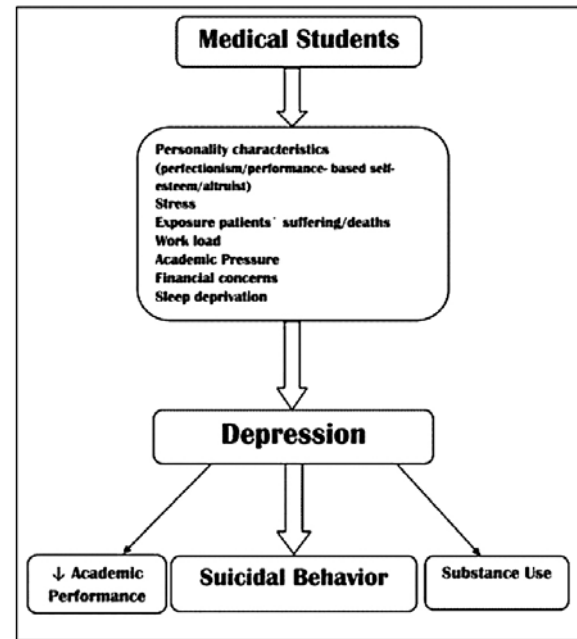


Fig 2 : Multiple factors attributing depression

Undergraduate (UG) Medical students are vulnerable to suffer from depression, anxiety and stress. Lifestyle modifications (LM) and Psychological Interventions (PI) have been found to be beneficial in a study of four months duration. These interventions helped to reduce depression, anxiety and stress among UG Medical students and also found beneficial objectively as evident from improvement in scoring from Internal Assessment at baseline and following LM & PI (IA1 & IA2)3

The desire to be excellent coupled with a competitive learning environment engages the classic "Type A" medical students in learning behavior that may be detrimental to psychological health. Type A behavior pattern is defined by Lohse et al as an action-emotion complex, with individuals characterized by ambition, display of highly competitive attitudes toward achievement, and feeling compelled to "work harder than Type B individuals to accomplish tasks, regardless of external stressors". They are said to have an exaggerated sense of urgency with regard to time, preferring to spend it on things they deem as priorities, and possibly becoming aggressive, hostile, or impatient in frustrating situations. These authors suggest that Type A characteristics begin with a predisposition for competitiveness and then lead to the manifestation of characteristics such as ambitiousness, aggressiveness, impatience, and physiological behaviors such as muscle tension, a hurried pace, and alertness.4

While anecdotally it is recognized that medical students exhibit Type A characteristics, there appears to be little evidence to support this, although a study by Alfulaij and Alnasir found that of 77, Year 1 medical students in Bahrain in 2013, 76.6% had Type A personality, as opposed to 23.4% with Type B. They also found that Type A personality was more prevalent among female medical students (63.6% as compared to 36.4%). These authors linked Type A personality with endeavor for perfectionism.5

The highest risk group for deterioration in psychological health during medical school was formed by those students with high conscientiousness and high neuroticism, while the group most protected from worsening psychological health was formed from those with high extroversion, low neuroticism, and low conscientiousness. However, conscientiousness is the trait most significantly associated with better medical school performance. Doctors who were working during COVID pandemic have a high prevalence of psychiatric morbidity. Age and having multiple comorbidities are significant predictive factors. Altruistic coping and a sense of greater goal are significant among the doctor community, in this pressing time.6

The "three pillars" from The Vanderbilt School of Medicine, which recommends the implementation of a well-being curriculum, student-led support, and faculty services. The core components of the University of Auckland SAFE-DRS curriculum are "Self-

Care Skills", "Accessing Help", "Focused Attention", "Emotional Intelligence", "Doctor as Patient and Colleague", "Reflective Practice", and "Stress Resistance". The recent addition to the Hippocratic Oath of doctors attending to their own health is encouraging.

Though in different studies it has been reciprocated in different around one-third to one-fourth medical students are suffering from depression but only around 20% of them seeks professional help. The female medical students are more likely to show symptoms of depression than their male counterparts. The students who have one or both parents as doctors are less likely to suffer from Depression probably due to more awareness and the first hand experience to witness stress among doctors during their upbringing.

The period of residency training is very stressful. Significant among the psychological problems of resident doctors emanating from this high level of stress is depression. The prevalence of depression was 17.3% in resident doctors and 1.3% in non-resident doctors ($p < 0.001$). One-fourth to one-third of the postgraduate medical trainees and residents develop clinical depression at some point in their training period although much higher rates were reported in some other studies.

Residency period during postgraduate training in medical profession is well known for physical and mental stress. There are many situational, professional, and personal sources of stress, which the author reviews: heavy work-load, sleep deprivation, difficult patients, poor learning environments, relocation issues, isolation and social problems, financial concerns, cultural issues, information overload, and career planning issues. Stress can also originate from gender-related issues and issues related to spouses and family members.

Whether burnout is a distinct phenomenon rather than a type of depression. As many as two thirds of people with depression do not realize that they have a treatable illness and therefore do not seek professional help. The presenting complaints often can be somatic, such as fatigue, headache, abdominal distress, or sleep problems. The common feature of the depressive disorders is the presence of sad, empty, or irritable mood. Burnout is an experience of physical, emotional, and mental exhaustion, caused by long-term involvement in situations that are emotionally demanding. It is loss of ability or interest to do something. Depressed residents are more likely to find sleep deprivation, fatigue, working hours, and lack of time to provide good patient care as significantly more stressful than non-depressed residents. Depression in resident physicians also appears to lead to career dissatisfaction. Residents dissatisfied with their career choice in medicine were twice as likely to be depressed. Depression in residents also appears to affect life outside of work. Marital problems were reported by 46% of the depressed interns versus 7% of the non-depressed. Suicide is a devastating consequence of depression in resident physicians. A study looking at emotional impairment in housestaff reported that 3% of those "emotionally impaired" attempted suicide and an additional 2% completed suicide. In that study, "emotionally impaired" referred to depression as well as other psychiatric disorders; however, the majority of the emotionally impaired were diagnosed with depression.⁷

Residents may be prone to feeling emotionally burdensome as a result of depression. Finally, residents become habituated to the suffering associated with self-injury and death. While there is no clear evidence that risk factors for resident depression are different than the general population, the need for confidential screening and treatment programs is clear.

Many studies throughout the world show that medical students suffer from depression, anxiety and stress due to their excessive work pressure, extensive syllabus and various other reasons due to the lifestyle they lead. This study proves that though depression, anxiety as well as stress may exist in medical students, these can be overcome by proper identification of its existence, bringing out the causes and providing appropriate Lifestyle Modification (LM) and Psychological Interventions (PI). The often students often become homesick and they can't adjust with their room-mates, peer group, the new environment or work culture they are now exposed to. Hence, they need faculties at their aid, whom they can depend on, confide in, for the solution of their mental anxiety, stress or depression.

Depression among medical students is a significant and concerning issue that has been well-documented in the literature. Medical education and training can be extremely demanding, stressful and emotionally challenging which can contribute to the development of depression and other mental health problems. Some other key factors that contribute to depression in medical students include,

1. **Academic pressure:** Medical school is known for its rigorous and competitive academic environment, with heavy workloads, high expectations, and a constant need to perform at a high level. The pressure to excel can lead to feelings of inadequacy and self-doubt.
2. **Long hours and sleep deprivation:** Medical students often experience long hours, irregular shifts, and sleep deprivation, which can negatively impact their physical and mental well-being.
3. **Emotional burden:** Dealing with patients who are suffering or facing life-threatening conditions can be emotionally challenging. Medical students may find it difficult to cope with the emotional burden of witnessing pain and suffering regularly.
4. **Lack of Work-life balance:** The demanding nature of medical training can lead to a lack of time for personal life, hobbies and social interactions, resulting in feelings of isolation and loneliness.
5. **Financial strain:** The cost of medical education can be exorbitant, leading to financial stress and pressure to succeed in order to secure a stable income in the future.
6. **Fear of making mistakes:** Medical students may fear making mistakes or harming patients adding to their anxiety and stress levels/
7. **Stigma and reluctance to seek help:** There can be a stigma associated with mental health issues in the medical community, making some students hesitant to seek help for fear of being perceived as weak or unfit for the profession.

Addressing depression in medical students requires a multifaceted approach involving educational institutions, faculty and the student themselves. Some strategies to support mental health and well-being in medical students include:

1. **Mental Health Programs:** Medical schools should implement mental health support programs that raise awareness about mental health issues, providing counselling services, and promote self-care practices.
2. **Peer support:** Encouraging peer support and establishing bond, connectivity and liaison. Some of the helpful strategies or programs are mentioned below.

Mentorship programs: It can help medical students feel more connected and supported throughout their education. The Gatekeeper Training has been initiated already by the Hon'ble Vice Chancellor, the West Bengal University of Health Sciences, Prof (Dr) Suhrita Paul.

Stress Management: Incorporating stress management techniques and mindfulness practices into the curriculum can help students cope with the demands of medical training.

Promoting work-life balance: Institutions should promote work-life balance by providing flexible schedules, encouraging breaks and supporting student's engagement in non-academic activities.

Reducing Stigma: Efforts should be made to reduce stigma surrounding mental health issues in the medical community, encouraging open discussions and seeking help when needed.

Monitoring student well-being: Faculty and administrators should regularly check in on student's well-being and mental health, providing resources and support when necessary.

Early intervention: Identifying signs of depression early and providing timely intervention can be crucial in preventing more severe mental health issues.

Conclusions: The high prevalence of depression among medical students demands regular screening for depression along with counselling services. personal factors (anxiety traits, medicine choice factors, relationship patterns and academic burnout) are relevant for maintenance of high levels of depression during medical training. Depression in medical students likely coincides with anxiety, internet addiction, sleep problems, and loneliness. Highly associated stressors were personal relationships, physical health, mental health, difficulties in social relationships, satisfaction with grades, and boredom with medical education. Emotional intelligence (EI) and perceived social support (PSS) are inversely correlated with depression and anxiety.



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When Can Typical Antipsychotics Still Be Used For Effective Outcomes?

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Abbreviations Used

CATIE - Clinical Antipsychotic Trials of Intervention Effectiveness

CUTLASS - Cost Utility of The Latest Antipsychotics in Severe Schizophrenia

FGAs - First Generation Antipsychotics

LAI - Long Acting Injectables

NHS - National Health Service

NIMH - National Institutes of Mental Health

SGAs - Second Generation Antipsychotics

TRS - Treatment Resistant Schizophrenia

WPA - World Psychiatric Association

Introduction

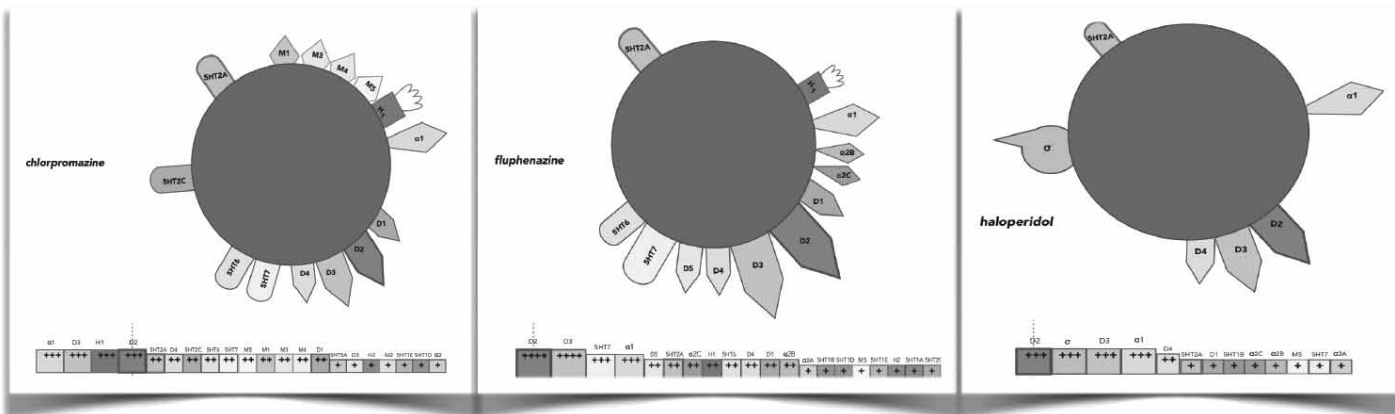
First-generation antipsychotics (FGAs) are drugs used primarily for the treatment of schizophrenia & related psychotic disorders. FGAs are also known as typical antipsychotics, conventional or classic antipsychotics & dopamine antagonists.

The use of FGAs has declined in the last few years, mainly because of an increase in prescriptions of second-generation agents. Since FGAs are considerably less expensive than newer antipsychotics, they remain a valuable option in the treatment of psychotic disorders.

FGAs reduce dopaminergic neurotransmission in the four dopamine pathways by blocking D2 receptors.

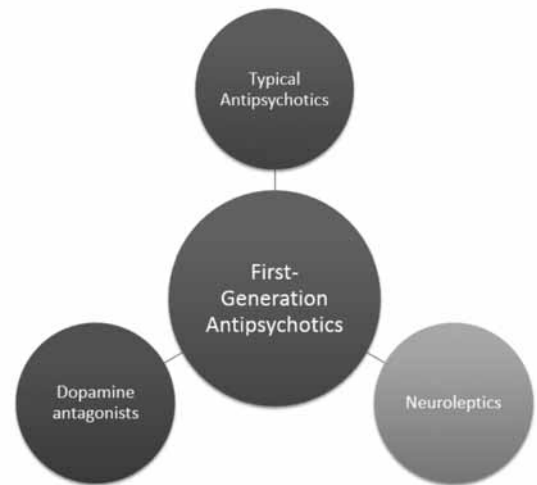
FGAs differ in potency, not effectiveness.

