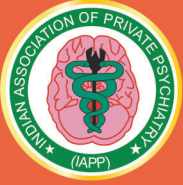


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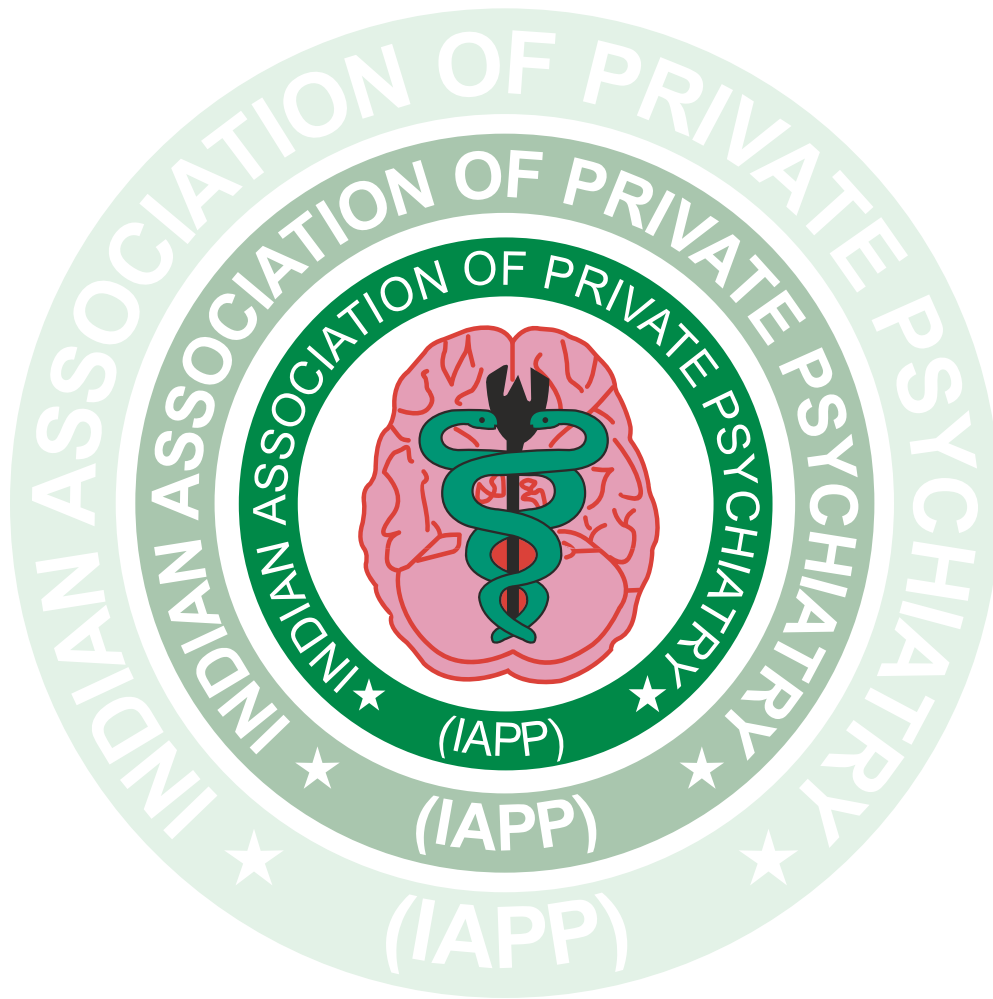
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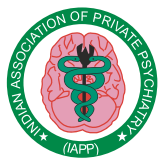


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2025

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Message



Dr. O P Singh

President

Indian Association of Private Psychiatry, West Bengal State Branch

To,
Prof. Ranjan Bhattacharyya,
Honorary Editor
Bengal Journal of Private Psychiatry

Greetings from President, IAPP, West Bengal State Branch. It's praiseworthy that you've regularise the Bengal Journal of Private Psychiatry since you've taken charges as the Editor. It's the only state branch who's regularly publishing their journal.

I would also likely to congratulate all the office bearers, esteemed members of IAPP, West Bengal State Branch and contributors of the journal.

Long live IAPP, West Bengal State Branch.

Long live IAPP.



Dr. O P Singh

President

Indian Association of Private Psychiatry West Bengal State Branch

Message



Dr. Sanjay Garg

Honorary Secretary

Indian Association of Private Psychiatry, West Bengal State Branch

To,
Prof. Ranjan Bhattacharyya,
Honorary Editor
Bengal Journal of Private Psychiatry
Indian Association of Private Psychiatry West Bengal State Branch

Dear Prof Bhattacharyya,

On behalf of Indian Association of Private Psychiatry West Bengal State Branch, as the Honorary Secretary, let me take this opportunity to congratulate you on your tenure as the Honorary Editor of Bengal Journal of Private Psychiatry of Indian Association of Private Psychiatry West Bengal State Branch.

Since you have taken over, the journal has reached new heights, and we have had consistent publications along with relevant and noteworthy articles required to a private practitioner.

As the secretary of Indian Association of Private Psychiatry West Bengal State Branch, with support from our President, Prof Dr O P Singh, it has always been our endeavor that our association strives to enhance the knowledge and skills of a private practitioner of psychiatry in West Bengal. Accordingly, we have always curated our educational programs to this need with involvement of maximum members with a mix of dynamic youngsters and experienced seniors.

Your dedication and hard work has helped the Bengal Journal of Private Psychiatry to flourish and as I bid adieu from this post of Honorary Secretary, I wish you and the journal more successes in future.

Yours sincerely,



Dr. Sanjay Garg

Honorary Secretary

Indian Association of Private Psychiatry West Bengal State Branch



Dr. Ranjan Bhattacharyya

Hony. Editor

Bengal Journal of Private Psychiatry

It gives immense pleasure to bring the volume 12, issue 1, August 2025 of Bengal Journal of Private Psychiatry before you. In the last four years, regular yearly issues are being published during PSYCON. I am indebted to Dr Mrugesh Vaishnav (National President), Dr Arun Marwale (Hony Secretary General), Dr Gautam Saha (National Vice President), Dr Vijay Nagecha (Hony National Treasurer) and Dr Prosenjit Ghosh (Hony National Editor) of Indian Association of Private Psychiatry for their constant support and encouragement. I am very proud and honored representing the state branch where I have Prof OP Singh as President, Dr Sanjay Garg as Hony Secretary, Dr Arabinda Brahma as Vice President, Dr Sanjay Saha as Hony Treasurer who constantly motivate me with support from EC members Dr Arnab Banerjee, Dr Sarmistha Chakrabarti, Dr Sujit Sarkhel, Dr Soumya Chatterjee, Dr Kaustav Chakraborty, Dr Pinaki Sarkar and Dr Debjani Bandyopadhyay.

The current BJPP issue has a message from our dynamic secretary Dr Sanjay Garg followed by Editor Speaks. We are skeptical about the CME credit hours especially when it comes in private practice which was highlighted by the Editor followed by Dr Garg's review on recent developments in Pharmacological management of bipolar disorder. The issue comprises of CME articles by Dr Jai Ranjan Ram, Dr Siddhartha Nandi, Dr Arnab Pathak, Dr Dipayan Sarkar, Dr Pranab Mahapatra, Dr Rajesh Kumar, Dr Tirthankar Dasgupta. Dr Suddhendu Chakraborty presented a case report followed by Drug Watch Eslicarbazine by Dr Ambarish Ghosh. The Medi quiz was drafted by Dr Pinaki Sarkar.

This Editon contains 52 pages with 14 articles, the decorative cover page was crafted by Dr Suddhendu Chakraborty. We received academic support from Torrent pharmaceuticals for this issue and personally would like to thank all the contributors who have agreed to share their intellectual properties with BJPP.

Long live Bengal Journal of Private Psychiatry

Long Live IAPP West Bengal State Branch

Long live IAPP.



Prof (Dr) Ranjan Bhattacharyya

Hony Editor, BJPP

CME Credit Hours, Continuing Professional Developments and Private Practitioners

Prof (Dr) Ranjan Bhattacharyya, Hony Editor, Bengal Journal of Private Psychiatry

In West Bengal, the **West Bengal Medical Council (WBMC)** has officially mandated that **doctors must earn at least 30 CPD (Continuing Professional Development) credit hours within every five-year period** to be eligible for renewal or updating of their medical registration. A minimum of **30 credit hours over 5 years** is mandatory for license renewal with WBMC. The policy was announced via a WBMC notice dated **April 4, 2025** and is effective immediately from that date. Attendance at **approved seminars, workshops, and CME events** converts time spent into credit hours, typically at a 1 hour = 1 credit point ratio. The exact credit assigned per event depends on the content and duration and is determined by WBMC upon accreditation request. Any CME program must include at least **30 minutes on medical ethics** to qualify for accreditation.