Commonly Used FGAs



History & Definitions

- First-generation antipsychotics are also known as: typical antipsychotics, dopamine antagonists, neuroleptics and classic antipsychotics. Each term has important historical & conceptual implications.
- The term "neuroleptic" refers to the ability of a drug to cause a syndrome known as "neuroleptosis".
- Dopamine antagonists proposes differentiating FGAs & SGAs based on general pharmacodynamic differences. According to this terminology, SGAs are known as dopamine-serotonin antagonists, mainly because of their high affinity for 5HT_{2A} receptors.
- Typical Antipsychotics is the most commonly used term in clinical practice. It is based on the view that SGAs have atypical properties, such as a low risk of EPS. Drugs that do not have atypical properties are considered typical or conventional antipsychotics.
- The problem was that the original concept of atypicality (low EPS risk) changed to a broader definition that included efficacy for negative & cognitive symptoms in schizophrenia.
- This definition was revised after the CATIE trial failed to confirm that SGAs are more effective than FGAs (with the exception of clozapine for treatment-resistant schizophrenia).
- In order to avoid confusion regarding effectiveness in schizophrenia, the WPA suggested the term first-generation antipsychotics



History & Definitions

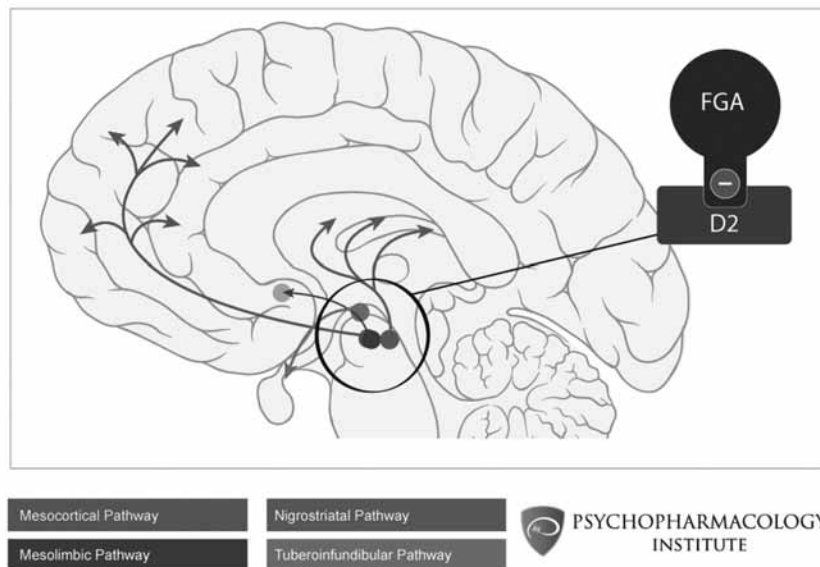
Classic and commonly used terms	Proposed new terms (WPA)
Neuroleptics (conventional antipsychotics, typical antipsychotics)	First generation antipsychotics
Atypical antipsychotics (serotonin-dopamine antagonists)	Second generation antipsychotics
Dopamine partial agonists (Aripiprazole)	Third generation antipsychotics

Mechanism of Action

- The exact mechanism of action of antipsychotic drugs is unknown.
- According to the dopamine theory of schizophrenia, positive symptoms are the result of overactivity in the mesolimbic dopamine pathway. This is in part based on the observation that drugs that increase dopaminergic availability (L-DOPA, cocaine, amphetamines) can trigger psychotomimetic effects in individuals not affected by schizophrenia.
- FGAs are D₂ antagonists & reduce dopaminergic neurotransmission in the four dopamine pathways.
- Mesocortical pathway
 - A dysfunction of this pathway is associated with cognitive impairments & disturbances of emotions & affect (negative symptoms). Blockade of the mesocortical pathway by high doses of first-generation antipsychotics can induce secondary negative symptoms & cognitive effects.

- Mesolimbic pathway
 - Overactivity is thought to be involved in the pathophysiology of positive symptoms of schizophrenia. Blockade of D2 receptors in the mesolimbic pathway has been proposed as a possible mechanism of antipsychotic action of first-generation agents.
- Nigrostriatal pathway
 - Antagonism of D2 receptors is associated with increased risk of extrapyramidal symptoms.
- Tuberoinfundibular pathway
 - Dopamine acts as a prolactin-inhibiting factor, D2 blockade increases prolactin levels by promoting its release in the pituitary gland.

First Generation Antipsychotics Are D₂ Antagonists



Chemical Classification

- Phenothiazines
- Non-phenothiazines - Butyrophenones
 - Thioxanthenes
 - Dihydroindolones
 - Dibenzepines
 - Diphenylbutylpiperidines

Chemical Class	Side Chain	Drug
Phenothiazines	Aliphatic (low/medium-potency agents)	Chlorpromazine
		Levomepromazine
		Promazine
		Triflupromazine
	Piperidine (low/medium potency agents)	Mesoridazine
		Pericyazine
		Pipotiazine
		Thioridazine
	Piperazine (medium/high-potency agents)	Perphenazine
		Fluphenazine
		Trifluoperazine

Chemical Class	Drug
Butyrophenones (high-potency agents)	Benperidol
	Droperidol
	Haloperidol
Thioxanthenes (low/medium-potency agents)	Clopenthixol
	Flupenthixol
	Thiothixene
	Zuclopenthixol
Dihydroindolones (low/medium-potency agents)	Molindone
Dibenzepines (low/medium-potency agents)	Clotiapine
	Loxapine
Diphenylbutylpiperidines (high-potency agents)	Fluspirilene
	Pimozide

Receptor Affinity Profile

	Dosage forms	D2 Activity	5HT2 Activity	Muscarinic Activity	Alpha-1 adrenergic Activity	Antihistamine Activity
Chlorpromazine (Thorazine)	T, I	++++	++++	++++	++++	++++
Fluphenazine (Prolixin)	T, L, LI (LA)	++++	++	+	+	++
Perphenazine (Trilafon)	T	++++	++++	+	++	+++
Trifluoperazine (Stelazine)	T	++++	+++	+	++	++
Thioridazine (Mellaril)	T	++++	++++	++++	++++	++++
Mesoridazine (Sereniti) *withdrawn from US market in 2004	T	++++	++++	+++	++++	++++
Haloperidol (Haldol)	T, L, LI (LA)	++++	++	+	+	+
Molindone (Moban) *discontinued by manufacturer in 2010	T	+++	+	++	+	+
Thiothixene (Navane)	C	++++	+	+	++	+++
Loxapine (Loxitane)	C	+++	++++	++	+++	++++

Level/degree of effect: (+) – low (++) – moderate (+++) – high (++++ – very high
Adapted from Hahn, Albers and Reist. Psychiatry, 2008 Edition

Adverse Effects Profile

Drug	Sedating effects	Anticholinergic effects	Extrapyramidal side effects	Hypotensive effects
Chlorpromazine	High	High	Low	IM-High
				PO-Moderate
Fluphenazine	Low	Low	Very high	Low
Haloperidol	Very low	Very low	Very high	Very low
Loxapine	Moderate	Low	Moderate	Moderate
Molindone	Very low	Low	Moderate	Low
Perphenazine	Low	Low	High	Low
Pimozide	Low	Low	High	Very low
Thioridazine	High	High	Low	High
Thiothixene	Low	Low	High	Low
Trifluoperazine	Low	Low	High	Low

Chlorpromazine Equivalent Dose

Drug	Maudsley Prescribing Guidelines	Manual of Clinical Psychopharmacology
Chlorpromazine	100 mg/day	100 mg/day
Fluphenazine	2 mg/day	2 mg/day
Trifluoperazine	5 mg/day	5 mg/day
Flupentixol	3 mg/day	
Zuclopentixol	25 mg/day	
Haloperidol	3 mg/day	2 mg/day
Sulpiride	200 mg/day	
Pimozide	2 mg/day	
Loxapine	10 mg/day	10 mg/day
Molindone		10 mg/day
Perphenazine		10 mg/day
Prochlorperazine		15 mg/day
Thioridazine		100 mg/day
Thiothixene		4 mg/day

FGAs vs. SGAs

Adverse effects profile

First Generation Antipsychotics

- Higher risk of neurological side effects



Second Generation Antipsychotics

- Higher risk of metabolic side effects



Are SGAs More Effective?

- One question matter of clinical debate is whether SGAs are more effective than FGAs.
- There are two important clinical trials that shed some light in this controversy.
- The first is the CATIE, funded by the NIMH. The other is the CUtLASS, conducted in the UK & funded by the NHS.
- According to the results from these trials:
 - There is no evidence of benefit of SGAs over FGAs, in the treatment of negative symptoms of schizophrenia.
 - Clozapine has shown clear utility in treatment-resistant schizophrenia.

FGAs vs. SGAs

Are SGAs more effective than FGAs?



Cost-effectiveness of first- v. second-generation antipsychotic drugs: results from a randomised controlled trial in schizophrenia responding poorly to previous therapy

L. M. DAVIES, S. LEWIS, P. B. JONES, T. R. E. BARNES, F. GAUGHAN, K. HAYHURST, A. MARKWICK and M. LLOYD on behalf of the CUtLASS team

BJPsych

- No evidence of benefit of SGAs over FGAs in the treatment of negative symptoms of schizophrenia
- Clozapine has shown clear utility in treatment-resistant schizophrenia

Rapid Tranquillisation

- Intramuscular olanzapine, haloperidol & promethazine combined are effective in the rapid tranquillisation of agitated or violent people as a result of mental illness.
- Important differences were, however, found in the effects of the two interventions.
- Olanzapine produced a calming effect within an hour of administration, but this seemed to wear off & additional medical attention & interventions were required, particularly after an hour.
- Haloperidol plus promethazine had a rapid calming effect but also put most patients to sleep rapidly, & this was maintained better over four hours than with olanzapine, reducing the need for additional medical involvement & intervention.
- The addition of promethazine facilitated sedation & prevented significant EPS, particularly dystonia, otherwise seen when haloperidol is used alone for rapid tranquillisation.
- Serious adverse effects were not seen with either intervention.
- Sleep is often not considered a desirable end point of rapid tranquillisation & calming patients without producing sleep is considered the ideal.
- In an analysis of the industry sponsored trials of olanzapine, where 1-3 doses of the drug were used for tranquillisation, olanzapine was considered to produce a calming effect distinct from sedation.
- In contrast to that it was found that olanzapine did not reliably produce this effect, as over 60% of patients given olanzapine were asleep during the hour after intervention.

- In addition, in settings where medical resources are scant or clinics are busy, the longer duration of action of haloperidol plus promethazine exposes people to dangerous behaviour for shorter periods, provides fewer occasions for doctors to be recalled, and results in less need for additional drugs over the first few hours. Thus haloperidol plus promethazine may be favoured over olanzapine.
- The combined drug costs nearly a third less than injectable olanzapine in India.
- If the costs of the additional drugs used & the utilisation of additional resources were totalled, the difference is likely to favour haloperidol plus promethazine.
- In India it is common to place violent people in physical restraints in addition to using drugs.
- The interventions did not result in statistically significant differences in proportion of patients restrained, although fewer people given haloperidol plus promethazine were restrained at all assessment points during the four hours after intervention.
- Patients given haloperidol plus promethazine required less medical attention or additional drugs in the four hours after intervention than those given olanzapine.
- In busy & chaotic emergency situations, this advantage may mean that haloperidol plus promethazine is preferable.

Long-acting Injectables

- LAIs can play an important role in improving adherence & preventing hospitalisations.
- LAIs should be considered in those with risk factors for medication non-adherence, for e.g., a history of non-adherence, severe symptoms, co-morbid substance use, cognitive impairment, ambivalence or negative attitudes towards medications & poor insight.
- By decreasing the number of times a patient has to decide to take a medication, & by promptly alerting clinicians & other providers to the onset of non-adherence when a patient misses a scheduled injection, LAIs are a useful part of the antipsychotic formulary.
- Research to date is clear in showing no efficacy or overall effectiveness advantage of newer LAIs (e.g., risperidone & paliperidone) over older LAI FGAs.
- None of the individual LAI FGAs has emerged as clearly superior in efficacy, although there is some suggestion of an advantage for zuclopenthixol decanoate in terms of time to discontinuation & hospitalisation, but perhaps at the expense of a greater side effect burden.
- Cochrane reviews have been completed for pipotiazine palmitate, flupentixol decanoate, zuclopenthixol decanoate, haloperidol decanoate & fluphenazine decanoate.
- The LAI SGAs, aripiprazole, paliperidone, risperidone & olanzapine, also have comparable efficacy but vary in their liability for particular adverse effects, such as weight gain, metabolic effects, EPS, & raised plasma prolactin.
- For example, LAI paliperidone is associated with substantial increases in serum prolactin, & LAI olanzapine can cause significant weight gain & is associated with a post-injection delirium/sedation syndrome, assumed to be caused by unintended partial intravascular injection or blood vessel injury.

Drug and Year of Approval	Primary Biological Targets	Specific Clinical Warnings ^{†,‡,*}	Incidence of Adverse Effects [§]	Pharmacological Interactions
First Generation Antipsychotics (FGAs)				
<u>Flupentixol decanoate</u> • United States: currently not approved • European countries: 1970	D ₁ , D ₂ , 5-HT _{2A} antagonist	• Teratogenic effects not established in humans. • Caution recommended in dose selection for the elderly. • Renal impairment: not studied (dosage adjustment suggested). • Hepatic impairment: not studied; particular caution and serum level monitoring advised.	Prolactin elevation (+++) Weight gain (++) Akathisia (++) Parkinsonism (++) Anticholinergic (++) Sedation (+) Hypotension (+)	• Need to ↓ dose in CYP2D6 poor metabolizers or during concomitant use of CYP2D6 inhibitors [§] .
<u>Fluphenazine decanoate</u> • United States: 1972 • European countries: 1970	D ₁ , D ₂ antagonist	• Teratogenic effects not established in humans. • Administration in the elderly should be cautiously considered and titrated doses are suggested. • Blood urea nitrogen monitoring recommended, eventually suspending the administration. • Use precluded by liver damage.	Parkinsonism (+++) Prolactin elevation (+++) Akathisia (++) Sedation (+) Weight gain (+) Anticholinergic (+) Hypotension (+)	• Need to ↓ dose in CYP2D6 poor metabolizers or during concomitant use of CYP2D6 inhibitors [§] .
<u>Haloperidol decanoate</u> • United States: 1986 • European countries: 1982	D ₂ , 5-HT _{2C} antagonist	• Cases of limb malformations after maternal use during pregnancy. • Dose adjustment suggested in the elderly, with a recommended dose ranging between 25 and 75 mg (starting dose 12.5–25 mg/month). • Renal and hepatic impairment: caution advised.	Akathisia (+++) Parkinsonism (+++) Prolactin elevation (++) Sedation (+) Weight gain (+) Anticholinergic (+) Hypotension (+)	• Need to ↑ dose during concomitant use of CYP3A4 inducers [§] . • Need to ↓ dose during concomitant use of CYP3A4 inhibitors [§] , CYP2D6 inhibitors [§] and combined CYP3A4 and CYP2D6 inhibitors [§] .
<u>Zuclopentixol decanoate</u> • United States: currently not approved • European countries: 1978	D ₁ , D ₂ , D ₃ antagonist	• Teratogenic effects not established in humans. • Caution recommended in dose selection for the elderly. • Usual doses in patients with reduced renal function (half the normal dosage in case of renal fatigue). • Hepatic impairment: half the recommended dosages; monitoring of liver function advised.	Prolactin elevation (+++) Sedation (++) Weight gain (++) Akathisia (++) Parkinsonism (++) Anticholinergic (++) Hypotension (+)	• Need to ↓ dose during concomitant use of CYP2D6 inhibitors [§] .

Penfluridol - Alternative to LAIs

- Penfluridol is a diphenylbutylpiperidine FGA which is similar in efficacy & tolerability to other FGAs.
- It is unusual in having a very long plasma half-life - at least 60 hours.
- After oral administration, peak levels are reached within 12 hours & drug can still be detected 168 hours after a single oral dose.
- Its long duration of action seems to be a result of rapid distribution into fat tissue, which acts as a drug reservoir, allowing penfluridol to be used as a once-weekly oral therapy for supervised ingestion - an alternative to LAIs.
- Several trials have examined the use of once-weekly oral penfluridol, usually in doses ranging from 5 mg to 160 mg per week.
- When given in this manner, it is at least as effective as depot FGAs & is better tolerated, overall.

In TRS

- D2 receptor occupancy is shown to increase from 55% with clozapine alone to 79% on addition of 4 mg of haloperidol to the clozapine.
- By this it can be argued that the benefits of clozapine are obtained without an optimal D2 blockade, & an addition of haloperidol can increase the D2 blockade, resulting in a possible situation of getting full benefit of D2 blockade along with the 'atypical' effect of clozapine or 'optimum' of atypical & conventional effects.

- In support of serotonergic mechanisms in antipsychotic efficacy, a combination of 5HT_{2A} antagonism along with D₂ blockade is the possible mechanism for the ideal pattern of effects on dopamine.
- It is reported that a combination of a specific 5HT_{2A} receptor antagonist & low dose of haloperidol can increase dopamine release in the prefrontal cortex while diminishing the ability of haloperidol alone to increase DA release in the limbic system.