Recently in a directive vide WBMC (Memo no 1493-C/28-2012 dated 24/6/2025) West Bengal Medical Council has laid down certain framework of earning Credit hours. It was mentioned at the very beginning (Page 1, clause 1) that the doctors registered with WBMC, will have to update their registration particulars after every 5 yrs either from date of registration/date of upgradation. The basic question comes here, does a doctor's clinical skill has an expiry date? It was also mentioned that they will have to collect 30 credit hours of CME from organizations registered under Society Act XXVI of 1961. What will be the case if this is organized by a Medical College (Government or Private) or district, subdivisional, rural, block, PHC level as these public set ups doesn't have their society registration.

Those whose validity of certificates expire in a short period of this notification (i.e dt 24/6/2025) and unable to collect the credit hours, they've to produce proportionate credit hours (an example has been cited if updating is done in 2025 and validity of registration is 2027, then proportionately validity of CME credit hours come to 10-12 instead of 30 hours.

S. No.	Registration / Renewal	Credit Point
1.	Whose registration renewal is due on or before 28.02.2025	Exempted from CME Credit Points
2.	Whose registration renewal is due in between 01.03.2025 to 28.02.2026	Shall obtain minimum 10 credit points for the purpose of renewal
3.	Whose registration renewal is due in between 01.03.2026 to 28.02.2027	Shall obtain minimum 20 credit points for the purpose of renewal
4.	Whose registration renewal is due in between 01.03.2027 to 28.02.2028	Shall obtain minimum 30 credit points for the purpose of renewal
5.	Whose registration renewal is due in between 01.03.2028 to 28.02.2029	Shall obtain minimum 40 credit points for the purpose of renewal
6.	Whose registration renewal is due in between 01.03.2029 to 28.02.2030 and 2030 onwards.	Shall obtain minimum 50 credit points for the purpose of renewal

Fig 1: Requirement for registration renewal

Sl. No	Event	Credit Points
1	Faculties of WBMES, Private Medical Colleges & Central Institutes in West Bengal	3 Credit points per year
2	Faculties in Decentralized Institute (having only post graduate course / DNB training)	2 Credit points per year
3	Post Graduate Trainees(MD/MS/DNB) Post Doctoral Trainees (DM,Mch,DNBSS)	2 Credit points per year
4	Senior Residents posted in medical colleges or any teaching institute(PG/DNB)	1 Credit points per year
5	General Duty Medical Officers/ Specialist Medical Officers posted in medical colleges or teaching institutes(PG/DNB)	1 Credit points per year
6	Doctors posted in Rural/Difficult area (as per the latest WB Govt norms)	2 Credit points per year

Fig 2: Designation and credit points earned

Four credit points to be awarded for authorship of a Medical Textbook (not mentioning about its authenticity, publication indexing, publisher details). WBMES faculties who are posted in administrative posts (Swasthya Bhawan, IHFW, WBHRB or faculty under central Government holding administrative posts) will earn four credit hours automatically by virtue of their portfolio per year. This hurt the basic essence of accountability and purpose of earning credit points. The question arises here, why the faculties in administrative posts will earn 4 credit points automatically?

7	Author of Chapter published in Medical Textbook or author of any medical textbook (Published during that 5 years period)	2 Credit points per chapter published. 4 credit point for any textbook published
8 9	Original Article published in any peer reviewed Indexed Journal (All co authors) Case Report published in any peer reviewed Indexed Journal (All co authors)	2 Credit points 1 Credit point
10	For doctors who are part of the editorial /advisor team of any national/ international indexed journal	2 credit points per journal per year
11	Paper presentation of original research article (Oral/Poster) during conferences (National/State/International)	1 Credit point for each paper/poster presented
12	Subscription of peer reviewed Indexed National/International Journals	1 Credit point per year for each journal
13	Speakers/Faculty/Chairman/Co-Chairman at any CME/Workshop	2 Credit point per session
14	For members of the organising committee /team of the CME :- Credit points will be same as the delegates	Additional 1 point
15	For outstation faculties or faculties/ speakers who will only take part in their own designated sessions	2 credit points per session
16	For faculties who stays throughout the entire length of CME as well as contribute to any program schedule for that CME	Credit points will be equal to delegates as well as additional 2 credit points for being speaker / panelist/chairperson.
17	If the faculty is also a part of the organising team he will get additional	1 additional point

Fig 3: Authors, Chairpersons, Editor's privilege

18	Credit Point calculation through the Online CME platform(which is accredited with credit hours)	• 1 Credit point for attending minimum 60 minutes of Online CME • 2 Credit point for attending more than 1 hour of Online CME • 3 credit point for more than 2hr online CME (Maximum 3 credit points can be procured per online CME per day)
19	MSVPs of Medical Colleges CMOHs of different districts	4 credit points per year
20	CMOHs of different districts	3 credit points per year
21	For WBMES faculties who are posted in any administrative post in bodies like Swasthya Bhawan,WBUHS,IHFW,WBHRB or any faculty under central Govt who is holding any administrative post	4 credit points per year
22	Doctors of WBPHAs (apart from CMOHs) and Doctors holding any administrative posts in Central Government institutes in West Bengal (apart from faculties)	2 credit points per year

Fig 4: Privilege of Administrative officers.

Similarly, MSVPs of Medical Colleges will earn 4 credit points automatically. No mention about such privileges for Dean and HODs. Three credit points to be awarded for faculties in Teaching hospitals (UG/PG). CMOH of different districts will earn 3 credit points per year. Therefore, it's evident that, credit hour system of WBMC heavily biased towards doctors in WBPHAC (West Bengal Public Health & Administrative Cadres). As evident from the directives the doctors in WBPHA (apart from CMOHs) and administrative doctors from Central Government posted in West Bengal will earn two credit points.

ALL EXEMPTED CATEGORIES WILL HAVE TO DO RENEWAL OF REGISTRATION.

- Ministers, MPs, MLAs, Public Representatives
- Indian Administrative Services Officers (I.A.S)
- Vice Chancellor of Health University
- Director of Medical Education
- Director Health Services
- Director/Principal of Medical Colleges
- Doctors working with Armed Forces.

Fig 5: Exempted VIP categories

Details of 65 years Exemptions Criteria

Doctors after completing 65 years will be exempted from credit hours but Renewal is mandatory. Doctors will have to comply to credit hour rules by Council till they complete 65 Years of age.

Submission of CME applications

The Organizers of CME should apply at online/offline before 45 days of starting of their programme. In their applications, the following information to be supplied:-

The application should be made addressed to the Registrar, West Bengal Medical Council at least 45 days before the conference with the following information:

- Name of the Organization conducting CME programme;
- Address;
- Society Registration Number with evidence;
- Venue of the Conference;
- Date of the Conference;
- Name of the Faculty with detailed qualification and experience;
- Expected number of attending delegates;
- Topics to be discussed in the Conference;
- Detailed programme schedule mentioning time, subject and name of the Speaker.

Fig 6: Exemption for senior citizens

The policymakers and administrative officers should earn credit points equally. No such extraordinary privileges are given in GMC (General Medical Council) in United Kingdom. The GMC was formed in 1858, 167 years prestigious and leading medical council of the world. The GMC administers the Professional and Linguistic Assessments Board Test (PLAB) which must be cleared by non-european Union overseas doctors before they may practice medicine in the UK as registered doctor.

This discrimination by WBMC for exemption category is not understandable. This is not going to help out the opportunity of upgradation and they will remain 'backdated'. The question arises whether WBMC being a regulatory statutory body can discriminate doctors as Government/Private or different cadres (WBMS, WBHS, WBPHAC) with respect to the upgradation of knowledge? Maximum ceiling of credit hours given 3 points/day to 5 points/day for an online and offline CME respectively and for a conference 10 points in total. West Bengal Medical Council is collecting INR 100 per delegate for registration. In some conferences, CME organizers post 1st July 2025 are asking INR 1000 for registration 100 delegates it amounts INR 1 lakhs. Article publications and paper presentations also have been given credit points but these are self-accomplishment not credit points earned. Credit points are not credit cards. Sole moto of credit hours is for upgradation and upregulation. There shouldn't be any backdoor policy. Signing in the attendance sheet may be manipulated. As mentioned, the council will deploy an observer.

For online CME screenshot at beginning and at the end is mandatory. The attendance varies during different phases of an online CME and a 'ghost attendee' may earn credit points without actual participants. Pharmaceutical company sponsored programs to be excluded from credit points. All the conferences are either directly or indirectly sponsored by pharmaceutical companies as 'unrestricted medical grant' and 'conflicts of interests' fall under the purview of 'Medical Ethics'.

It was also mentioned that 33% credit points may be earned from outside West Bengal. If anyone earns credit points of more than 33% weightage outside West Bengal from centres of National and International importances, they are not eligible. Does higher education have regional biases? Out of the CPD credit hours maximum 35% and 70% may be based on online mode for urban and rural doctors respectively. Again, this is a discrimination which is untoward for. A rural doctor has to give more effort to earn CPDs as one can get maximum 3 credit hours in online mode. The internet connectivity and job challenges in doctors in rural practices are really compelling.

In conclusion, as per WBMC directives the following principles are now recommended

For Organizers:

- Must apply to WBMC at least one month prior to an event, including schedule, speakers, venue, delegate numbers, etc.
- Event organizers must pay Rs. 100 per delegate per day as a deposit before hosting the CME wbmc.wb.gov.in.
- Bundle of documents—attendee certificates, schedule, attendance sheets—must be submitted to WBMC post-event.

For Doctors:

- Only registered medical practitioners are eligible to claim CPD credits (faculty do not count).
- You receive an official certificate stating the approved credit hours for the session.
- Submit these certificates during your next registration renewal process.
- WBMC examines submitted certificates to verify you've reached the 30-hour threshold

As per the Gazette notification by National Medical Commission, Ethics and Medical Registration Board dated 2/8/2023, in page 84, in Guideline 10, Continuous Professional Development Guidelines mentioned in details qwhich has 12 subclauses. In clause 7, there are six important directives to State Medical Council.

7. ROLES AND RESPONSIBILITIES OF STATE MEDICAL COUNCILS:

State Medical Councils have a special role in the conduct of Continuing Professional Development of RMPs. These include:

- Updating and maintain the database/records of RMPs
- Dissemination of CPD activities for RMPs to register
- Auto-reminders of CPD activities to ensure maximum completion of required credit hours, registration of such activities
- suggestions for CPD based on their area of practice/ subject expertise/local epidemiology/ disease patterns etc

[भाग III—खण्ड 4]

भारत का राजपत्र : असाधारण

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- Creation of a portal linked to EMRB for uploading of CPD credit points for each RMP.
 - To get the review of proposed CPD programs submitted by organizers, State Medical Councils are encouraged to use the expertise of the Medical Education Units present in the Medical Colleges of the State.
- State Health Department may also develop CPD for District Hospitals in consultation with SMCs.

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Fig 7: Roles and responsibilities of State Medical Council

Recent Developments in the Pharmacological Management of Bipolar Disorder

Dr Sanjay Garg, HOD – Psychiatry, Fortis Hospitals, Kolkata

Outline

- Bipolar disorder
- Recent Developments in the Pharmacological Management

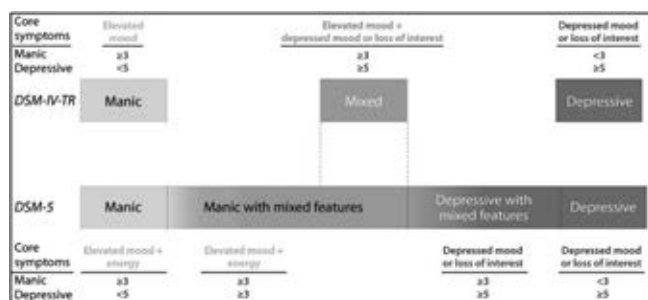
Bipolar “Burden”

- Lifetime prevalence ranges from 0.6 - 2.4% worldwide.¹
- Usually a lifelong disease, hence requiring lifelong treatment strategies.¹
- Often lead to functional impairment and reduced quality of life.²
- Burden extends to family members, including caregiver.²
- Highest suicide rate: 20-times higher than the rate among the general population.²

1. Front Psychiatry. 2020 May 7;11:377. doi: 10.3389/fpsyt.2020.00377.

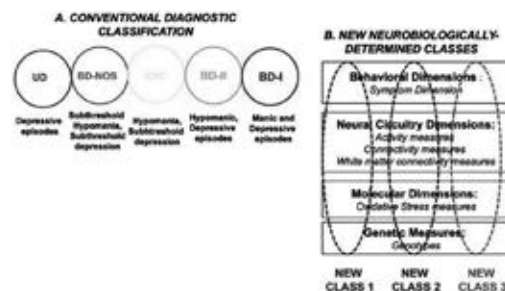
2. Nat Rev Dis Primers. 2018 Mar 8;4:18008.x

Conceptualization of Bipolar Disorders (BD) according to DSM-IV-TR versus DSM-5



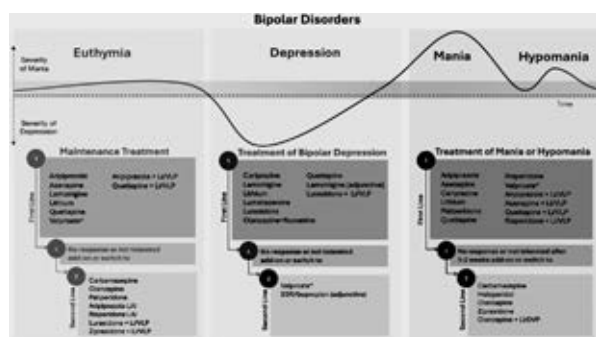
American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th Edition. 2013.

Conventional diagnostic classification criteria for affective disorders compared with neurobiologically defined classes of illness



Lancet. 2013 May 11; 381(9878): 1663–1671

Recent Developments in the Pharmacological Management



Emerging treatment

- Ketamine/esketamine
- Scopolamine
- Dexmedetomidine
- Endoxifen

Ketamine

- Anesthetic, antidepressant, and psychotomimetic agent
- **Mechanism of action:** N-methyl-D-aspartate (NMDA) receptor antagonist
- **Current use:** treatment-resistant, unipolar major depression and suicide ideation, low-dose IV ketamine infusion as a standalone treatment at subpsychedelic dosages
- Antidepressant actions target lack of interest and enjoyment.
- Generally safe and effective for treatment-resistant BD.
- **Adverse effects:** dissociation, elevated pulse and/or blood pressure, headache, nausea, anxiety, changes in vision, and muscle tension; however, these effects are generally well tolerated and usually abate within 2 hours of administration.
- **Dose:** 0.5 mg/kg, IV ketamine has a rapid onset (~30 seconds) and short elimination half-life (~2-4 hours), but its antidepressant effect lasts for 1 week following a single infusion.

US Pharm. 2024;49(5):22-34. BMJ 2023;381:e073591

- The treatment holds superiority over placebo for up to 12 days, with 1-week-long superiority consistently observed in BD patients.
- Small studies have shown comparable effects of intravenous ketamine, in bipolar depression with no short-term evidence of increased mood switching or mood instability. Larger phase 2 studies (NCT05004896) are being conducted which will need to be followed by larger phase 3 studies.
- Although several current clinical trials report promising results with acute use, more are needed to further ascertain the tolerability, safety, and efficacy of long-term use.
- **Frequent IV infusions of racemic ketamine may be intolerable**, so ongoing studies are evaluating the efficacy of esketamine, the L-isomer of ketamine, nasal spray.

US Pharm. 2024;49(5):22-34. BMJ 2023;381:e073591

Scopolamine

- **Current use:** postoperative nausea, motion sickness, and hypersalivation.
- Due to its antidepressant properties, it is being **investigated as a rapid treatment option to reduce depressive symptoms in moderate-to-severe BD**.
- The antidepressant actions of scopolamine were gleaned from observations that physostigmine, a cholinesterase inhibitor, exacerbated depressive symptoms and promoted emotional instability in individuals with BD.
- **Mechanism of action: Scopolamine exerts opposite effects to those of physostigmine by inhibiting postganglionic cholinergic receptors.**
- **As a pan-muscarinic antagonist, scopolamine reduces the hypersensitivity associated with depressive episodes.**

US Pharm. 2024;49(5):22-34.

- Findings from studies examining the utility of IV scopolamine in individuals with schizophrenia are promising and indicate potential for overlapping use in BD with no serious adverse effects.
- **A phase IIb clinical trial investigating the use of IV scopolamine to treat BD is currently under way.**
- **Successful outcomes with IV scopolamine could pave the way for at-home administration as a dermal patch.**

US Pharm. 2024;49(5):22-34.

Dexmedetomidine

- Mechanism of action: selective alpha-2 adrenergic receptor agonist with a quick onset of action and short half-life.
- Its hypnotic action has been leveraged to successfully treat mild-to-moderate agitation
- associated with BD and schizophrenia.
- The noninvasive sublingual formulation (120-mg and 180-mg doses) exhibits no dopaminergic activity, which prevents EPS, such as akathisia and dystonia; these adverse effects are commonly seen with other treatments for acute agitation (e.g., intramuscular benzodiazepines).

- Patients aged ≥ 65 years or with any degree of hepatic impairment should be dose-adjusted accordingly and may require subsequent dosing after initial administration.
- Concomitant use with opioids, hypnotics, sedatives, anesthetics, and medications that may cause QT prolongation should be avoided, as dexmedetomidine is metabolized by cytochrome P450 2A6 (CYP2A6).

US Pharm. 2024;49(5):22-34.

- Encouraging results have been seen in small studies of mania with the selective estrogen receptor modulator endoxifen,
- Hypothesized to inhibit protein kinase C, a potential mechanistic target of lithium treatment.
- Clinical studies remain small.
- Showed early remission as early as day 4.
- Low potential for side effects

BMJ 2023;381:e073591

Novel atypical antipsychotics, amilsupride and bifeprunox

- Currently being tested in phase 3 trials (NCT05169710 and NCT00134459) and could gain approval for bipolar depression.
- These drugs could offer advantages such as greater antidepressant effects, fewer side effects, and better long-term tolerability, but these assumptions must be tested empirically.