Patient age and sex	Diagnosis	Primary medication before augmentation	BPRS before augmentation	Augmentation agent	BPRS after 8 weeks of augmentation
63 M	Paranoid schizophrenia	Clozapine 100 mg AM and 400 mg h.s.	49	Haloperidol 50 mg q, 4 weeks	31
43 M	Undifferentiated schizophrenia	Clozapine 300 mg AM and 400 mg h.s.	36	Prolixin Dec 50 mg q, 4 weeks	26
53 M	Disorganized schizophrenia	Clozapine 300 AM and 500 h.s.	60	Haloperidol 2 mg p.o. h.s.	29

BRIEF REPORTS

Aripiprazole Versus Haloperidol in Combination With Clozapine for Treatment-Resistant Schizophrenia

A 12-Month, Randomized, Naturalistic Trial

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- While the effectiveness of clozapine augmentation with a second antipsychotic agent is not clearly demonstrated yet, results from this study suggest that augmentation with aripiprazole offers no substantial benefit over haloperidol in efficacy.
- Aripiprazole was perceived more tolerable than haloperidol.

In Metabolic Syndrome

TABLE 2. Glucose Levels and Other Characteristics of 14 Patients With Schizophrenia or Schizoaffective Disorder Who Developed Abnormally High Glucose Levels (>125 mg/dl) Over 14 Weeks of Treatment With Four Antipsychotic Medications^a

Patient	Treatment	Ethnicity	Gender	Baseline Body Mass Index (kg/m ²)	Baseline Weight (kg)	Age (years)	Glucose Level (mg/dl)		
							Baseline	8 Weeks	14 Weeks
1	Clozapine	African American	Male	30.1	82.0	54	102	193	95
2	Clozapine	White	Male	18.1	55.3	65	84	145	—
3	Clozapine	African American	Male	30.3	95.4	44	80	177	—
4	Clozapine	African American	Male	18.2	51.8	40	93	144	87
5	Clozapine	African American	Male	22.6	57.4	51	110	149	158
6	Clozapine	African American	Male	23.7	76.8	52	108	120	131
7	Haloperidol	White	Male	34.2	81.6	43	100	107	132
8	Olanzapine	African American	Male	33.0	98.2	48	107	135	202
9	Olanzapine	African American	Male	30.6	102.0	59	112	128	150
10	Olanzapine	African American	Female	30.6	73.5	43	123	97	147
11	Olanzapine	African American	Male	27.4	83.8	41	95	126	113
12	Risperidone	White	Male	26.6	81.5	43	108	155	—
13	Risperidone	African American	Male	32.5	88.5	55	108	97	135
14	Risperidone	African American	Male	44.7	105.7	34	113	101	132

TABLE 3. Glucose Levels and Other Characteristics of Seven Patients With Schizophrenia or Schizoaffective Disorder Who Had Abnormally High Glucose Levels (>125 mg/dl) Before Treatment With Three Antipsychotic Medications^a

Patient	Treatment	Ethnicity	Gender	Baseline Body Mass Index (kg/m ²)	Baseline Weight (kg)	Age (years)	Glucose Level (mg/dl)		
							Baseline	8 Weeks	14 Weeks
1	Haloperidol	African American	Male	26.2	79.2	46	190	127	120
2	Olanzapine	White	Male	29.5	82.8	54	436	360	—
3	Olanzapine	Hispanic	Male	30.3	80.0	47	297	49	253
4	Olanzapine	African American	Male	26.5	72.2	56	127	214	—
5	Risperidone	African American	Male	33.3	82.7	56	255	147	169
6	Risperidone	African American	Male	22.8	62.2	48	303	217	254
7	Risperidone	African American	Male	24.5	73.9	54	135	242	—

^a None of the patients randomly assigned to risperidone treatment had abnormally high baseline glucose levels.

- 14% of patients (6 given clozapine, 4 given olanzapine, 3 given risperidone & 1 given haloperidol) developed abnormally high glucose levels (>125 mg/dl) during the course of their study treatment.
- Clozapine showed a trend toward a higher number of patients shifting glucose levels from normal baseline levels to clinically abnormal levels after 14 weeks of treatment.
- Olanzapine-treated & clozapine-treated groups had significant elevations in post-load glucose levels at all time.

- Weight gain at endpoint was significantly related to cholesterol elevations in the clozapine group & marginally in the olanzapine group.
- Significant weight gains, which were highest for olanzapine, followed by clozapine & risperidone.

TABLE 4. Change in Cholesterol Levels of 101 Patients With Schizophrenia or Schizoaffective Disorder Over 14 Weeks of Treatment With Four Antipsychotic Medications

Treatment	Baseline			8 Weeks						14 Weeks							
	N	Cholesterol Level (mg/dl)		N	Cholesterol Level (mg/dl)		Change From Baseline (mg/dl)		Analysis		N	Cholesterol Level (mg/dl)		Change From Baseline (mg/dl)		Analysis	
		Mean	SD		Mean	SD	Mean	SD	t	p		Mean	SD	Mean	SD	t	p
Clozapine	28	174.2	31.7	27	189.0	31.7	14.7	30.5	2.50	<0.02	17	196.5	35.1	16.3	39.6	1.70	n.s.
Haloperidol	25	176.5	32.2	25	171.7	27.7	-4.9	17.7	1.37	n.s.	20	171.7	36.2	-4.4	25.2	0.77	n.s.
Olanzapine	26	179.8	37.4	26	192.1	33.9	12.3	28.1	2.22	<0.04	22	197.6	36.2	20.1	26.8	3.52	<0.002
Risperidone	22	184.2	30.4	22	188.4	48.2	4.2	29.7	0.66	n.s.	14	188.8	49.2	9.2	36.7	0.94	n.s.

- Statistically significant increases in mean cholesterol levels after treatment with olanzapine & clozapine, which remained overall within normal clinical range.
- There was no elevation in cholesterol levels with risperidone & haloperidol.

In Pregnant Women

- There were significantly more LGA (large for gestational age) infants among those exposed in-utero to SGAs than among those exposed to either FGAs or reference agents.
- The mean birth weight was also found to be significantly greater in the SGAs exposure group than the FGAs exposure group.
- Although tolerability, teratogenicity & neonatal withdrawal effects are better with SGAs.

Preferred Over SGAs In ...

- Acute mania.
- Delusional disorders.
- Severe agitation & aggression.
- Tourette disorder - haloperidol & pimozide most commonly used.
- Agitation & aggression in dementia & delirium - low dose of high potency FGAs like haloperidol is recommended.

Conclusion

- Following the publication of CATIE & CUTLASS studies, the WPA reviewed the evidence relating to the relative efficacy of 51 FGAs & 11 SGAs & concluded that, if differences in EPS could be minimised (by careful dosing) & anticholinergic use avoided, there was no convincing evidence to support any advantage for SGAs over FGAs.
- Fear of serious side-effects such as NMS, EPS should not limit psychiatrists from prescribing cost-effective typical antipsychotics.
- Typical antipsychotics are a boon during emergency situations, & if intolerance to atypical antipsychotics is evident.
- Regular monitoring & careful titrations are key to the successful management of psychosis by typical antipsychotics.

Conventional Mood Stabilizers vs Atypical Antipsychotics in Maintenance Treatment: When to Choose which Agent?

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General Principles of Treatment in Maintenance Phase

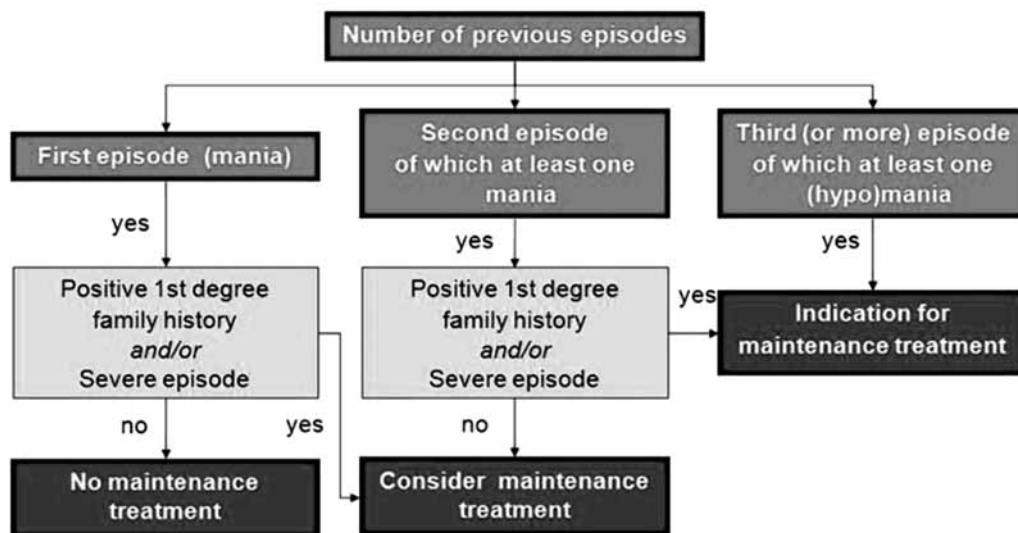
Primary goal of maintenance treatment is to

- Prevent the recurrence of episode of either polarity
- Reduce/eliminate the residual symptoms
- Improve the overall functioning of the patient
- Preferred strategy is for continuous rather than intermittent treatment
- Medications effective in the acute phase should be continued during the maintenance phase, even if it's not the first line.
- While selecting the agent during the acute episode - consider patient's preference, cost, clinical factors (which may influence the long term outcome), recurrence of episodes and side effects.
- It is generally recommended to continue treatment with the drug that was effective in the previous mood period

Options for Maintenance therapy

- Conventional mood stabilizers - lithium, valproate, lamotrigine, CBZ
- Atypical Antipsychotics - aripiprazole, quetiapine, olanzapine, risperidone, ziprasidone, lurasidone, asenapine etc.
- Current drugs approved for maintenance therapy in bipolar disorder by the FDA - lithium, lamotrigine, aripiprazole, olanzapine, quetiapine (immediate-release) and ziprasidone.
- Approval has also been given to risperidone long acting injection as monotherapy or adjunct, as well as aripiprazole long acting injection for monotherapy in Bipolar I disorder
- > Conventional mood stabilisers were used to be the mainstay of treatment
- > However, in recent times, atypical antipsychotics are gaining evidence and approval for use in maintenance of Bipolar disorders.
- > Recent guidelines recommend the use of atypical antipsychotics as first line treatment in maintenance phase.

Algorithm for Indication for Maintenance Treatment



Guidelines of Long-Term Bipolar Treatment

Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018: Guidelines for the Management of Patients with Bipolar Disorder

1. Review general principles and assess medication status
2. Initiate or optimize first line treatment and check adherence
3. Add on or switch therapy (alternate first-line agents)
4. Add on or switch therapy (second-line agents)
5. Add on or switch therapy (third-line agents)

Treatments recommended for maintenance in Bipolar Disorder

- Lithium is the gold standard for maintenance treatment, effective in both manic and depressive episodes and have anti-suicidal effects.
- Lamotrigine is effective in predominantly depressive polarity and comorbid anxiety.
- Quetiapine is effective in both mania and depression, prophylactic efficacy is greater for mania than depression
- Asenapine-effective in both mania and depression, prophylactic efficacy is greater for mania than depression
- The evidence suggests that monotherapy with a single mood stabilizer is often ineffective, and patients may require a combination of drugs to achieve stability.

	Level of evidence by phase of treatment					Considerations for treatment selection			
	Maintenance			Acute		Acute	Maintenance		
	Prevention of any mood episode	Prevention of depression	Prevention of mania	Depression	Mania	Safety concerns	Tolerability concerns	Safety concerns	Tolerability concerns
First-line treatments									
Lithium	●	●	●	●	●	+	+	++	++
Quetiapine	●	●	●	●	●	+	++	++	++
Divalproex	●	●	●	●	●	-	+	++	+
Lamotrigine	●	●	●	●	■	++	-	-	-
Asenapine	●	●	●	n.d.	●	-	+	-	+
Quetiapine + Li/DVP	●	●	●	●	●	+	++	+++	++
Aripiprazole + Li/DVP	●	n.d.	●	●	●	+	+	++	++
Aripiprazole	●	n.d.	●	●	●	-	+	-	+
Aripiprazole OM	●	n.d.	●	n.d.	n.d.	-	+	-	+
Second-line treatments									
Olanzapine	●	●	●	●	●	+	++	+++	++
Risperidone LAI	●	n.d.	●	n.d.	n.d.	-	+	+	++
Risperidone LAI (adj)	●	●	●	n.d.	n.d.	+	++	+++	++
Carbamazepine	●	●	●	●	●	++	++	+	++
Paliperidone (>6 mg)	●	n.d.	●	n.d.	●	-	+	+	++
Lurasidone + Li/DVP	●	●	●	●	n.d.	+	++	++	++/-
Ziprasidone + Li/DVP	●	n.d.	●	●	●	++	++	++	+

DVP, divalproex; LAI, long-acting injectable; Li, lithium; OM, once monthly.

●, level 1 evidence; ●, level 2 evidence; ●, level 3 evidence; ●, level 4 evidence; ■, level 1 negative evidence; ■, level 2 negative evidence; ■, level 3 negative evidence; ■, level 4 negative evidence; n.d., no data; - limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection.

Treatment recommendations for maintenance of Bipolar II disorder

- Monotherapy with quetiapine, lithium and lamotrigine are first-line options.
- Monotherapy with venlafaxine is second-line options.
- Divalproex, carbamazepine, escitalopram, other antidepressants, and risperidone (mainly for prevention of hypomania) may be considered as third-line options.

Recommendation	Agent	Evidence level
First-line	Quetiapine	Level 1
	Lithium	Level 2
	Lamotrigine	Level 2
Second-line	Venlafaxine	Level 2
Third-line	Carbamazepine	Level 3
	Divalproex	Level 3
	Escitalopram	Level 3
	Fluoxetine	Level 3
	Other antidepressants	Level 3
	Risperidone ^a	Level 4

^aPrimarily for prevention of hypomania.

British Association for Psychopharmacology Evidence-based Guidelines for treating Bipolar Disorder (Revised third edition)

- Prevention of new episodes – long-term treatment following a single severe manic episode
- Evidence: lithium, olanzapine, aripiprazole, quetiapine, risperidone LAI (long-acting injection) and valproate prevent manic relapse.
- Lamotrigine, lithium, quetiapine and lurasidone were shown to prevent depressive relapse.
- If the patient fails to respond to monotherapy, consider long-term combination treatment.
- When the burden of disease is mania, combine two predominantly antimanic agents (e.g., lithium, valproate with atypical antipsychotics).
- When the burden is depressive, a combination of lithium, lamotrigine, quetiapine, lurasidone or olanzapine may be more appropriate.