BMJ 2023;381:e073591

Other therapies

- Therapies targeting the glutamatergic system: combination of dextromethorphan and its pharmacokinetic (CYP2D6) inhibitor bupropion,
- Recently approved for treatment resistant depression
 - Yet to be tested in bipolar depression
 - Novel GABAergic compound zuranolone is currently being evaluated by the FDA for the treatment of major depressive disorder and could also be subsequently studied in bipolar depression.

BMJ 2023;381:e073591

- Phase 2 academic studies
 - **N-acetylcysteine:** most studied, a putative mitochondrial modulator, which initially showed promising results only to be followed by null findings in larger more recent studies.
 - **Anti-inflammatory Drugs:** small initial studies of anti-inflammatory agents provided impetus for further study, subsequent phase 2 studies for celecoxib, minocycline, and the antibody infliximab (a tumor necrosis factor antagonist) have not shown efficacy for bipolar depression.
 - Secondary analyses have suggested that specific anti-inflammatory agents might be effective only for a subset of patients, such as those with elevated markers of inflammation or a history of childhood adversity however, such hypotheses must be confirmed in adequately powered independent studies.

BMJ 2023;381:e073591

Summary

- Lack of clinical data for early intervention in patients with BD.
- Various treatment options currently available for the management of BD have their limitations.
- Many molecules showing promise in management of patients with BD.

DORAs - Beyond Insomnia

Dr Jai Ranjan Ram, Consultant Psychiatrist

True or False?

- Taking a sleeping pill regularly may prevent dementia?
- Taking a sleeping pill regularly may reduce drug seeking behaviour?

The Basics

- Orexins/hypocretins are neuropeptides that exist in two isoforms
- It is derived from a common precursor (prepro-orexin)
- They were isolated independently in 1998 by two research groups
- The orexin/hypocretin isoforms—orexin-A and orexin-B (hypocretin-2)— are synthesized by a small group of neurons located in the lateral and dorsal areas of the hypothalamus.
- They bind to two G-protein coupled receptors, the orexin-A1 receptor (OX1R) and the orexin-B2 receptor (OX2R)

The two orexin receptors are extensively distributed throughout the brain, supporting a diffuse network of projection fibers that target cortical, subcortical, and brainstem regions, establishing the orexin system.

This system is involved in a variety of behavioural and physiological functions (e.g. energy homeostasis, emotion regulation, and reward),

HOWEVER, it predominantly projects to brain areas involved in the regulation of wakefulness and sleep, such as cholinergic neurons in the basal forebrain and noradrenergic neurons in the locus coeruleus

Role in Sleep-Wakefulness

- In the sleep–wake flip-flop model, orexin neurons facilitate prolonged wakefulness by enhancing the activity of aminergic neurons, which in turn inhibit sleep-promoting GABAergic neurons in the ventrolateral preoptic area.
- Conversely, when orexin neurons are switched to the OFF state, aminergic neurons are not activated and sleep is promoted by the GABAergic neurons.
- In line with these results, orexin neurons discharge has been shown to be more pronounced during wakefulness and almost absent during sleep

The importance of orexin neurotransmission has been recognized by studying narcolepsy type 1, a sleep disorder characterized by the autoimmune- mediated loss of orexin neurons.

This has served as a pathological model of orexin suppression.

Consistent with the role of orexin in the sleep–wake cycle, patients with narcolepsy type 1 experience excessive daytime sleepiness plus other symptoms

Hence suspected Narcolepsy is a contraindication for DORA

- Both OX1R and OX2R play a role in the maintenance of vigilance and wakefulness
- However, while OX2R is mainly responsible for sleep–wake rhythm regulation, OX1R is significantly involved in reward modulation and emotional regulation, in line with its high expression in the locus coeruleus.
- So, co-administration of OX1R and OX2R antagonists showed less sleep-promoting effects compared with a single OX2R antagonist in rats.
- This suggests that sleep-promoting effects could be efficiently achieved by selectively antagonizing OX2R

Sleep Disorders and Neuro-Degenerative Diseases

Alzheimer's and Orexin

- There is evidence in Alzheimer's disease (AD) which shows the correlation of high CSF orexin levels with a more marked sleep impairment
- Consistently, an association between orexin activity, amyloid- β pathology, and circadian sleep–wake rhythm disruptions has been reported
- Sleep promotion has been hypothesized as a therapeutic approach for counteracting the deposition of amyloid- β and the formation of amyloid plaques in the brain

There is potential bidirectional mechanism where orexin dysregulation disrupts sleep, thereby increasing amyloid- β formation, which in turn detrimentally affects sleep, further impacting orexin transmission.

Therefore, in the long-term, countering orexin dysregulation and addressing sleep disruptions could potentially result in a reduction in amyloid- β accumulation

Preclinical studies showed that chronic administration of the DORA Suvorexant reduces amyloid- β pathology and mitigates cognitive impairment as measured by behavioral tests in APP mice

- In addition, a human study documented that use of Suvorexant, the first approved DORA, acutely reduced tau phosphorylation and amyloid- β levels in the central nervous system.
- Contrast with Benzos to be noted

Role in Addiction

- Consistent with their anatomical position within the lateral hypothalamus, orexin neurons were originally identified as playing a key role in feeding behavior, with exogenous application of orexins shown to increase food intake.
- This effect was blocked by antagonism of orexin receptors.
- This role for orexins in appetitive behavior has since been extended to a range of reward-related processes, including drug abuse and addiction

Indirect evidence for a role for orexins in addiction came from a series of interesting clinical observations of patients suffering from narcolepsy with cataplexy.

A number of clinical case studies reported that narcoleptic patients rarely develop stimulant abuse, despite long-term treatment with stimulant medications including amphetamines

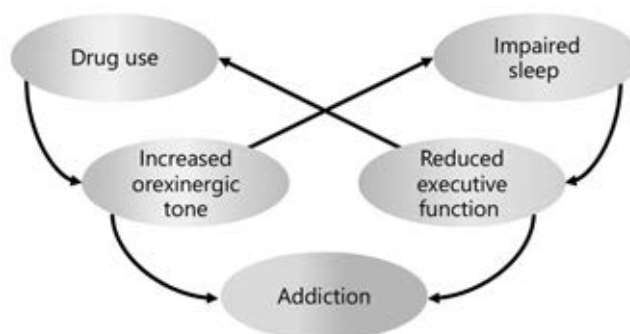
Consistent with this, Georgescu et al. reported that orexin cells are activated after chronic morphine use and withdrawal

In 2005, a research lab implicated orexin signaling in drug-seeking behavior by showing that activation of LH orexin neurons is strongly correlated with conditioned preference for environmental contexts associated with cocaine or morphine use

Orexin neurons translate this “motivational activation” into organized acts of psychological and physiological processes that support adaptive behaviors.

With respect to addiction behaviors, researchers have argued that orexin neurons are not involved in modulating the primary reinforcing effects of drugs of abuse per se, but are critical to regulating motivated responding for these drugs

- In the context of drug-seeking, the orexin system also plays a role in stress regulation.
- Stress is a major contributing factor to the development and maintenance of SUDs
- Stress relief is a common cause of initial substance misuse in healthy individuals .
- In animal models, stress facilitates the acquisition of drug self- administration, craving , and reinstatement of extinguished drug-seeking.
- Orexins play a critical role in modulating behavioral and physiological responses to stress, particularly concerning stress-elicited drug- seeking.
- There is evidence that compounds that block orexin signaling are highly effective at reducing stress-elicited seeking of opioids, stimulants, and alcohol .
- Given the fundamental role of stress in drug addiction, OXR antagonists may effectively treat SUDs by decreasing relapse associated with stressful life events.



OBESITY New understandings of Psychopathology

Dr Siddhartha Nandi, MBBS(Hons), MD Psychiatry,
Post Doctoral Fellowship(PDF) in Child and Adolescent Mental Health (Mumbai)

Outline

- Definition of Obesity
- Association between mental illness and obesity
- Stress, biology and obesity

Definition



- The World Health Organization(WHO) defines obesity as a body mass index (BMI) of 30 or higher in adults.

$$\text{BMI} = \frac{\text{Weight in kilogram}}{(\text{Height in meter})^2}$$

Association between Mental Illness and Obesity

- Adult with serious and persistent mental illness (SPMI) more likely to have obesity, heart disease and diabetes(Chwastiak et al., 2011).
- BMI change over a 5 year period inversely associated with mental health quality of life in both Australian men and women (Cameron, et al. 2011)

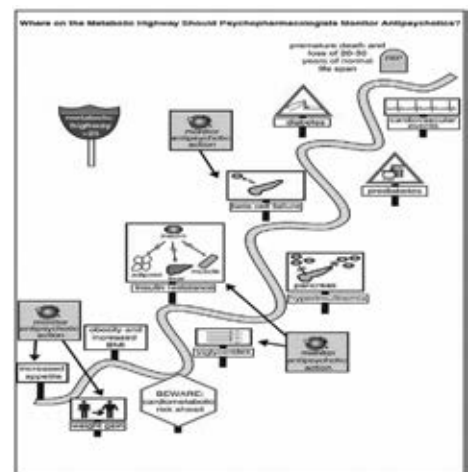
Psychotropic medication

- Psychotropic medications associated with obesity and metabolic disturbance:
- Second generation antipsychotic medication
- High metabolic risk – clozapine, olanzapine
- Moderate metabolic risk – risperidone, paliperidone, quetiapine
- Low metabolic risk – ziprasidone, aripiprazole, lurasidone, brexpiprazole?, cariprazine?