Nice Guidelines

- Consider lithium as a first-line, long-term pharmacological treatment for bipolar disorder
- If lithium is ineffective - consider adding valproate
- If lithium is poorly tolerated, or is not suitable -
 - consider valproate or olanzapine
 - Quetiapine - if it has been effective during an episode of mania or bipolar depression

Indian Psychiatric Society Clinical Practice Guidelines for Bipolar Disorder

- Best evidence for maintenance treatment is available for lithium and valproate.
- In recent years evidence has also emerged for use of atypical antipsychotics (olanzapine, quetiapine, risperidone, aripiprazole) in prevention of recurrence of both depressive and manic episodes.
- However, may be avoided, if possible, because of associated higher risk of EPS & metabolic side effects.
- Long acting risperidone is beneficial in prevention of recurrence.
- Lamotrigine – efficacious in prevention of depressive episodes, but not for manic episodes.
- Olanzapine, aripiprazole, ziprasidone and asenapine – effective in prevention of recurrence of manic episodes, but not for depressive episodes.

Guideline for treatment of bipolar disorder by the Japanese Society of Mood Disorders, 2012

- Most recommended treatment - Lithium
- Next recommended treatment.
 - Lamotrigine
 - Olanzapine
 - Quetiapine
 - Combination of lithium or valproic acid and Quetiapine
 - Combination of Lithium and Lamotrigine
 - Aripiprazole
 - Combination of Lithium and aripiprazole
 - Combination of lithium and valproic acid
 - Valproic acid
- Other recommended treatment
 - CBZ
 - Risperidone depot
 - Combination among mood, stabilisers or combination of mood, stabilisers and a typical antipsychotic drugs.
 - Thyroid hormone.
- Treatments that are not recommended - Use of antidepressants, Treatment with antidepressant monotherapy.

The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017)

1st step - take predominant polarity into consideration, start with lithium, aripiprazole, olanzapine, paliperidone, quetiapine or Risperidone long acting monotherapy

2nd step - add lithium/ fluoxetine to first step option, lithium + CBZ, quetiapine+Lithium/Valproate, Olanzapine/Aripiprazole+mood stabiliser.

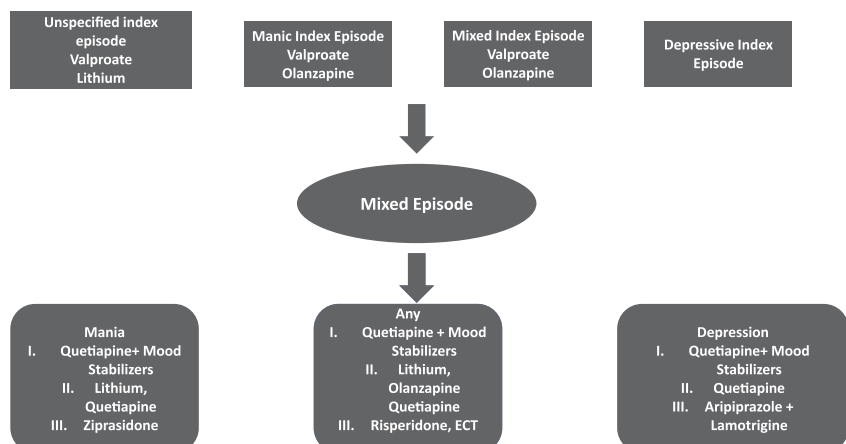
3rd step - Add RLAI, valproate, CBZ, lamotrigine on 2nd step

4th step - take predominant polarity into consideration and add an agent with proven efficacy against the acute phase, no matter whether it has proven maintenance efficacy

5th step - consider any combination that have not been tried, consider maintenance ECT.

Not recommended - adding memantine on mood stabiliser, aripiprazole +lamotrigine/valproate, lamotrigine+valproate, lithium+lamotrigine/oxCBZ.

Guidelines for Prevention of Mixed Episodes



Comparison of Guidelines

	CINP 2017	WFSBP 2013 ^a	CANMAT and ISBD 2013	NICE 2014 ^b	BAP 2016 ^b
Aripiprazole	1	1	1	-	3
Lithium	1	1	1	1	1
Olanzapine	1	2	1	1	2
Paliperidone	1	3	2	-	3
Quetiapine	1	1	1	1	2
Risperidone	1	2	-	-	3
RLAI	1	-	1	-	2
OFC	2	-	2	-	-
Carbamazepine	2	4	2	-	2
Valproate	2	3	1	1	2
Lamotrigine	3	1	1	-	2
Haloperidol	4	-	-	-	3
Venlafaxine	4	-	-	-	-
ECT	5	4	3	-	-
Ziprasidone	5	3	-	-	3
Continue most recent episode treatment	NR	-	-	1	-
Antidepressants	-	3	NR	-	4
Asenapine	-	4	3	-	3
Gabapentin	-	4	NR	NR	-
Topiramate	-	4	NR	-	-

Abbreviations: ECT, electroconvulsive therapy; NR, not recommended; OFC, olanzapine-fluoxetine combination; RLAI, risperidone long-acting injectable.

The grading is not uniform; instead it reflects the grading utilized by individual guidelines and the table aims only to give an image of how different guidelines prioritize treatment options.

^a WFSBP: Recommendation grades and subsequent positioning could be either based on efficacy in the prevention of mania, depression or any episode. Thus, numbers do not reflect the sequence of treatment in an individual patient.

^b NICE and BAP ordering is on the basis of line of treatment.

Recommended Dosage in Maintenance

Agent	Recommended Dosage	Polarity
Quetiapine	300 – 800 mg/d	Mania/Mixed, Depression
Olanzapine	5 – 20 mg/d	Mania/Mixed, Depression
Lithium	0.6 – 1.2 mEq/L	Mania/Mixed, Depression
Lamotrigine	50 – 400 mg/d	Depression
Aripiprazole	10 – 30 mg/d	Mania/Mixed features
RLAI	25 – 50 mg/biweekly	Mania
Paliperidone	3 – 12 mg/d	Mania
Valproate	45 – 100 mg/L	Mania/ Mixed features
Carbamazepine	4 – 12 mg/L	Mania
Ziprasidone	80 – 160 mg/d	Mania/Mixed features
Fluoxetine	10 – 40 mg/d	Depression
Lurasidone	20 – 80 mg/d	Mania/Mixed, Depression

	Recommended drugs
Bipolar Disorder with predominant Manic episodes	Lithium Quetiapine Aripiprazole Risperidone, RLAI Lurasidone Olanzapine Paliperidone
Bipolar Disorders with Predominant Depressive Episodes	Quetiapine Lithium Lamotrigine Olanzapine
Bipolar Disorders with Mixed Episodes	Quetiapine Lithium Aripiprazole Risperidone Olanzapine, RLAI

Conventional Mood Stabilizer vs Atypical Antipsychotics

Mood Stabilizer	Atypical Antipsychotics
- Valproate is not considered as first line treatment option in most guidelines due to side effects, especially in women in reproductive age group. - Lithium has high discontinuation rate due to side effects like tremors, weight gain, renal issues and regular level estimation. - Lamotrigine - uses are limited to depressive polarity, not much useful in mixed/manic features.	- Atypical antipsychotics are better tolerated - Have shown efficacy in manic, depressive and mixed phases. - Aripiprazole, cariprazine, lurasidone are less associated with metabolic side effects makes them agent of choice in long term management. - Residual cognitive, anxiety symptoms can be better controlled with improved quality of life.

Efficacy, Safety and Treatment Failure

- Population based study on 5L + bipolar patient with long term treatment for 1 year
- Monotherapy for bipolar disorder was more frequently initiated with atypical antipsychotics than with mood stabilisers.
- The rate of treatment failure was very high in all age groups and for all therapeutic strategies.
- Based on the outcomes considered, atypical antipsychotics perform at par with mood stabilizers in the whole study population.
- They were slightly more effective than mood stabilizers in younger patients

Conclusion

- Lithium is still considered the Gold Standard drug in maintenance.
- However, atypical antipsychotic monotherapy is increasingly used in maintenance.
- Most of the current guidelines emphasise on atypical antipsychotic monotherapy for maintenance of Bipolar disorder.
- Combination therapy is to be considered only for those who have not responded to the optimal dose of monotherapy.
- Combination of mood stabilizer and atypical antipsychotics are preferred combination for long term stability.
- Patients on long term antipsychotic treatment must be monitored for side effects like metabolic syndrome and EPS.

Preferred pharmacological management options for treating depression in pregnancy

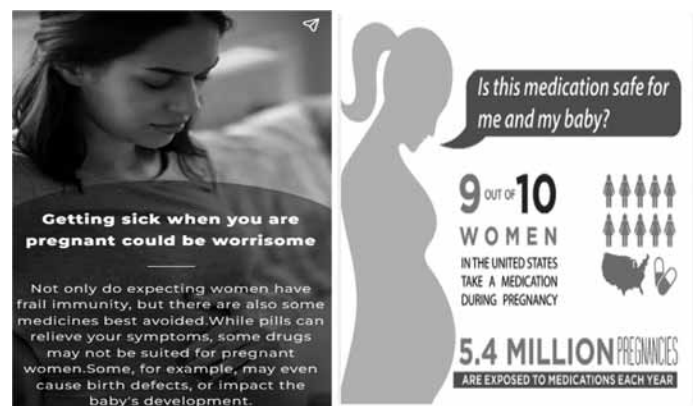
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Treating for two: Medicine and Pregnancy

- Almost every pregnant person will face a decision about taking medicines before and during pregnancy.
- Many people need to take medicine to stay healthy during pregnancy. However, not all medicines are safe to take during pregnancy.
- Some medicines may cause birth defects, pregnancy loss, prematurity, infant death, or developmental disabilities.
- **Treating for Two** is an initiative that aims to improve the health of people and their babies by identifying the safest treatment options for common conditions before, during, and after pregnancy.



- Pregnancy and the puerperium are at times sufficiently stressful to provoke mental illness.
- Psychiatric illness during pregnancy is an independent risk factor for congenital malformation and perinatal mortality.
- Affective illness increases the risk of pre-term delivery
- Prevalence of antenatal depression 11 % (Cochrane data base by Dennis and associates)
- During pregnancy, changes in plasma volume and increases in hepatic metabolism and renal clearance may significantly affect drug levels.

Maternal depression and adverse reproductive outcomes

1. Miscarriage
2. Growth effects: low birth weight (LBW) (born <2500 g) or small for gestational age (SGA) (typically birth weight <10% of age-adjusted weight) infants
3. Preterm delivery
4. Neonatal effects: irritability, less activity and attentiveness, and fewer facial expressions
5. Long-term effects on offspring

Potential risks factors of drugs

1. Miscarriage
2. Teratogenesis (major malformations (1st trimester exposure))
3. Neonatal toxicities (third-trimester exposure)
4. Long term neurobehavioral effect and increase risk of physical health problems in adult life.

The impact of antidepressants on birth outcomes

More than 80% of women take at least one dose of a medication, exclusive of vitamins, during pregnancy

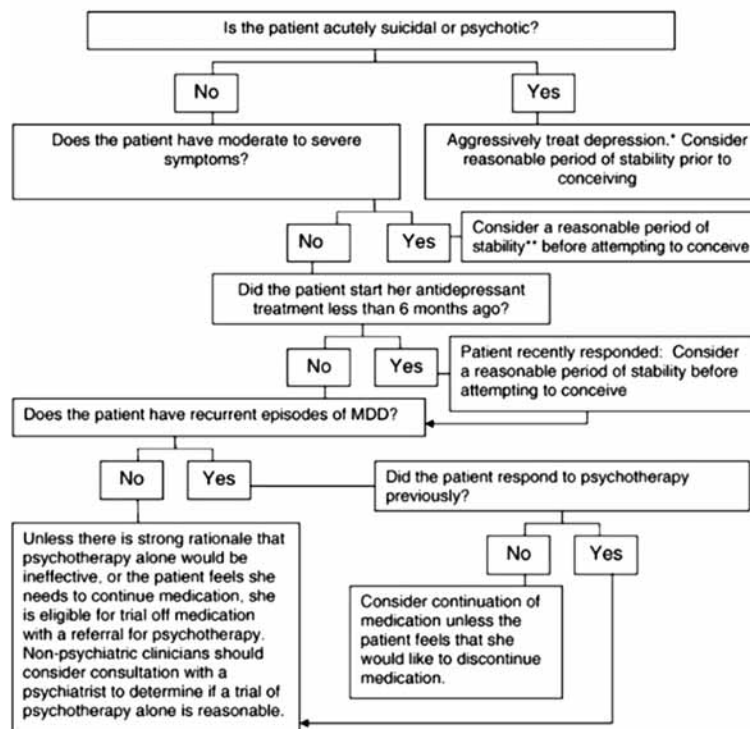
1. Miscarriage
2. Growth effects
3. Gestational age effects
4. Structural malformations
5. Neonatal neurobehavioral outcomes

FDA CATEGORIZATION OF DRUGS FOR USE IN PREGNANCY[18]

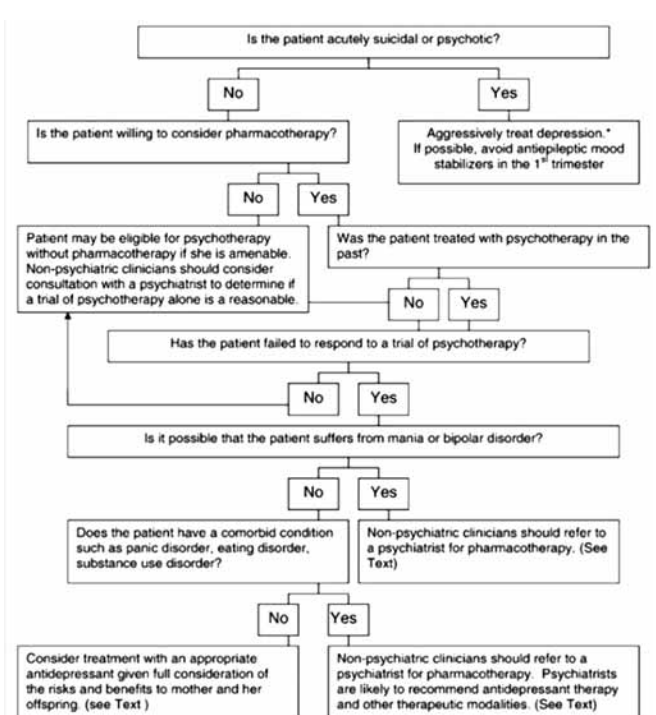
Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women. Or Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. Or No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have

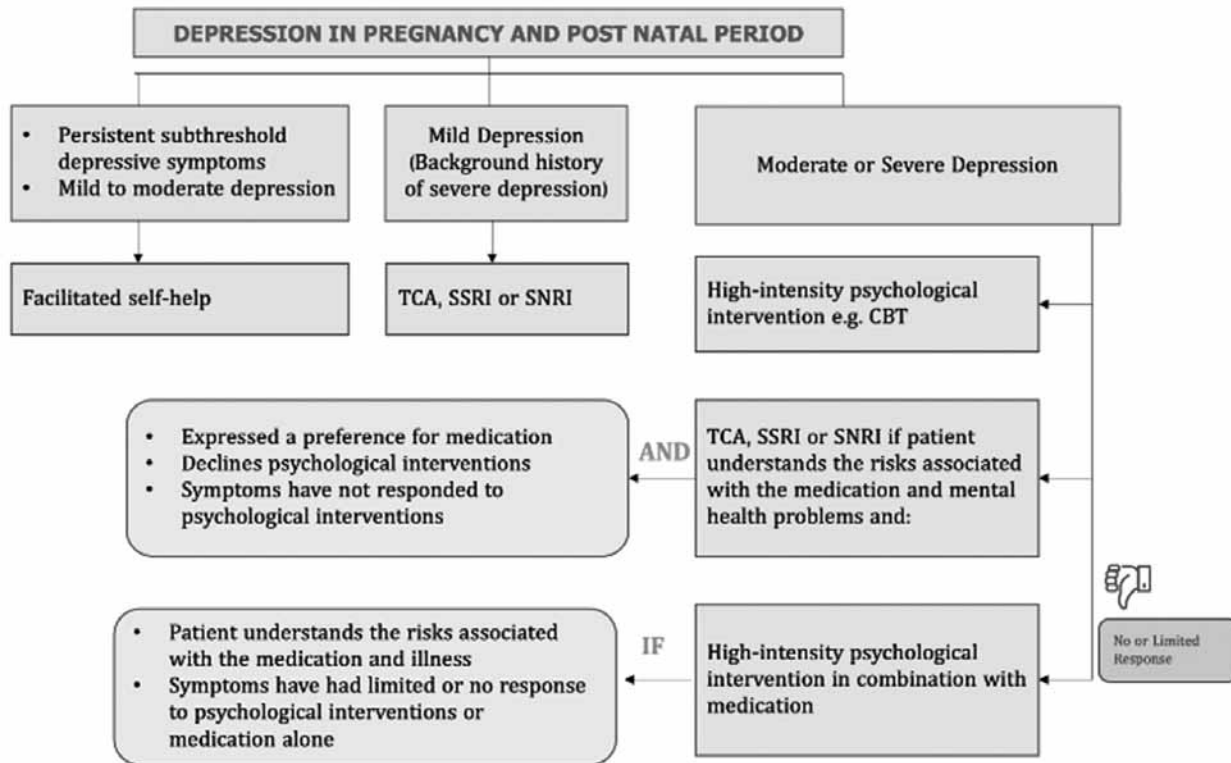
- Fluoxetine and citalopram : reproductive safety 1st line choices
- Among SSRI Paroxetine use is controversial (chance of ASD&VSD)
- TCA and bupropion : use in pregnancy
- Among TCA desipramine and nortriptyline preferred
- SNRI (venlafaxine), SSNRI (duloxetine) during pregnancy data is limited.
- Complementary and alternative medicine(CAM) for treatment of depressive disorders in women omega-3-fatty acids, john's wort (Hypericum perforatum), S-Adenosyl-methionine.

Patient is contemplating pregnancy and is undergoing pharmacological treatment for depression.

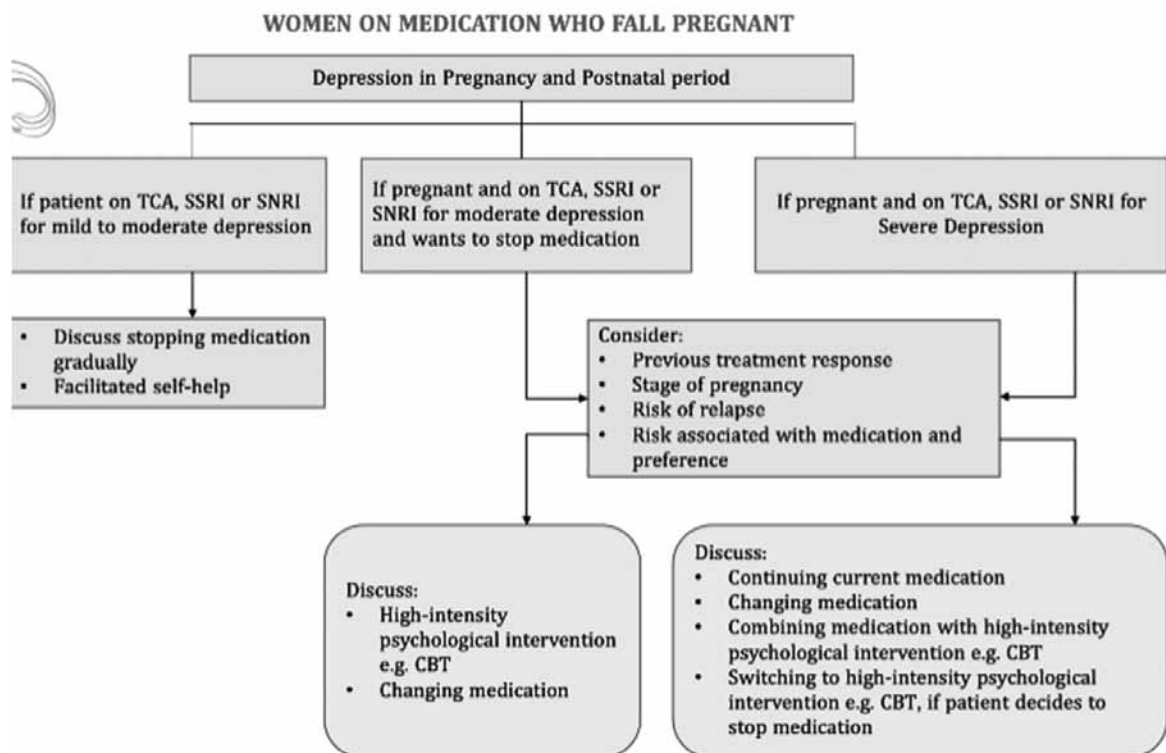


Patient is in episode of MDD, is pregnant and is not taking antidepressants.





National Collaborating Centre for Mental Health (UK). "Antenatal and postnatal mental health: Clinical management and service guidance: Updated edition." British Psychological Society, 2014.



National Collaborating Centre for Mental Health (UK). "Antenatal and postnatal mental health: Clinical management and service guidance: Updated edition." British Psychological Society, 2014.

TCA

- TCAs pass through the placental barrier.
- If TCAs are to be used, then nortriptyline and desipramine are recommended as they are less anticholinergic and hypotensive than amitriptyline and imipramine.
- Clomipramine is not recommended in pregnancy due to a possible link with cardiovascular defects.
- TCAs can increase the risk of preterm delivery and use in 3rd trimester can result in neonatal withdrawal.

SSRIs

- Sertraline is the SSRI that has the lowest known risk in pregnancy.
- Sertraline has the least passage through the placental barrier.
- SSRI's taken after 20 weeks gestation may be associated with an increased risk of persistent pulmonary hypertension in the newborn (PPHN) – paroxetine is most associated. [Bernard et al., 2017]
- There is also a significantly increased risk of the infants developing a **poor neonatal adaptation syndrome (PNAS)** in the first week postpartum with up to 30% of infants having symptoms.

Recent Research: [Anderson et al., 2020]

- A recent study of 30,630 mothers of infants with birth defects showed that elevated adjusted odds ratios (aORs) were observed for individual selective serotonin reuptake inhibitors (SSRIs) and selected congenital heart defects (CHD)
- Fluoxetine and anomalous pulmonary venous return: aOR, 2.56 (1.10-5.93). After partially accounting for underlying conditions, this association was attenuated: aOR, 1.89 (0.56-6.42). This pattern was observed for many SSRI-CHD combinations. [Read more on the interpretation of Odds ratios]
- Associations between SSRIs and non-CHD birth defects often persisted or strengthened after partially accounting for underlying conditions (e.g., citalopram and diaphragmatic hernia: aOR, 5.11 (1.29-20.24)).
- Venlafaxine had elevated associations with multiple defects that persisted after partially accounting for underlying conditions (e.g., anencephaly and craniorachischisis: aOR, 9.14 (1.91-43.83).)

WITHDRAWING ANTIDEPRESSANTS IN PREGNANCY

- Tapering down the dose of an SSRI or SNRI in the late third trimester has been proposed as a strategy to reduce the severity of the PNAS.
- All antidepressants carry the risk of withdrawal or toxicity in neonates; in most cases the effects are self-limiting.
- Significant amounts of SSRI's, TCAs and Venlafaxine cross the placental barrier and late pregnancy exposure can be associated with neonatal withdrawal syndromes and subtle neuro-behavioural outcomes although these do not persist into early childhood
- SSRI withdrawal occurs in 1 out of 4 cases
- All exposed babies to be monitored for withdrawal 3 days after birth
- Involve obstetricians, neonatologists and other perinatal disciplines

Anti-depressant and Breast feeding

- Risk-Benefit Analysis
- Imipramine, Nortriptyline and Sertraline are present in breast milk at low levels.
- Citalopram and Fluoxetine are present at high levels.
- SSRI's and Venlafaxine pass into breast milk in small amounts, and a risk-benefit analysis should be performed
- Information about individual antidepressants and their passage through breast milk can be found on websites such as LactMed.
- Consideration needs to be paid to the medication's side-effects and the impact upon the nursing mother, such as sedation that might interfere with night time feeds and breastfeeding.

- Lowest effective dose
- Lowest risk to mother & fetus
- Least drugs
- Pharmacokinetics and dynamic adjustment as per physiological alteration
- Inform the obstetric team of psychotropic use and possible complications
- Document all decisions

Risks of not treating depression in pregnancy

- Harm to the mother through poor self care, lack of obstetric care or self-harm
- Harm to the fetus or neonate (ranging from neglect to infanticide)

Treatment with antidepressants

- Use of antidepressants during pregnancy is common
- Relapse rates are high in those with a history of depression who discontinue medication.
- Antidepressants increase the risk of pre-term delivery, respiratory distress in neonates
- Hypertensions, pre-eclampsia, and post partum hemorrhage in mothers

Recommendations for the treatment of depression in pregnancy

- Patients who are already receiving antidepressants and are at high risk of relapse are best maintained on antidepressants during and after pregnancy
- Those who develop a moderate or severe depressive illness during pregnancy should be treated with antidepressant
- Most experience with amitriptyline, imipramine, sertraline and fluoxetine
- Paroxetine may be less safe than other SSRIs
- Women who take SSRIs may be at increase of PPH
- When taken in late pregnancy, SSRI may increase of Persistent pulmonary hypertension of the newborn.
- The neonates may experience discontinuation symptoms (with SSRI particularly high with short half-life drugs such as paroxetine and venlafaxine)

Ragging: Its Psycho-social effects & overview of the approach for Mental Health Professionals

Dr. Sayantan Chattopadhyay, Dr. Pinaki Sarkar

Chattopadhyay S, Sarkar P. Ragging, its Psycho-social effects & effects & overview of the approach for Mental Health Professionals. Beng J Priv Psychiatry 2023; 10 (1): 62-69

INTRODUCTION:

Ragging is any disorderly conduct that has the effect of teasing or handling with rudeness any student, which causes or is likely to cause annoyance, harm or to raise fear in a junior so as to adversely affect the psyche of the junior. Ragging is practiced all over the world, with different nomenclature like hazing in the USA and Canada, bizutage in France and Belgium, doop in Holland, nollning in Sweden, novatada in Spain, praxe in Portugal, rabnong in Thailand, ospek in Indonesia, ragging in Pakistan and Sri Lanka, ijime in Japan, trote in Brazil, mechoneo in Chile, albisotaj in Morocco, Mopokaste in Finnish and similar practices in the Congo, South Africa, Colombia, Argentina, and Lithuania among others. The first recorded cases of ragging were in the 8th century BC during the Olympics in Greece.[1] Ragging has been frequently associated with a broad spectrum of physical, behavioural, emotional, and social problems among the victims. It independently increases suicide risks. Some of the reasons given by students for ragging are that they were also ragged by their seniors; a sense of superiority; and introduction. Mohan Rao et. al has done a study covering 10,632 students from 37 educational institutions spread across 12 states in India. Findings show that almost 40 percent of students admitted to having experienced some kind of ragging. College-wise analysis of the results showed marked variations in the prevalence of ragging among colleges, thus pointing to the role of institutional factors in the occurrence of ragging.[2]

Variations in responses are also seen based on the kind of course pursued, gender, and place of residence of students, thus indicating that these are critical factors in influencing the prevalence, severity, and kinds of ragging practices. Other factors perpetuating ragging are the use of alcohol in hostels and the lack of implementation of serious anti-ragging measures by college authorities.[1] Ragging is a serious violation of human rights. Ragging not only is a socio-legal problem but also has a certain psychological basis. Possible reasons that initiate ragging include giving a sense of authority to seniors, being a means of retaliation (previous history of being ragged and a way of getting back by venting his frustrations on the freshmen), satisfaction of sadistic pleasures, peer pressure and that ragging makes a "fashion statement". Many senior students live under the misconception that ragging makes a style statement and will put them in the 'influential crowd' of their college (Chopra, 2009). Agarwal (2005) notes that in India, a myth that ragging makes students bold has always existed. This has given a passive social acceptance to this practice. As long as this exists, ragging will never see its demise. Ragging is the biggest fear of any student entering college, especially those moving away from home to live in hostels. Agarwal et al. (2007) suggest that ragging is a criminal problem which has psychological roots and is a social ignorance & classifies them as Dress Code Ragging, Formal Introduction, Verbal Torture, Sexual Abuse, Playing the Fool, Hostel Ragging, and Drug Abuse. It is somewhat like giving a dowry. The magnitude of the problem is so enormous that a top-down law enforcement approach may not be adequate to solve it.[3]

Various practical steps to control ragging must include strict role of authorities, ban on alcohol within college and hostels, surprise raids in hostels at night, postings (with accommodation) of wardens in hostels, separate hostels for juniors, presence of college "disciplinary committee" and "cultural committee," strict punishments for those involved in ragging, actions by Medical Council of India (MCI) and University Grants Commission(UGC) against the erring colleges and universities and formulation of

anti-ragging laws. Ragging should be declared a public health problem because it involves the physical, mental and social exploitation of not only an individual but also of his/her family and the society as a whole.

Extent of Ragging in India

The Coalition to Uproot Ragging from Education (CURE), an NGO working against ragging, has been monitoring the incidents of ragging reported in the media and highlights the current trend of ragging in the country through its annual status report. The highest number of incidents was reported from Uttar Pradesh (97), Andhra Pradesh (75), West Bengal (73), Tamil Nadu (54), Kerala (48), Madhya Pradesh (48), Maharashtra (42), and Punjab (35). A total of 71 deaths due to ragging was reported in that period with Andhra Pradesh (11), Tamil Nadu (8), Maharashtra (8), Uttar Pradesh (7), Karnataka (6) and West Bengal (6) registering the maximum deaths due to ragging.[4]

REPORTED INCIDENTS OF RAGGING DISAGGREGATED BY NATURE

Cases leading to injury	199
Cases involving sexual abuse	128
Cases leading to group violence and disturbance	129
Cases involving drug abuse, alcohol and smoking	35
Cases involving caste, religion and regionalism	25

APPROACH SO FAR

It was in the late 70s in the aftermath of the death of two freshers in a Regional Engineering College that the Government of India for the first time issued a notification banning ragging in the country. However, despite the national ban, incidents did not come down, prompting several universities to bring ordinances and state governments to issue executive orders or bring modifications in their state education act or initiate legislation against ragging. The Supreme Court's interventions in 1999 and later in 2006 led to the formation of committees with clear mandates to address the problem of ragging, and has no doubt increased our understanding of the phenomenon and the ways in which it is viewed.[4]

Prof K.P.S. Unny Committee Report (1999)

Raghavan Committee Report (2007)

State Laws against Ragging

Different state laws have laid down varying punishments for ragging. While the Chhattisgarh Anti-ragging Act states that an offender could be imprisoned for up to five years or fined up to Rs. 5000, the Andhra Pradesh Act lays down a provision of imprisonment ranging from six months to 10 years and fine up to Rs. 10,000. Similarly, other State Acts (of Maharashtra, Tamil Nadu, Kerala, West Bengal, and Assam) have punishment ranging from six months to two years and a fine up to Rs. 10,000.