- Mood stabilizers (lithium, valproate)
 - Tricyclic Antidepressants (TCAs)
 - Anticholinergic side effects
 - Selective Serotonin Reuptake Inhibitors (SSRIs) Findings inconsistent
- Generally considered “weight-neutral”

Longitudinal relationship between Mental Illness & Obesity

- Childhood depression associated with overweight & obesity.
- Symptomatology rates depend on informant and method of assessment (maternal and child report often differ)
- Prospective studies show an association between childhood depression and obesity later in life (Goodman & Whitaker, 2002).



Stress, Biology and Obesity

- Hypothalamic-Pituitary-Adrenal Axis (HPA)
- Metabolic Syndrome
- Abdominal fat

In summary • HPA Axis dysregulation has been associated with: Obesity, metabolic syndrome, bulimia, binge eating disorder and anorexia.

Cortisol “the stress hormone”

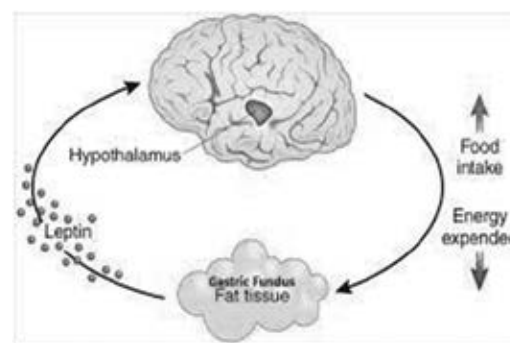
- The principal glucocorticoid.
- Secreted by the adrenal glands.
- Controls the inflammatory response.
- Stimulates insulin release.
- Stimulates gluconeogenesis (creation of glucose) to ensure an adequate fuel supply.
- Increases mobilization of free fatty acids, making them a more available energy source
- Stimulates protein catabolism to release amino acids for use in repair, enzyme synthesis, and energy production
- Acts as an anti-inflammatory agent
- Depresses immune reactions
- Increases the vasoconstriction caused by epinephrine

Cortisol Research Highlights

- Correlations found between Cortisol levels, BMI and waist to hip ratio. (Rosmund et al., 1998)
- Higher levels of cortisol measured in obese females who gained weight in response to a stressful event than age- and weight-matched obese or lean control females (Vicennati et al., 2009)
- Association between depression and BMI was mediated by cortisol reactivity in girls. (Dockray et al., 2009)

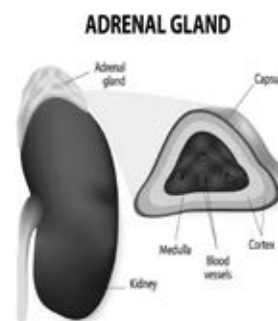
Leptin

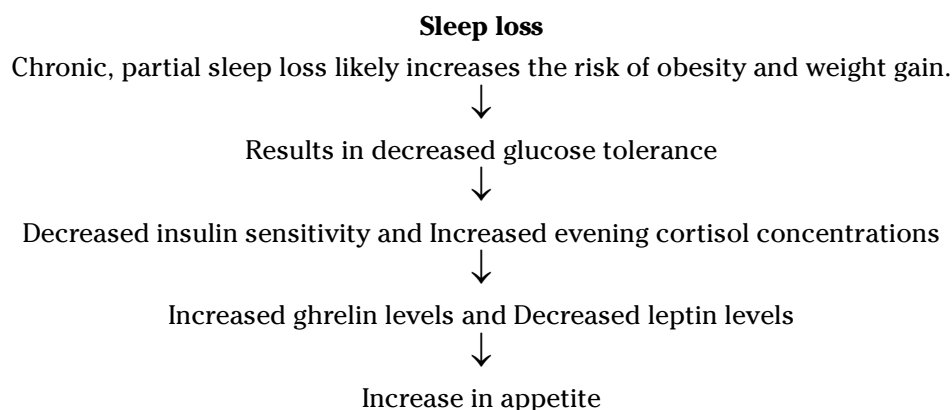
- Amino Acid synthesized in adipose cells and secreted in proportion to fat mass
- Signals CNS regarding fat stores to control food intake
- Part of an asymmetric weight regulating feedback loop
- Decreased Leptin levels from fat loss lower metabolism and reduce sensitivity to meal-ending signals, increasing caloric intake.
- Increased Leptin levels from fat gain do not necessarily lead to appetite reduction.
- Levels show circadian rhythm and are significantly decreased by sleep deprivation
- Several studies have shown that glucocorticoid agonists modulate leptin levels



Ghrelin

- Gastric hormone produced in the stomach and pancreas
- Acts centrally to increase food intake
- Increased levels measured during sleep deprivation
- Inverse relationship with BMI
- Investigation of anti-obesity vaccine in animals
- Problematic due to multiple roles played by ghrelin (learning & memory, tissue repair, muscle repair, bone strength, sleep duration)





The role of exercise

- In addition to burning calories...
- Normalizes cortisol, insulin, blood glucose, growth hormone, thyroid etc...
- May reduce Ghrelin levels
- Psychological Pathways
- Improvements in mood may reduce emotional eating . Annesi and Gorjala (2010) evaluated an exercise program for obesity-Only 19% of mean loss in weight could be directly attributed to caloric expenditure from exercise.

Pharmacologic Intervention?

- Effect sizes for both pharmacological and non-pharmacological interventions are low to medium with non-pharmacological demonstrating slight superiority (Megna et al., 2011)
- Anorectics
- Sibutramine (SNRI) – withdrawn from U.S. and E.U. markets due to adverse cardiac events and stroke
- Phentermine (amphetamine) – psychological dependence, tolerance, rebound weight gain
- SSRI medication - Binge Eating Disorder
- Modest effect sizes
- Low recovery rates
- Combination of medication and psychotherapy associated with better outcome than either alone.

Primary Care Assessment & Intervention

- Assess, educate, target:
- Sleep deficit
- Depression
- Social Support
- Psychosocial stressors
- Intervention appropriate for stage of change
- Treatment must be multidisciplinary
- Partner with a mental health provider

Recent Advances in Schizophrenia Treatment: Focus on Pimavanserine

Dr Arnab Pathak, Consultant Psychiatrist, DESUN Hospital

SINCE THE ERA OF “ A NEW VEGETATIVE (AUTONOMIC) STABILIZER”

Chlorpromazine (Thorazine) was synthesized on 11th dec, 1951 by Paul Charpentier, as a possible potentiator of GA.

- The potential use of CPZ in Psychiatry was first recognized by Henri Laborit (1952).
- Mechanism: Dopamine D2 receptor antagonist.
- Impact: Revolutionized treatment, reduced institutionalization.
- Side Effects: Extrapyramidal symptoms (EPS), tardive dyskinesia.

1960s – Expansion of First-Generation Antipsychotics (FGAs)

Haloperidol (Haldol): - High-potency FGA (1960s).

- Advantages: Less sedation, cost-effective.
- Disadvantages: High risk of EPS.
- Other FGAs: - Fluphenazine, Perphenazine, and Thiothixene.

1970s – Dopamine Hypothesis

Key Discovery: - Excessive dopamine activity in the mesolimbic pathway underlies psychotic symptoms.

Impact: - Reinforced the use of dopamine-blocking antipsychotics. - Guided future drug development.

1980s–1990s – Second-Generation Antipsychotics (SGAs)-

Clozapine (Clozaril): - First SGA (1989).

- Advantages: Superior efficacy in treatment-resistant cases, lower EPS risk.
- Disadvantages: Risk of agranulocytosis. Risperidone (Risperdal): - Introduced in 1993.
- Advantages: Balanced efficacy and tolerability. Olanzapine (Zyprexa):- Introduced in 1996.
- Advantages: Strong efficacy.
- Disadvantages: Metabolic side effects (weight gain, diabetes)

2000s – New SGAs and Long-Acting

Aripiprazole (Abilify): - Introduced in 2002. -

Mechanism: Partial dopamine agonist.

Advantages: Lower risk of metabolic side effects and EPS.- Long-Acting Injectables (LAIs) :-

Examples: Risperidone Consta, Invega Sustenna, Abilify Maintena. - Advantages: Improved adherence, reduced relapse rates.

2010s-Novel Mechanisms and Personalized

- Brexpiprazole (Rexulti) and Cariprazine (Vraylar):- Introduced in 2015.
- Advantages: Improved tolerability, efficacy for negative symptoms.-

Need for advances in pharmacotherapy

Gaps in pharmacologic therapy, need for agents that :

- Future therapies aim to address deficits in cognition and social functioning.
- Are capable of treating negative symptoms
- Improve treatment-resistant schizophrenia
- Have improved Adverse effect (AE) profiles
- Improve adherence



Fellner C. New schizophrenia treatments address unmet clinical needs. P T. 2017;42(2):130-134.

Recent Advances in Schizophrenia Treatment

- Novel antipsychotic mechanisms beyond dopamine blockade.
- Targeting serotonin receptors, glutamate system, and inflammation.
- Pimavanserine as a promising addition.

TAAR1 Agonism

Trace amine-associated receptor 1 (TAAR1) agonists

- Reduces presynaptic dopamine synthesis and release
- Increase glutamatergic signaling in the prefrontal cortex.

The first TAAR1 agonist to reach clinical trials, SEP-363856 (Ulotaront)

- A full TAAR1 agonist
- Ulotaront has shown efficacy in treating schizophrenia in Phase 2 clinical trials. Koblan et al., 2020

Ralmitaront

- A partial TAAR1 agonist .
- Low rates of extra-pyramidal, metabolic, and other side effects
- May improve comorbid metabolic dysfunction in schizophrenia patients
- TAAR1 is a G-protein-coupled receptor (GPCR) that is expressed in cortical, limbic, and midbrain monoaminergic regions. It is activated by endogenous trace amines.

Muscarinic Receptor Agonism

- Stimulation of the M4 muscarinic auto-receptor in the brain reduces acetylcholine release from interneurons reduction in dopamine transmission
- Xanomeline is a preferential M1/M4 muscarinic receptor agonist studied for its probable role in treatment of Schizophrenia . Shekhar et al., 2008
- peripheral muscarinic M1 receptor agonist effects, particularly gastrointestinal (GI; e.g., nausea/vomiting) and syncope.
- Xanomeline was combined with a peripherally active anticholinergic drug (trospium chloride) that does not cross the blood-brain barrier. This combination, xanomeline/trospium chloride known as KarXT is widely studied. Brannan et al., 2021a; Correll et al., 2022b
- KarXT is also currently being evaluated in a phase 3 study as well as in augmentation therapy in patients with schizophrenia with a suboptimal response to their current atypical antipsychotic treatment.

Glutamatergic Modulation

Glycine and D Serine is a necessary co-agonist of the NMDAR.

- A phase 2 study of augmentation therapy with bitopertin, a high-affinity glycine transporter type I inhibitor that blocks glycine reuptake showed benefit for negative symptoms in a per-protocol population (Umbricht et al., 2014
- A phase 2 study of add-on therapy with the potent and selective glycine transporter type I inhibitor iclepertin, demonstrated significant improvements in cognition over 12 weeks of treatment in patients with schizophrenia (Fleischhacker et al., 2021).

- A phase 2 study is evaluating iclepertin added to current antipsychotic therapy and computer-based training for cognitive symptoms of schizophrenia,
- Sodium benzoate was initially studied as a DAAO inhibitor, but it does not appear to impact D-serine levels in vivo, and the exact mechanism of action is unclear (Huang et al., 2023)
- In a phase 2 study, add-on therapy with another DAAO inhibitor luvadaxistat, was not effective for negative symptoms of schizophrenia but showed a signal for improving cognitive symptoms (Murthy et al., 2021)

Serotonin Receptor Inverse Agonist

- Lumateperone
- 60 X higher antagonistic affinity at 5-HT_{2A} than D₂ receptors.
- Presynaptic D₂ receptor agonist + postsynaptic D₂ receptor blocker.
- Increases the phosphorylation of glun2b glutamergic receptors in the limbic system, thus enhancing the NMDA receptor's activity.
- MOA: modulates serotonin, dopamine and glutamate neurotransmission
- Novel treatment agent for SCZ
- Behavioral symptoms in Alzheimer's disease and bipolar disorder

Pimavanserin

a novel antipsychotic approved by the FDA in September 2014 in the treatment of PD psychosis, reducing hallucinations and delusions without affecting motor function,

Mechanism of Action

- Pimavanserin is a potent 5-HT_{2A} inverse agonist and 5-HT_{2C} inverse agonist, with 5-fold greater affinity for the 5-HT_{2A} receptor.
- It blocks the basal (constitutive activity) of the 5-HT_{2A} receptor and
- also has some though limited antagonistic action at the receptor.
- Uniquely, it does not bind to dopamine, histamine, muscarinic, or adrenergic receptors thus is not associated with side effects such as anticholinergic effects, orthostasis, or sedation that are commonly seen with the use of atypical antipsychotics.

Pharmacokinetics

- Median T_{max} – AC - 279 (active metabolite) - 6 hr (4 -24)
- Distribution -
- High protein bound In Human plasma (95%)
- Metabolism - Predominately metabolized by CYP3A4 and CYP3A5 .
- Half-Life Pimavanserin: ~57 hours, AC-279 (Active metabolite): ~200 hours

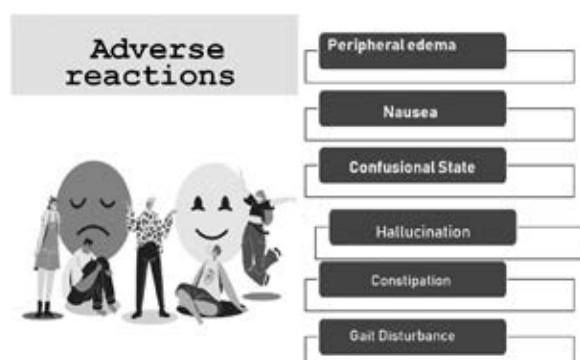
Use in special populations

- **Paediatric Use**
- The safety and effectiveness of Pimavanserin have not been established in paediatric patients.
- **Geriatric Use**
- No dose adjustment is required for elderly patients
- **Hepatic Impairment**
- No dosage adjustment for Pimavanserin is recommended in patients with hepatic impairment based on the exposure differences observed in patients with and without hepatic impairment in a hepatic impairment study.
- **Renal Impairment**
- No dosage adjustment for Pimavanserin is needed in patients with mild to severe renal impairment or end-stage renal disease (ESRD). In a renal impairment study, dialysis did not appear to affect the concentrations of Pimavanserin significantly

- **Pregnancy & Lactation** There are no data on Pimavanserin use in pregnant or lactating women that would allow assessment of the drug-associated risk of major congenital malformations or miscarriage.

Contraindications and adverse effects

- Pimavanserin is contraindicated in patients with a history of a
- hypersensitivity reaction to Pimavanserin .
- Rash, urticaria, and reactions consistent with angioedema (e.g., tongue swelling, circumoral oedema, throat tightness, and dyspnea) have been reported.
- Other adverse effects reported were somnolence, falls, agitation, and aggression.
- Pimavanserin should be avoided in patients with a history of cardiac arrhythmias, symptomatic bradycardia, hypokalaemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval.



Drug interactions

- Concomitant use of Pimavanserin with a strong CYP3A4 inhibitor increases Pimavanserin exposure.
- Concomitant use of drugs that prolong the QT interval may add to the QT effects of Pimavanserin and increase the risk of cardiac arrhythmia;
- Including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin.)

Literature for use in Schizophrenia

- (Pimavanserin for negative symptoms of schizophrenia: results from the A DVA NC E phase 2 randomised, placebo- controlled trial in North America and Europe Bugarski- Kirola, Dragana et al. The Lancet Psychiatry, Volume 9, Issue 1, 46 - 58)
- The change in total NSA-16 score from baseline to week 26 was significantly improved with pimavanserin (least squares mean -10.4 [SE 0.67]) versus placebo (least squares mean -8.5 [0.67]; $p=0.043$; effect size: 0.211). The number of patients with treatment-emergent adverse events (TEAEs) was similar between groups: 80 (40%) patients experienced TEAEs in the pimavanserin group and 71 (35%) in the placebo group.

Conclusion

- Pimavanserin represents a novel approach to schizophrenia treatment.
- Provides an alternative for patients with treatment resistance or side effect concerns.
- Further research needed to optimize its role in clinical practice.

Challenges

- High cost and accessibility concerns.
- Not effective for all schizophrenia subtypes.
- Ongoing research needed for long-term effects and broader use cases

Schizophrenia: New Understanding of Psychopathology

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Email: drdipayans@yahoo.com

Schizophrenia is a **severe mental** disorder, which affects about 0.75% of the world's population (Moreno-Kustner et al., 2018),

Although schizophrenia is a low-prevalence disorder, it was the 12th most disabling disorder among 310 diseases and injuries globally in 2016

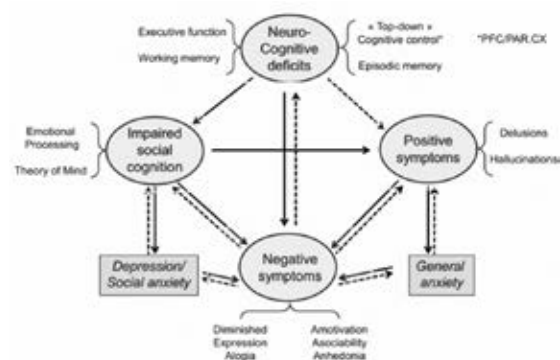
Schizophrenia is characterized by psychosis, an abnormal condition of the mind, which leads to difficulties determining what is real and what is not.