EPIDEMIOLOGY

Prevalence of Ragging

- Ragging continues to be widely prevalent with almost 40 per cent of the sample saying they were ragged in some form.
- Institutions vary greatly in the prevalence of ragging indicating that factors particular to individual institutions - their unique psychosocial ecosystem - play an important role in determining whether ragging happens.
- Ragging is more prevalent among male students compared to female students, among hostellers compared to day-scholars, and among students in professional courses compared to other colleges.[4]

Gender Bias: Power game with Masculinization

Ragging serves as a ritual of coming of age, and signals to both the ragger and the victim a rite in the shaping of masculinity. In that context, physical ragging among boys becomes a test of physical endurance and a way to prove their manhood. It is therefore commonly seen that male students who cannot bear ragging are considered 'weak' or 'effeminate'. For the same reason, male students with physical characteristics not considered masculine enough are ridiculed and targeted more during ragging. Some raggers also mentioned that there is stiff competition among boys to secure students' union position which in a way not only forces juniors to interact with their seniors but also comply with their requests thus making them vulnerable to ragging.[4]

Place of Residence and Prevalence of Ragging

Higher percentage of hostellers than day-scholars and students from professional courses than degree courses reported facing mild and severe ragging. In a few FGDs, students said that day-scholars are not ragged much and ragging is mainly done in hostels after the dining hours. Factors such as hierarchy, groupism, lack of surveillance and other inhibitory controls, which influence the occurrence of ragging in general, become more profound in the hostel ecosystem thus exacerbating the prevalence and severity of ragging.[4]

Types of Ragging

Q. What kind of ragging did you face?

Options		Overall Percentage			
a	None	33.4%	f	Approaching opposite sex on some pretext e.g. proposal	8.8%
b	Giving introduction to seniors	53.3%	g	Drinking and smoking	3.0%
c	Wishing seniors and addressing them as Sir/Ma'am	32.5%	h	Doing assignments for seniors	13.3%
d	Following a dress code	23.5%	i	Spending/giving money to seniors	3.1%
e	Singing and dancing	24.2%	j	Physical ragging (beating, physical punishments, etc.)	4.2%
			k	Using bad language/words	10.8%
			l	Sexual ragging	1.4%
			m	Other	0.9%
			n	Did not answer	6%

Substance Use: Mandatory Starter for Ragging?

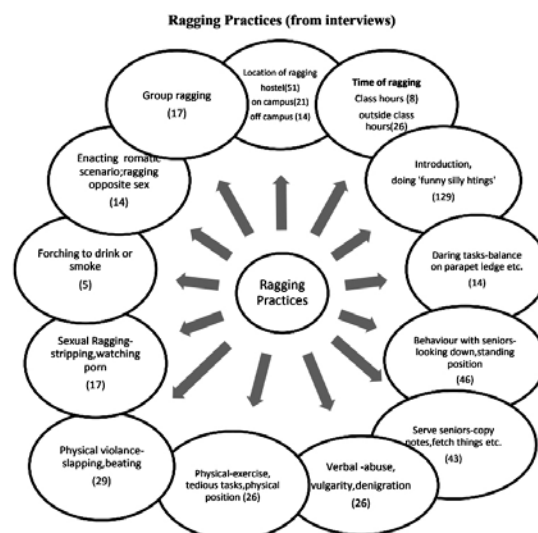
Analysis of qualitative data and media cases show that in a large number of ragging incidents, juniors are forced to smoke and drink and, in some cases, even consume drugs such as marijuana. Several students are forcibly introduced to smoking and drinking by their seniors as a part of the ragging ritual.

Physical Ragging

A higher percentage of physical ragging involving physical punishment, beating, etc. was reported from medical and engineering colleges. A large number of raging cases of serious physical injuries leading to hospitalization, death, or suicide of students have been reported in the media.[4]

Q. What kind of ragging did you face?

		Gender		Type of study		Place of Residence	
		Male	Female	Degree	Professional	Hosteller	Day-Scholar
a	None	30.5%	37.7%	45.4%	31.5%	26.2%	41.4%
b	Giving introduction to seniors	56.0%	50.0%	47.1%	60.4%	62.7%	43.7%
c	Wishing seniors; addressing them as Sir/Ma'am	33.2%	31.4%	25.5%	38.4%	44.2%	20.7%
d	Following a dress code	26.0%	20.1%	14.2%	29.7%	31.6%	14.9%
e	Singing & dancing	25.7%	22.2%	18.4%	28.8%	31.6%	16.6%
f	Approaching opposite sex on some pretext e.g. proposal	11.3%	5.8%	4.9%	11.2%	11.3%	6.3%
g	Drinking and smoking	4.2%	1.5%	2.4%	3.5%	3.9%	2.0%
h	Doing assignments for seniors	16.6%	9.0%	4.0%	18.4%	18.8%	7.5%
i	Spending/giving money to seniors	3.8%	2.3%	1.3%	4.1%	3.4%	3.1%
j	Physical ragging (beating, physical punishments, etc.)	6.6%	1.3%	2.5%	5.4%	6.2%	2.1%
k	Using bad language/words	16.7%	3.3%	5.7%	14.0%	15.3%	6.1%
l	Sexual ragging	2.1%	.5%	.8%	1.8%	1.7%	1.0%



Sexual Ragging

Proportion & Types of Sexual Ragging in College?

S.No	Options	Overall Percentage
a)	Yes	4%
b)	No	96%
c)	Did not answer	3.7%

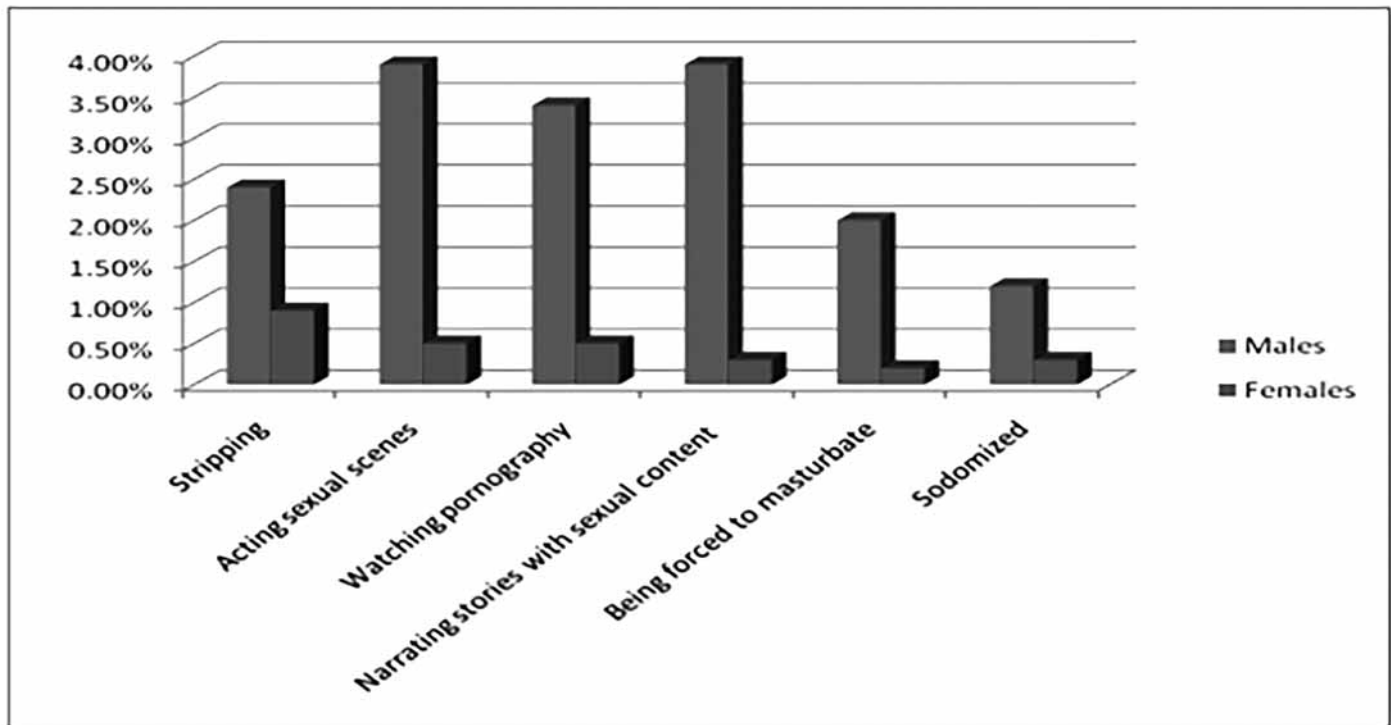
In a government medical college in Uttar Pradesh, the research team was told that the college has a tradition in which male freshers are required to blow condoms and throw them at female freshers or the female seniors they liked. This practice is termed as 'Medical Introduction' and sometimes this happens even in the presence of faculty members. In a group discussion with the male students from a hotel management institute in West Bengal, students talked about a particular ragging tradition in the institute in which the freshers are instructed to always carry a condom with them. Here a condom is called a '7th essential' by the students other essential items being knives, serving spoons, etc. which the students have to carry with them for their practical classes.[4]

TYPES OF SEXUAL RAGGING

S. No.	Options	Overall Percentage
a)	Stripping	1.8%
b)	Acting sexual scenes	2.5%
c)	Watching pornography	2.1%
d)	Narrating stories with sexual content	2.4%

e)	Being forced to masturbate	1.3%
f)	Sodomized	0.9%
g)	Other	1.9%

Gender wise distribution of sexual ragging

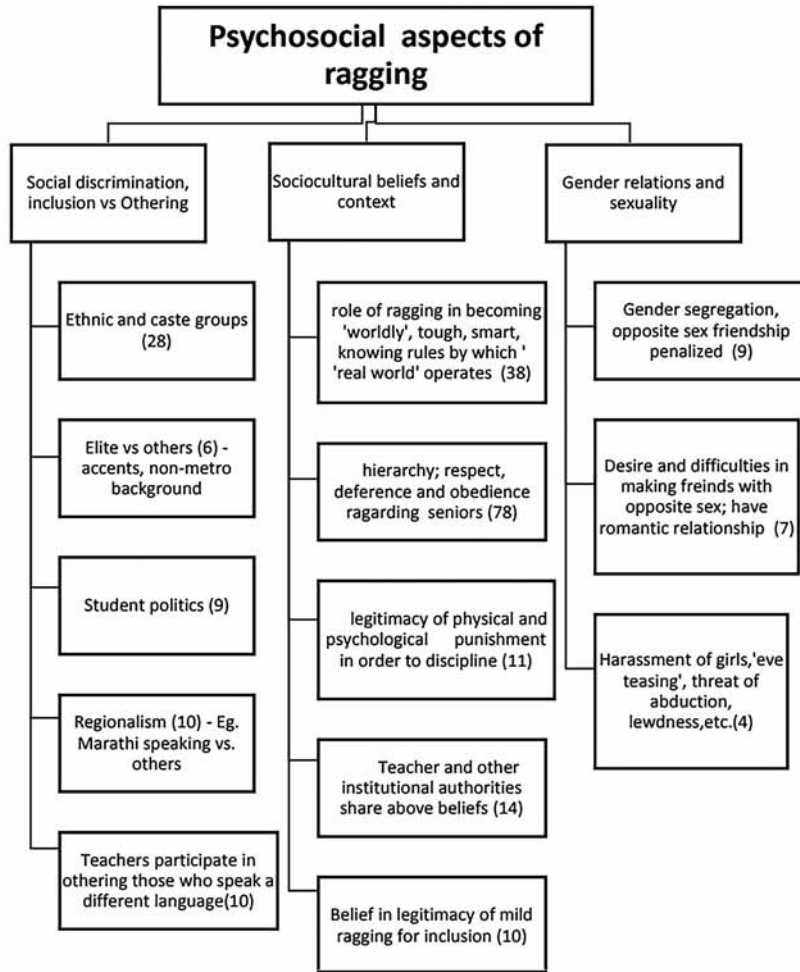


Psychological Impact of Ragging on Students

Ragging with Academic performances & Psychosocial effect

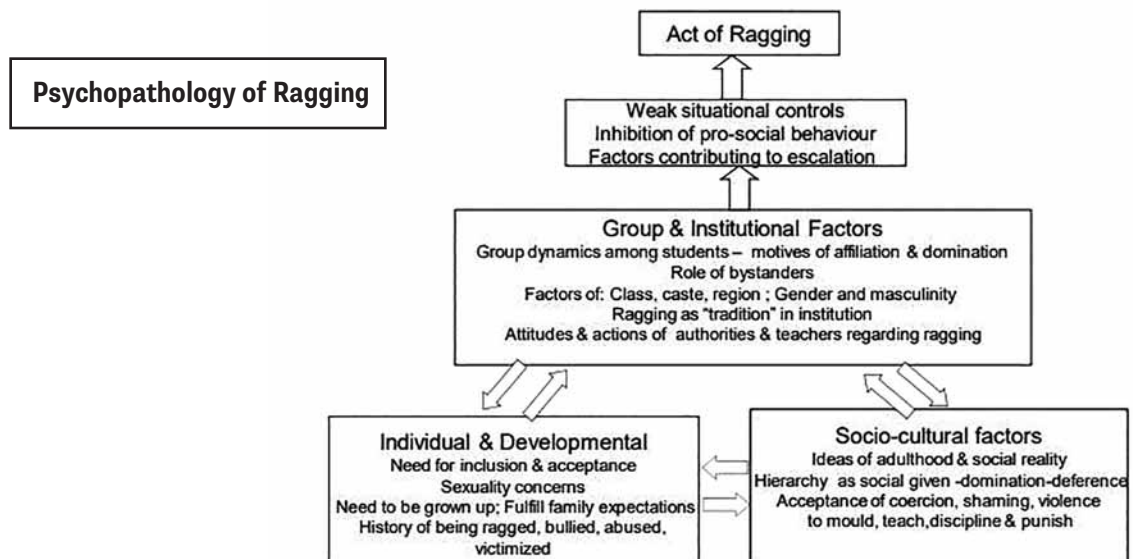
	Options	Gender		Place of Residence		Batch Year		
		Male	Female	Hosteller	Day-Scholar	1 st	2 nd	3 rd & 4 th
a.	Loss of focus/concentration	28.2%	21.4%	28.7%	18.9%	28.9%	24.8%	19.3%
b.	Missed classes	20.9%	12.2%	18.7%	15.8%	19.1%	17.9%	14.5%
c.	Couldn't complete assignments on time	15.7%	12.8%	16.6%	11.6%	15.6%	15.3%	11.8%
d.	Decrease in Grades/performance	14.6%	8.3%	14.2%	9%	13.7%	11.7%	9.3%
e.	Others	5.8%	4.9%	6.9%	2.9%	4.5%	7.1%	5.2%

*All calculations in the table are based on students who admitted to being mildly or severely ragged



A tentative psychosocial model of ragging

TENTATIVE PSYCHOSOCIAL MODEL OF RAGGING



Conclusion & Recommendation

A. Short-Term Recommendations

1. Institutional Role in Fostering Inclusion, Belonging, and Acceptance of New Students

2. Maintenance of Support Systems

Surveillance systems are largely understood to mean CCTV cameras. 'Surveillance' therefore needs to comprise a human system of guardianship—of wardens, mentors, including senior students to be in regular contact with newcomers and to include them in activities such as games/ sports and extra-curricular, in colleges and in their residential facilities (hostels), where ragging frequently occurs. In contrast to the dominance-submission relationship enforced through the intimidation and fear associated with ragging, newcomers can be exposed to another version of authority— one that is firm, yet fair and caring.