In addition, schizophrenia can include symptoms such as social withdrawal, anhedonia, amotivation, social cognitive impairment, neurocognitive dysfunction (Engelstad et al., 2019, Stratton et al., 2017), and deficits in working memory, processing speed, and executive function.

Schizophrenia is characterized by psychosis, an abnormal condition of the mind, which leads to difficulties determining **what is real and what is not**.

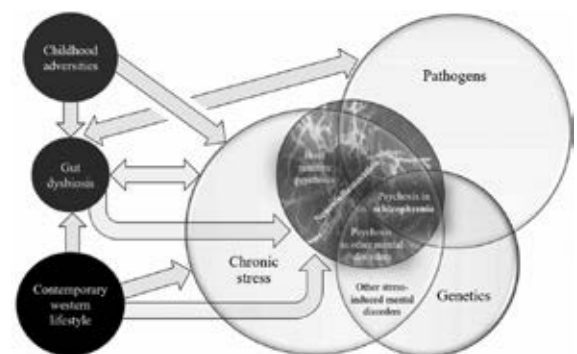
In addition, schizophrenia can include symptoms such as **social withdrawal, anhedonia, amotivation, social cognitive impairment, neurocognitive dysfunction** (Engelstad et al., 2019, Stratton et al., 2017), and **deficits in working memory, processing speed, and executive function**

A meta-analysis reported that a pooled proportion of **6.48% of all homicide offenders** had a schizophrenia diagnosis (Large et al., 2009), which is much **higher than the lifetime prevalence estimates of schizophrenia (0.48–0.75%)**



Recent research suggests **complex interplay** between **genetic factors, brain circuitry disruptions, and environmental influences**,

With a focus on the importance of **cognitive impairments** alongside the traditional positive and negative symptoms, indicating that schizophrenia may be best viewed as a **neurodevelopmental disorder** impacting various brain networks rather than solely a dopamine imbalance.



Key points about the new understanding of schizophrenia psychopathology:

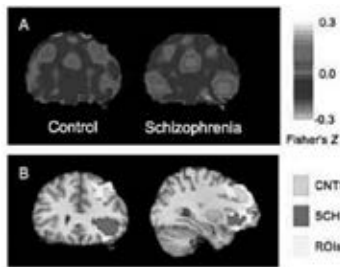
Beyond dopamine:

While dopamine dysfunction remains a significant factor, research now implicates other neurotransmitters like **glutamate and GABA**, **suggesting a more complex neurochemical imbalance** underlying the disorder.

Cognitive deficits as core feature:

Cognitive impairments, **including problems with attention, working memory, and executive function**, are now

recognized as central to schizophrenia and may even **precede the onset of psychotic symptoms**.



Brain connectivity abnormalities:

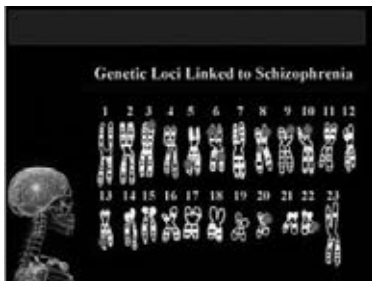
Studies using **neuroimaging techniques** indicate disruptions in brain connectivity, particularly within frontotemporal circuits, which are thought to contribute to both positive and negative symptoms.

Developmental perspective:

Research emphasizes the potential **role of early life experiences and disruptions in brain development** as contributing factors to schizophrenia vulnerability.

Heterogeneity of symptoms:

Recognizing that schizophrenia presents with diverse symptom profiles across individuals, highlighting the need for **personalized treatment approaches**.



The role of genetics:

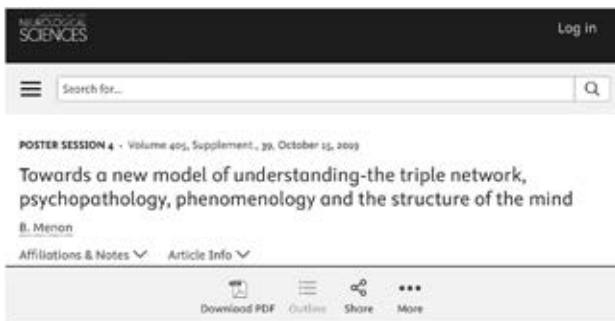
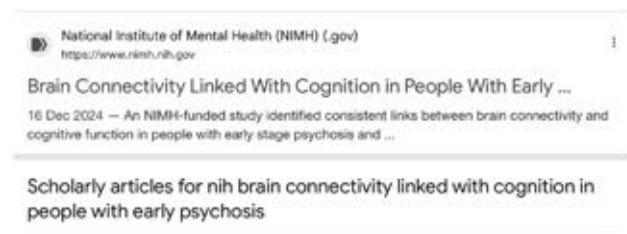
Ongoing research is identifying specific gene variants associated with increased risk for schizophrenia, potentially leading to better understanding of disease mechanisms and targeted therapies.

Early intervention and prevention:

Early identification of individuals at high risk for psychosis, coupled with early intervention strategies, is gaining momentum to potentially **mitigate the severity of the disorder**.

The cognitive difficulties are often early symptoms that appear before the onset of psychosis.

In a study funded by the National Institute of Mental Health, researchers identified consistent links between brain connectivity and cognitive function in people with **early stage psychosis and in people at high risk who later developed psychosis**.



With progress in **neurosciences, neuroimaging** and brain stimulation techniques, mental illnesses are now being seen as **development anomalies at the molecular-structural level** of synapses, resulting in **abnormal cross wiring** in areas responsible for complex cognitive and emotional processing.

These include the multimodal association cortices situated in the **prefrontal lobes, the insula in the temporal lobes, midline cortical structures, and their connections to the thalamus, amygdala and the basal ganglia**.

Three key networks have been identified which are considered

the brain hubs for complex perceptual, emotional and behavior processing

Namely the salience network (SN), the central executive network (CEN) and the default mode network (DMN).

The **triple network** is the final pathway where multiple etiological factors converge to produce the clinical picture in neuro-psychiatric disorders.

A triple network model of aberrant saliency mapping and cognitive dysfunction in psychopathology has been put forward recently and an attempt is being made to understand core cognitive networks and their dysfunction across multiple disorders including **schizophrenia, depression, anxiety, autism and dementia**.

High heritability,

Decreased **reproductive success**.

Chronic stress, low-grade systemic inflammation, and gut dysbiosis, increase susceptibility to schizophrenia.

The new etiological synthesis of schizophrenia indicates that an **interaction between host genotype, microbe infection**, and chronic stress causes schizophrenia, with neuroinflammation and gut dysbiosis mediating this

etiological pathway.

A large **Swedish study** found.....

Males with schizophrenia had **fertility rates** that were as low as 23% of the reference population (accounting for age, sex, and family size), while fertility rates in females with schizophrenia were 47% of the reference population (Power et al., 2013).

This suggests that **causal variants (alleles)** that are associated with increased schizophrenia risk are **more recessive** than expected by chance and are therefore likely to have experienced negative selection over evolutionary time (Zietsch et al., 2015).

This negative selection pressure can be inferred from *directional dominance*, that is, **deleterious alleles having a higher likelihood of being more recessive while beneficial alleles are more likely to be dominant.**

The parasite x genotype x stress interaction model

It supports

etiological puzzle

evolutionary concept

parasitological

psycho-immunological

Role of neuro-inflammation in schizophrenia

Post mortem findings(Trepanier et al,2016)

Elevated marker **SERPINA 3 and IFITM** (interferon-induced transmembrane protein)

Ultra-resistant schizophrenia(UTRS) – chronic low grade peripheral inflammation.

PET studies.

Mongan et al. (2021) tested whether **plasma proteomic biomarkers** could predict if a person at risk for psychosis is likely to develop a psychotic disorder years later.

The method was able to **correctly identify those who would go on to develop a psychotic disorder in 67.8% of high-risk cases, and it correctly identified those who would not in 75.8% of cases.**

Cause Vs. Affect???

The role of pathogens in the etiology of schizophrenia

Toxoplasma

Parasite x and stress x

Other pathogen associated with schizophrenia

Schizophrenia as a disease of modern lifestyle

Schizophrenia becomes linearly more common farther away from the equator and towards colder climates (Kinney et al., 2009).

Urban Vs. Rural !!!

Microbiota and schizophrenia

Gut microbiota is known to modulate brain function and behavior, with **many mental disorders** now being associated with **disturbed gut microbiota.**

This **microbiota-gut-brain axis** signaling influences **brain development, immune homeostasis, blood-brain barrier development, neurogenesis, myelination, dendrite formation, and neurotransmission** (Kelly et al., 2021, Yuan et al., 2019).