3. Institutional Response to Ragging:

Implementation of UGC Protocol and Guidelines

4. Widening the Role of the Anti-ragging Cell of UGC

Currently, the primary focus of the anti-ragging cell in the UGC is to deal with the complaints of ragging. The cell should also actively function as a nodal body to disseminate various information/literature pertaining to harmful effects of ragging, ways to curb the practice and improve the psychosocial climate in institutions, etc. through booklets, websites, and audio-visual material. The cell should also conduct seminars, workshops, essaywriting competitions, etc., and engage students, faculty, and college management in its endeavour to eradicate ragging.

5. Accountability

While the NAAC (National Assessment and Accreditation Council) takes into account the issue of institutional response to ragging, this is attended to by most institutions in a perfunctory and mechanical manner.

6. Psychosocial Support and Counseling

Psychosocial support and counseling should be offered to victims as well as perpetrators so that the potential for cyclical abuse is neutralized. While it is desirable to have counselors in every college, it is recognized that there is a shortage of human resources and skills in this area. Therefore, it is recommended that every college identifies a nodal agency offering counseling/training services and nominates one or two faculty volunteers to train at these agencies and, in collaboration with them, offer support to affected students. Also, the UGC should budget for the provision of counselors and should have a list of recognized nodal agencies which can be accessed for counseling services, till such time as these capacities are developed within institutions. For victims, counseling would need to focus on issues of support, reassurance, and safety on the one hand, and on identity, assertiveness, and efficacy on the other; for some victims, the impact may be in the nature of trauma in which case, referral systems for more specialized care, must be made accessible. Many of them are unable to deal with the 'freedoms' they are dealing with for the first time, in impersonal institutional spaces. Above all, our young people are not socialized to deal with issues of gender and sexuality. Ragging is a college-related custom that reflects social power dynamics around seniority compounded by compulsions related to gender. Thus, the counselor's community engagement should be in collaboration with existing committees within the institution, such as the gender sensitization committee, to foster a culture of conversations toward an egalitarian ideology formation. This engagement could be in the form of sensitization/training modules on power inequalities, prejudice, discrimination, exclusion, harassment, and violence, using creative methods such as drama, art, films, and other media. Involving the new students early in this process will foster inclusion and a sense of belongingness in them.

7. Promotion of Diversity

It is important for all educators in our country to appreciate and celebrate the huge diversities of India, in terms of ethnicity, language, religion, sexuality etc. One platform to flag off this idea of diversity is, for example, for students to organize food festivals celebrating cuisines from different states and communities of India. Sexual minorities face a great deal of discrimination, including sexual violence and ragging. Institutions need to be disability-sensitive in a proactive manner such as providing for toilets and other infrastructure that is disabled-friendly.

B. Long-Term Recommendations

1. Interventions at School Level

Studies need to make strong recommendations on operationalizing two major concepts—inclusive education and life skills education.

2. Peer Support

Life skills programs at this stage need to move from individual and personal to the public and social spheres addressing issues such as by-stander response to situations of violence and social injustice.

3. Institutional Cultures and Pedagogies

Some examples of how this may be done are i) Programs and activities that foster civic engagement and responsibility, critical reflection on social issues, and deliberation on values; ii) Cocurricular activities such as sports, music, theatre, social service to enable a sense of aesthetic engagement, openness, and affiliation; iii) Creation of opportunities for student engagement and voice in college decisions, including student membership on college boards/committees so as to foster ideas of responsible agency and citizenship; iv) Pedagogies that stimulate students to question and seek answers on their own so that sensitive reflection is the style of responding; v) An institutional climate that is supportive and fair, with faculty who are attuned and interested in student development, that will become the foundation of a dynamic culture that is just, progressive and open to change towards an egalitarian society.[4][5]

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1. Garg R. Ragging: a public health problem in India. *Indian J Med Sci.* 2009 Jun;63(6):263-71. PMID: 19602763.
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HOW LONG TO CONTINUE MAINTENANCE PHARMACOTHERAPY?

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Introduction

- OCD is a common and often a highly disabling condition that was considered untreatable before the 1960s.
- RCTs and meta-analyses have consistently demonstrated the efficacy of SSRIs and clomipramine and behaviorally oriented therapies (BT and CBT) in the treatment of OCD.
- A high dose of SSRIs should be considered as the first line pharmacological treatment for OCD.
- Obsessive-compulsive disorder (OCD) affects up to 2.5% of the population of the course of a lifetime and produces substantial morbidity.
- Approximately 70% of patients can experience significant symptomatic relief with appropriate pharmacotherapy.
- Medications have to be continued for at least 12 weeks for adequate treatment response.
- Remission of moderate or severe OCD is uncommon, and long-term management is often necessary.
- Perhaps the most important conclusion from this review of pharmacotherapeutic options is that there is a relative paucity of well-established treatment options in OCD, when SSRI treatment fails.
- Pittenger C, Bloch MH. Pharmacological treatment of obsessive-compulsive disorder. *Psychiatr Clin North Am.* 2014 Sep;37(3):375-91.

Points to ponder

- The findings from the present large, multicenter study indicate early onset and long duration of illness as overall negative predictors of long-term outcome in OCD.
- Dell'Osso B, Benatti B, Buoli M et al; ICOCs group. The influence of age at onset and duration of illness on long-term outcome in patients with obsessive-compulsive disorder: a report from the International College of Obsessive Compulsive Spectrum Disorders (ICOCs). *Eur Neuropsychopharmacol.* 2013 Aug;23(8):865-71.
- Discontinuation is associated with relapse and loss of quality of life, implying treatment should continue long-term.
- Fineberg NA, Reghunandanan S, Brown A, Pampaloni I. Pharmacotherapy of obsessive-compulsive disorder: evidence-based treatment and beyond. *Aust N Z J Psychiatry.* 2013 Feb;47(2):121-41. doi: 10.1177/0004867412461958. Epub 2012 Nov 2. PMID: 23125399.
- A substantial minority of patients, perhaps as many as a third, get little benefit from available treatments.
- Remission of symptoms is rare in those with moderate to severe disease, even with the best treatments we currently have to offer
- Christopher Pittenger, Pharmacotherapeutic strategies and new targets in OCD. *Curr Top Behav Neurosci.* 2021; 49: 331-384.
- Despite the proven efficacy of SSRIs and clomipramine in OCD, as shown above, about 40% to 60% of patients show no or just partial symptom improvement to a treatment with a first-line drug.

- McDougle CJ, Goodman WK, Leckman JF, Price LH. The psychopharmacology of obsessive-compulsive disorder: implications for treatment and pathogenesis. *Psychiatr Clin North Am.* 1993;16:749-766.
- 40-60% of OCD patients exhibit disabling residual symptoms, indicating the need for innovative pharmacological treatments, different augmentation strategies, and novel physical treatment techniques.
- Pallanti, S.; Quercioli, L. Treatment-refractory obsessive-compulsive disorder: methodological issues, operational definitions and therapeutic lines. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 2006, 30(3), 400-412.
- Hirschtritt, M.E.; Bloch, M.H.; Mathews, C.A. Obsessive-compulsive disorder: Advances in diagnosis and treatment. *JAMA*, 2017, 317(13), 1358-1367.
- The most effective pharmacological treatment is the combination of an SSRI agent with CBT.
- Refractory OCD symptoms can improve with high SSRI dosages or augmentation with an atypical antipsychotic drug, mainly risperidone and aripiprazole.
- Del Casale et al. Psychopharmacological Treatment of Obsessive-Compulsive Disorder (OCD) REVIEW ARTICLE *Current Neuropharmacology*, 2019, 17, 710-736
- A meta-analysis of the RCTs found a statistically significant superior efficacy of SSRIs compared with placebo in relapse prevention.
- Fineberg NA, Pampaloni I, Pallanti S, et al. Sustained response versus relapse: the pharmacotherapeutic goal for obsessive-compulsive disorder. *Int Clin Psychopharmacol* 2007;22(6):313-22
- Patients who improve with pharmacotherapy have a higher chance of relapse on treatment discontinuation.
- Grant JE, Mancebo MC, Weinhandl E, et al. Longitudinal course of pharmacotherapy in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 2013; 28(4):200-5

How long to continue Pharmacotherapy

- Treatment guidelines recommend continuation of medications for at least 1-2 years to prevent relapse and to allow further improvement.
- Koran LM, Hanna GL, Hollander E, et al. American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. *Am J Psychiatry* 2007;164(7 Suppl):5-53
- Ongoing improvement with SSRIs has been observed both over short term (20-24 weeks) and long term (1 year) in treatment continuation studies.
- Jakubovski E, Diniz JB, Valerio C, et al. Clinical predictors of long-term outcome in obsessive-compulsive disorder. *Depress Anxiety* 2013;30(8):763-72
- Taken together, the available evidence suggests that SSRIs should be continued for relapse prevention for at least 1-2 years after remission.
- Treatment discontinuation should be decided considering various factors such as severity and duration of the illness, number of previous episodes, history of relapse upon discontinuation, presence of residual symptoms and concurrent psychosocial difficulties.
- It should be emphasized that discontinuation of SSRIs should be carefully considered and in most patients continued treatment may be necessary in view of high rates of relapse upon discontinuation.
- Fineberg NA, Pampaloni I, Pallanti S, et al. Sustained response versus relapse: the pharmacotherapeutic goal for obsessive-compulsive disorder. *Int Clin Psychopharmacol* 2007;22(6):313-22
- APA guidelines recommend upward titration to the maximum FDA-approved doses by 4-6 weeks and continuation in that dose for another 6-8 weeks or so to determine efficacy.
- Koran LM, Hanna GL, Hollander E, Nestadt G, Simpson HB. American Psychiatric A (2007): Practice guideline for the treatment of patients with obsessive-compulsive disorder. *The American Journal of Psychiatry*. 164:5-53.

- An open discontinuation study also reported significantly higher 6-month, 1-year, and 2-year relapse rates for the patients whose SRI treatment was discontinued
- Rates of relapse appear to be increased after discontinuation of SRI treatment but cannot be precisely specified.
- Given these observations, discontinuation of pharmacotherapy should be carefully considered, and for most patients, continued treatment of some form is recommended.
- Practice Guideline for the Treatment of Patients With Obsessive-Compulsive Disorder. APA

Conclusion

- Although an attempt may be made to taper and stop SSRI after 1-2 years of sustained remission, most patients may require indefinite continued treatment with a SSRI.
- A recovery-oriented approach would eventually reshape the assessment of individual patients, foster a multidimensional assessment, and ultimately lead to a more personalized and likely much more successful treatment.

Is Baclofen the answer where Benzodiazepines are not suitable?

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AWS

- Common but Complex neuropsychiatric condition
- Associated complications - Seizures & Delirium - Severity of Dependence
- Presence of physical comorbidity & Psychiatric comorbidity
- Protracted withdrawal
- Resistant alcohol withdrawal

TREATMENT OF aws

- Signs & Sx of AWS - Result of Hyperexcitable brain
- Alcohol enhances brain 's main inhibitory systems via GABA A receptor for which it is an agonist like BNZ
- Alcohol antagonist action on NMDA receptor suppresses the excitatory system leading to overall CNS depressant effect
- Chronic exposure to alcohol- Down-regulation of GABA A receptors & up-regulation of NMDA receptors
- AWS- Balance between GABAergic & Glutamergic system reverses with decreased inhibition & increased CNS excitation

BNZ in AWS

- Cross tolerance between alcohol & BNZ both agonist for GABA A/BNZ receptor, underpins the effective action of BNZ in suppressing AWS
- 1st line treatment
- Data on comparison of different BNZ among themselves, BNZ combined with other drug versus other drugs & fixed v/s symptom triggered regimens are very limited
- Difficult to draw precise conclusions about relative effectiveness & safety of BNZ against other drugs b/o large heterogeneity of trials both in interventions & assessment of outcomes

Baclofen in AWS

- BNZ though are drug category of choice, other agents are considered in situation of relative contraindication
- Baclofen may have advantage over alternatives in presence of liver disease or risk abuse of medication
- Specific agonist for GABA B receptor which provides a negative feedback loop for GABAergic system- thereby downregulating GABA A activity & mimicking some of the effects of alcohol induced action on GABA A receptor
- Excreted through kidney- unlike BNZ has minimal liver metabolism

- Rising incidence of alcohol related liver disease, sometimes undiagnosed at presentation- non benzodiazepines esp Baclofen a viable alternative to shorter acting BNZ

Evidence for baclofen in AWS

- Open label trials conducted after preclinical studies which showed that Baclofen prevents withdrawal Sx in rats.
- In the earliest case series, rapid improvement of CIWA score was seen with Baclofen 10 mg 8 hourly in 5 patients with severe AWS (Addolarato, 2002)
- One single case study showed efficacy in DT (Addolarato, 2003)
- Retrospective casenote review of 17 patients treated with Baclofen at St Anthony Hospital Oklahoma USA, Baclofen was found to suppress AWS in 12 out of 14 patients where AWS hadn't commenced. Of 3 remaining pts where AWS commenced, there was one treatment success based on predetermined criteria.
- A 2006 RCT with Baclofen 10 mg TDS & DZM found that Baclofen was comparable in efficacy & tolerability to DZM, median CIWA Ar scores in Baclofen group decreased from over 20 at baseline to <15 on day 2 & less than 10 on day 3, a comparable decrease to DZM group.
- Another Double blinded trial with 19 randomized to placebo and 25 to Baclofen 10mg TDS, CIWA Ar scores decreased from 12 at day 1 to <9 on day 2 to about 8 on day 3.
- Indian Study on comparison of Baclofen 30 mg & Chlordiazepoxide 75 mg, both arm of 30 patients each, showed a similar reduction of AWS, but Chlordiazepoxide provided quicker & more effective detoxification.

Can we draw any conclusion now?

- Evidences are limited
- Poor study design, low quality of evidence
- Currently routine treatment with baclofen at a dose of 30 mg per day is not recommended outside trials and BNZ should be used as 1st line treatment
- BNZ use is favoured in managing both planned & unplanned AWS
- Given that tailored & significantly higher doses of Baclofen are used in a no. of trials in maintenance of abstinence, it is surprising that higher doses have not been studied for AWS
- Given that Baclofen has a good safety profile in alcohol related liver diseases & these pts respond to low doses, it may be useful in these patients.
- Effects of Baclofen in different symptoms of AWS needs investigation

Case Presentation on Peripheral Neuropathy

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Patient Details

Mrs Karmakar, 55 yrs old,

Address: Panchanantala, Berhampore

Occupation : Housewife, Handedness: Right handed, Education: Graduate

Presenting Complaints

Tingling and burning sensations of both lower limbs since the last 7 months.

Decreased sensation in both lower limbs since the last 4 months.

Weakness of both lower limbs since the last 4 months.

Difficulty in walking since the last 2 months.

Tingling of both upper limbs since the last 2 months.

Weakness of both upper limbs since the last 1 month.

Back pain since the last 1 month.

History of Present Illness Since April 2022

The patient was apparently normal till 7 months back when she developed tingling of both her lower limbs which was insidious in onset and gradually progressive. It initially started in bilateral toes at the onset of the illness which gradually extended till the ankles over 1 month and over a period of 3 months, up to both the knees.

There is history of burning sensation over both lower limbs over the last 7 months, which also progressed in a similar fashion till the knees over 3 months.

Now, these symptoms are present till the whole of both lower limbs till the hips.

Since July 2022

The patient also developed decreased sensations over both her lower limbs 3 months later, which started bilaterally in the toes, gradually progressed till the knees over a span of one month and has now extended till mid thigh.

She is able to perceive hot and cold sensations in her lower limbs but now to a reduced extent.

According to the patient, she is not able to feel the bedsheet upto her mid thigh now.

She also tells history of not being able to sense the presence of a wound over her left sole which she came across accidentally while looking at her feet recently.

Around the same time the patient also noticed weakness of both her lower limbs, initially starting with difficulty in getting up from squatting position.

This progressed over 2 weeks with difficulty in walking due to buckling of both her knees and difficulty in gripping chappals but she was able to guide her feet into the chappals.

History of slippage of chappals after walking a small distance without her knowledge present.

No history of tripping or difficulty in negotiating narrow pathways but she has difficulty in walking over uneven surfaces.

September 2022

5 months later, the patient noticed tingling over the tips of both of her fingers, which then progressed till the mid forearm over a span of one month. No burning or pin and needle sensation or loss of sensation.

Since, the last one month the patient also noticed weakness of both upper limbs in the form of difficulty in gripping objects/ wearing dress/ holding pen/ mixing bolus of food/ tearing chapathis.

Now, she also has difficulty in lifting the food up to her mouth but once she is able to do so, she can guide the food to the mouth without smearing.

No history of difficulty in lifting the arms above the head.

October 2022

After one month, the patient also noticed tremulousness of both upper limbs, aggravated while doing activities.

History of low back pain, dull aching type, diffuse and present throughout since the last 1 month, with no radiation and not aggravated by coughing but was aggravated after admission after she underwent lumbar puncture.

She gives history of Wash Basin phenomenon since the last 2 months.

No history of thinning of limbs/ cramps / stiffness / twitching of muscles.

No history of difficulty in sitting up from supine position / lifting the head / rolling over on the bed.

No history of fever / upper respiratory infections preceding the illness.

No symptoms suggestive of cranial nerve dysfunction.

No history of bowel or bladder incontinence.

No history of loss of weight or loss of appetite.

No history of electric shock like sensations over the spine or over the legs.

Activities of Daily Living

The patient is able to stand without support but needs one person support while walking.

The patient needs to look down at her toes while walking.

She is able to guide her legs in to the chappals.

She is able to hold food and guide food to mouth with some difficulty but without smearing.

She is able to reach out to objects higher up than herself.

She is able to sit up from lying position and to roll over the bed.

Past History

Known case of diabetes mellitus since last 7 years, on oral hypoglycemic agents.

Known case of hypothyroidism since the last 10 years.

History of generalised dryness of skin since the last 2 years - shown to dermatologist, and prescribed topical medication with minimal improvement.

No history of hypertension, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, tuberculosis or epilepsy.

No history of previous surgery.

No history of similar illness in the past.

No history of similar illness in the family.

Personal History

Diet - Mixed.

Sleep - Adequate

Appetite - Normal

Bowel and bladder habits normal.

Non- smoker, non- alcoholic, no h/o tobacco chewing.

Medication History

Tab. METFORMIN 500+ VILDAGLIPTIN 50..... 1- 0 -1

Tab. Levothyroxine 100 OD

General Physical Examination

Elderly Female

Conscious, Oriented, Cooperative

Moderately built and nourished

No pallor, icterus, cyanosis, clubbing, lymphadenopathy or pedal edema

Vitals normal

Dryness of Skin over the whole body +

Linear abrasion over left sole +, healed.

Tongue hyperpigmentation.

No knuckle hyperpigmentation.

Central Nervous System Examination

HIGHER MENTAL FUNCTIONS:

Conscious, oriented

MMSE: 28/30

Cranial nerves: Normal

MOTOR SYSTEM

Nutrition

Right arm 28 cm

Left arm 28 cm

Right forearm 19 cm

Left forearm 18 cm

Right thigh 32 cm

Left Thigh 31 cm

Right leg 26 cm

Left leg 26 cm

Tone

Hypotonia of all four limbs.

POWER:	
NECK	POWER
Flexion	5/5
Extension	5/5

Upper limb		
Shoulder	Right	Left
Abduction	4+/5	4+/5
Adduction	4+/5	4+/5
Flexion	4+/5	4+/5
Extension	4+/5	4+/5
Internal Rotation	4+/5	4+/5
External Rotation	4+/5	4+/5

Small Muscles Of Hand	Right	Left
Abductor Pollicis Brevis Adductor Pollicis Flexor Pollicis Brevis	Weak	Weak
Opponens Pollicis	Weak	Weak
Abductor Digiti Minimi Flexor Digiti Minimi Opponens Digiti minimi	Weak	Weak
Lumbricals and interossei	Weak	Weak

ELBOW	Right	Left
Flexion	4/5	4/5
Extension	4/5	4/5

WRIST	Right	Left
Flexion	3/5	3/5
Extension	3/5	3/5

FINGER	Right	Left
Abduction	3/5	3/5
Adduction	3/5	3/5
Hand grip	Poor	Poor

FOOT	Right	Left
Plantar Flexion	3/5	3/5
Dorsi Flexion	3/5	3/5
Toe grip	Poor	Poor

Superficial Reflexes

Reflex	Right	Left
Corneal Reflex	+	-
Conjunctival Reflex	+	-
Abdominal Reflex	Absent	Absent
Plantar Response	Mute	Mute
Anal Reflex	Present	Present

Primitive Reflexes: Absent

The Motor System Examination shows hypotonia of all four limbs with distal muscle weakness in both upper and lower limb.

SENSORY SYSTEM

UPPER LIMB

Fine Touch (Cotton tip), pain (pin prick), joint position, temperature (cold tuning fork) and vibration impaired distally till mid-forearm and spread proximally.

LOWER LIMB

Fine Touch (Cotton tip), pain (pin prick), joint position, temperature (cold tuning fork) and vibration impaired distally more than proximally; spared above groin.

COORDINATION AND ABNORMAL MOVEMENTS

Coordination:

- 1) No Cerebellar Signs
- 2) Romberg's Sign : Positive
- 3) Gait: The patient is able to walk with one person support and has to continuously look at her feet while walking.

Abnormal Movements:

Postural Tremor present bilaterally.

Other Systems

Findings of Cardiovascular, Respiratory and Per abdomen are non contributory.

DIAGNOSIS

Neurological Deficits:

LMN type of weakness of both upper and lower limbs, distal more than proximal.

Sensory impairment distally in all four limbs.

Sensory ataxia.

Anatomical Localisation:

Peripheral nerves: Motor and Sensory fibres affected.

Pathological Diagnosis:

- Axonal degeneration

Etiology:

- Metabolic (Diabetes)
- Inflammatory.

INVESTIGATIONS

CBC, LFT, RFT and Serum electrolytes, Serum Folate, Uric Acid and Urine routine – within normal limits.

RBS - 307 mg/ dL

HbA1c : 9.2 %

ANCA, CRP, RA Factor - Negative

ANA Profile - all negative

Serum ACE - within normal limits

Vitamin B12- > 2000 pg/ ml

2D echo - Mild Septal Hypertrophy, doubtful RWMA, EF 50%

INVESTIGATION OF CHOICE FOR ANATOMIC LOCALISATION

Nerve Conduction Study:

Conclusion: Sensory predominant axonopathy.

MIND IT

Quiz Masters: Dr Tirthankar Dasgupta & Dr Ranjan Bhattacharyya

Presented in HOPECON 2023

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1. **What is the primary diagnostic criteria for major depressive disorder?**
 - A) Sleep disturbances
 - B) Anhedonia
 - C) Reduced energy levels
 - D) Depressed mood most of the day
2. **Name three common symptoms of generalised anxiety disorder.**
 - A) Delusions
 - B) Excessive worry
 - C) Hallucinations
 - D) Impaired memory
3. **What is the first line treatment for OCD?**
 - A) Benzodiazepines
 - B) Antipsychotics
 - C) Selective serotonin reuptake inhibitors (SSRIs)
 - D) Mood stabilizers
4. **What is the hallmark for schizophrenia?**
 - A) Panic attacks
 - B) Intrusive thoughts
 - C) Psychosis, including hallucinations and delusions
 - D) Mood swings
5. **Differentiate bipolar 1 and 2 disorders.**
 - A) Type I involves depression episodes only, while Type II involves manic episodes.
 - B) Type I involves manic episodes only, while Type II involves depression episodes.
 - C) Type I involves manic episodes and may also include depressive episodes, while Type II involves hypomanic episodes and depressive episodes.
 - D) Type I and Type II are the same disorder with different names.
6. **Define the term dissociative disorder**
 - A) A fear of public speaking and social situations
 - B) Repeated, intrusive thoughts or images
 - C) The presence of two or more distinct identities or personality states, often accompanied by memory gaps
 - D) A chronic and pervasive feeling of emptiness and instability in relationships
7. **What are the common side effects of antipsychotic medications?**
 - A) Increased anxiety and restlessness
 - B) Insomnia and weight loss
 - C) Sedation, dry mouth, and extrapyramidal symptoms (e.g., tremors, stiffness)
 - D) Increased libido and euphoria
8. **What is the primary neurotransmitter implicated in depression?**
 - A) Serotonin
 - B) Dopamine
 - C) Acetylcholine
 - D) Gamma-aminobutyric acid (GABA)
9. **Which is considered as first line of treatment in borderline personality disorder?**
 - A) Antipsychotic medications
 - B) Mood stabilizers
 - C) Dialectical behavior therapy (DBT)
 - D) Benzodiazepines

10. Which brain structure is primarily implicated in storage and formation of new memories?

- A) Amygdala
- B) Thalamus
- C) Hippocampus
- D) Prefrontal cortex

11. What is the characteristic feature of avoidant personality disorder?

- A) Intense fear of social situations
- B) Grandiose sense of self-importance
- C) Persistent feelings of inadequacy and social inhibition
- D) Impulsive and reckless behavior

12. Which of the following medications used in bipolar depression?

- A) Fluoxetine
- B) Venlafaxine
- C) Lamotrigine
- D) Methylphenidate

13. What is the primary neurotransmitter involved in reward pathway of brain?

- A) Serotonin
- B) Norepinephrine
- C) Dopamine
- D) Glutamate

14. Which of the following is the core symptoms of depression?

- A) Depressed mood or loss of interest/pleasure in activities
- B) Fear of being in public places
- C) Excessive and irrational worry
- D) Recurrent and intrusive thoughts or images

15. Which type of therapy focuses on exploring unconscious conflict and early childhood experiences?

- A) Cognitive-behavioral therapy (CBT)
- B) Dialectical behavior therapy (DBT)
- C) Interpersonal therapy (IPT)
- D) Psychoanalysis

16. What is primary mechanism of action of benzodiazepines?

- A) Inhibition of serotonin reuptake
- B) Blockade of dopamine receptors
- C) Modulation of glutamate receptors
- D) Enhancement of gamma-aminobutyric acid (GABA) activity

17. Which of the following is common cognitive distortions in GAD ?

- A) Black-and-white thinking
- B) Personalization
- C) Catastrophizing
- D) Excessive worry about a variety of topics

18. What is the primary etiology of dissociative disorder

- A) Trauma and abuse during childhood
- B) Genetic predisposition
- C) Neurological dysfunction
- D) Complex interaction of biological, psychological, and environmental factors

19. Which of the following is norepinephrine reuptake inhibitor

- A) Fluoxetine
- B) Venlafaxine
- C) Bupropion
- D) Atomoxetine

20. What is the primary difference between somatic symptom disorder and illness anxiety disorder

- A) Age of onset
- B) Severity of symptoms
- C) Focus of the symptoms (physical sensations vs. preoccupation with having a serious illness)
- D) Duration of symptoms

IDENTIFY WITH PICTORIAL CUES

21. A genetic disorder characterized by a range of physical, cognitive, and behavioral abnormalities, including intellectual disability and distinctive facial features.

22. A genetic disorder characterized by intellectual disability, physical abnormalities, and a higher risk of certain medical conditions, such as heart defects and leukaemia.

23. A phenomenon seen in neurological disorder characterized by the inability to recognize familiar faces, despite intact vision and cognitive abilities.
24. A neurodevelopmental disorder characterized by impairments in social interaction, restricted interests, repetitive behaviours, and difficulties with communication.
25. A neurologic disorder characterized by deficits in written language, right-left disorientation, finger agnosia, and acalculia.

26. A sleep disorder characterized by excessive daytime sleepiness, often accompanied by sudden loss of muscle tone (cataplexy) triggered by emotions.
27. A neurocognitive disorder characterized by the progressive loss of intellectual and social skills, along with personality changes and behavioral disturbances.
28. A movement disorder characterized by involuntary jerking or writhing movements, typically involving the face, neck, and limbs.



Question 21



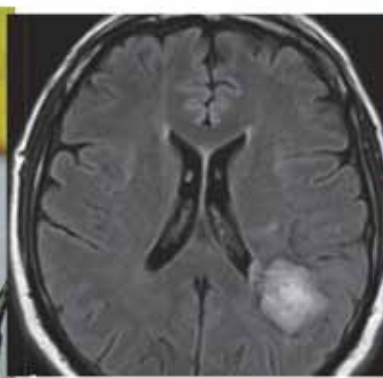
Question 22



Question 23



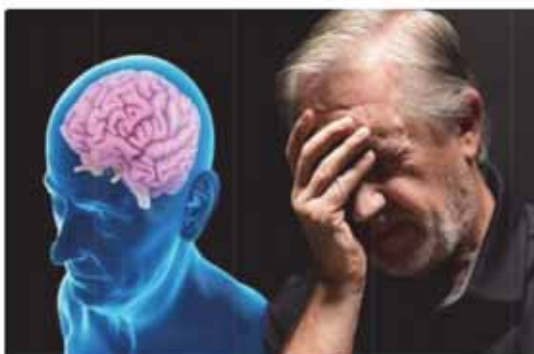
Question 24



Question 25



Question 26



Question 27



Question 28

Answers of Psychiatry Quiz (Mind It)

1. D) Depressed mood most of the day
2. B) Excessive worry
3. C) Selective serotonin reuptake inhibitors (SSRIs)
4. C) Psychosis, including hallucinations and delusions
5. C) Type I involves manic episodes and may also include depressive episodes, while Type II involves hypomanic episodes and depressive episodes.
6. C) The presence of two or more distinct identities or personality states, often accompanied by memory gaps
7. C) Sedation, dry mouth, and extrapyramidal symptoms (e.g., tremors, stiffness)
8. A) Serotonin
9. C) Dialectical behavior therapy (DBT)
10. C) Hippocampus
11. C) Persistent feelings of inadequacy and social inhibition
12. C) Lamotrigine
13. C) Dopamine
14. A) Depressed mood or loss of interest/pleasure in activities
15. D) Psychoanalysis
16. D) Enhancement of gamma-aminobutyric acid (GABA) activity
17. C) Catastrophizing
18. A) Trauma and abuse during childhood
19. B) Venlafaxine
20. C) Focus of the symptoms (physical sensations vs. preoccupation with having a serious illness)
21. Down syndrome
22. Turner syndrome
23. Prosopagnosia
24. Autism spectrum disorder
25. Gerstmann-Straussler-Scheinker syndrome
26. Narcolepsy with cataplexy
27. Alzheimer's disease
27. Tardive dyskinesia

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