Balanced polymorphism hypothesis

Balanced polymorphism hypothesis

The mismatch hypothesis

The social brain hypothesis

Psychosis as an evolutionary adaptation to changing environments

Kin selection: benefit experienced by family members of affected individuals

Schizophrenia, sexual selection, and life history evolution

Conclusion

Current evidence indicates that schizophrenia is **not an evolutionary adaption nor a byproduct of other adaptations** like most previous evolutionary hypotheses of schizophrenia have suggested.

Instead, as **schizophrenia is very rare among people with non-westernized lifestyles** and much more common in people with contemporary western lifestyles, the environmental mismatch hypothesis provides the most plausible evolutionary explanation for schizophrenia.

At a mechanistic level, **chronic stress often seems to be the triggering factor of psychosis, with neuroinflammation, microbial infection(s), and gut dysbiosis mediating this relationship**

Parasites and chronic stress play an important role in the etiology of schizophrenia

Therapeutic interventions aimed at improving cognitive function are being explored as a potential **treatment strategy** for schizophrenia.

New Treatment Approaches in Bipolar Disorder: Lumateperone

Dr. Pranab Mahapatra, Associate Professor in the Department of Psychiatry at Kalinga Institute of Medical Sciences, KIIT University, Bhubaneswar, Odisha

Bipolar disorder is a chronic condition that carries a substantial disease burden.

MDD and bipolar disorder are serious mental illnesses that primarily manifest through severe depressive episodes, substantially diminishing quality of life.

Between 25% and 35% of individuals suffering from MDD or bipolar depression experience major depressive episodes (MDEs) with mixed features, making their clinical presentations more complex.

Depressive episodes are more common than mania or hypomania in both bipolar I and bipolar II disorder.

These episodes are associated with worse prognosis, greater impairment, decreased quality of life, higher morbidity, and increased suicide rates.

Diagnostic Criteria (DSM-5 & DSM-5-TR) The mixed features specifier :

Presence of three or more of the following seven symptoms

- Elevated Mood
- Inflated Self-Esteem
- Increased Talkativeness
- Racing Thoughts
- Increased Energy or Goal-Directed Activity
- Engagement in Risky Activities
- Decreased Need for Sleep

First-Line Monotherapy Recommendations for Bipolar I Depression:

Mood stabilizers such as lithium, lamotrigine, and valproate.

Second-generation antipsychotics such as quetiapine, lurasidone, and cariprazine.

Note: Limited studies and recommendations for bipolar II depression.

Use of Mood Stabilizers in Maintenance Therapy:

Mood stabilizers are used continuously to prevent episodes of depression and mania.

However, breakthrough episodes of depression frequently occur during maintenance monotherapy with mood stabilizers.

Role of Modern Antidepressants:

- Used as adjunctive therapy to treat acute depressive episodes in bipolar disorder.
- Efficacy not extensively studied or established.
- Associated with the potential risk of inducing a manic or hypomanic switch.

FDA-Approved Antipsychotics as Adjunctive Therapy:

Antipsychotics like lumateperone and lurasidone have been studied and approved as adjunct treatments to lithium or valproate for depressive episodes associated with bipolar I disorder.

Antipsychotics approved for the treatment of bipolar I depression include lumateperone, quetiapine, olanzapine/fluoxetine combination, lurasidone, and cariprazine.

Lumateperone and quetiapine are also approved for the treatment of bipolar II depression.

Need for New Treatments:

There is an urgent need for new treatments that are both efficacious and exhibit favorable tolerability.

These treatments are needed as both monotherapy and adjunctive therapy with mood stabilizers for managing depression in patients with bipolar I or II disorder.

Side Effects of Antipsychotics:

Many antipsychotics are associated with a considerable side effect burden.

Common side effects include weight gain, extrapyramidal symptoms (EPS), and metabolic abnormalities, which may reduce their tolerability.

FDA Approval and Use: Lumateperone

Lumateperone (lumateperone tosylate, ITI-007) is approved by the US Food and Drug Administration (FDA) for treating schizophrenia and depressive episodes associated with both bipolar I and bipolar II disorder. It is approved for use both as monotherapy and as adjunctive therapy with lithium or valproate.

Mechanism of Action:

Lumateperone acts by modulating several key neurotransmitters involved in serious mental illnesses.

It functions as a potent serotonin 5-HT_{2A} receptor antagonist, a dopamine D₂ receptor presynaptic partial agonist and postsynaptic antagonist, and a D₁ receptor-dependent indirect modulator of both AMPA and NMDA currents.

Additionally, it serves as a serotonin reuptake inhibitor.

Other Features:

Lumateperone shows negligible binding to H₁ histaminergic, 5-HT_{2C}, and muscarinic receptors, which minimizes potential adverse cognitive effects and metabolic disturbances, including weight gain.

It features a significant separation in binding affinities, approximately 60-fold, between the 5-HT_{2A} and D₂ receptors.

It exhibits lower striatal D₂ receptor occupancy (39%) at clinically relevant doses compared to other antipsychotics, which typically show 65%-80% occupancy.

The presynaptic partial agonist activity at D₂ receptors helps in reducing the risk of extrapyramidal symptoms (EPS).

STUDY/TRIAL	STUDY DESIGN	KEY FINDINGS
Calabrese et al. (2021) (Phase 3 Monotherapy Trial)	Randomized, double-blind, placebo-controlled, multicenter, monotherapy trial	Significant improvement in depressive symptoms (MADRS and CGI-BP-S) in bipolar I and II depression.
Calabrese et al. (2023) (Phase 3 Adjunctive Therapy Trial)	Randomized, double-blind, placebo-controlled, multicenter, adjunctive therapy (with lithium/valproate) trial	Lumateperone 42 mg significantly improved depressive symptoms (MADRS and CGI-BP-S) when added to mood stabilizers.
McIntyre et al. (2020) (Post hoc analysis of Phase 3 Trial)	Post hoc analysis of randomized, placebo-controlled trial	Effective in reducing depressive and mixed symptoms, with favorable tolerability profile.

Abbreviations: MADRS: Montgomery–Åsberg Depression Rating Scale, CGI-BP-S: Clinical Global Impressions Scale–Bipolar Version–Severity

Lumateperone: study findings and advantages:

Effective in Reducing Depression Symptoms: Lumateperone 42 mg significantly improves MADRS total scores and CGI-BP-S depression subscores as an adjunct to mood stabilizers.

Safety and Tolerability:

Low incidence of extrapyramidal symptoms (EPS).

Minimal impact on weight and metabolic parameters.

Suicidal Ideation: Lower rates of suicidal ideation in the Lumateperone groups compared to placebo.

Quality of Life Improvements: Treatment associated with enhanced quality of life.

Promising Add-on Therapy: Lumateperone 42 mg shows potential as an effective adjunctive treatment for bipolar I or II depression.

Conclusion

Effective Treatment: Lumateperone significantly improves depressive symptoms in bipolar disorder.

Safe and Tolerable: Comparable adverse effects to placebo, with minimal EPS and metabolic impacts.

Reduces Suicidal Ideation: Notably lowers rates of suicidal thoughts.

Enhances Quality of Life: Patients experience improved life quality.

Promising Add-On: Effective as adjunct therapy, with potential for broader use.

New Understanding of Psychopathology

Dr Rajesh Kumar, Professor & Head, Department of Psychiatry, IGIMS, Patna

What is psychopathology?

- "Psycho" refers to "mind"
- "Pathology" refers to "disease"



- It is the field of study that deals with mental, emotional and behavioural problems.
- It involves research into the classification, diagnosis, causation, prevention and treatment of psychological disorders.

Understanding Psychopathology

- Behaviors appears
 - Unpredictable
 - Irrational
 - Harmful
 - Deviate from accepted contemporary social norms
- Many forms of psychopathology are accompanied by what appear to be changes in the individuals personality or behavior

The Four Ds of Abnormality

- Deviance • Distress • Dysfunction • Duration

The Triad of Psychopathology

Complex psychiatric disorder characterized by dysfunction in three domains including emotional processing, cognitive processing, and psychomotor dimensions

Evolution in the understanding of psychopathology

- Supernatural • Magico-religious • Spiritual • Sociocultural • Psychological • Biological

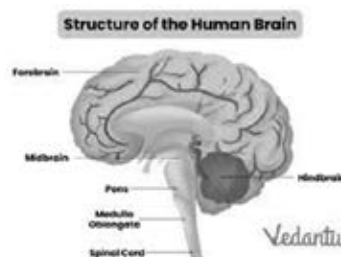
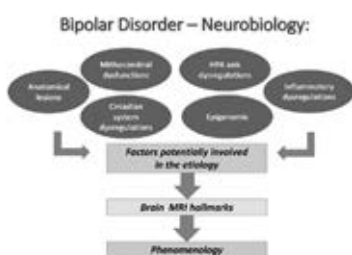
Bio-psycho-social paradigm

- Genetics • Environment • Social interactions

Highly heritable and have shared susceptibility genes with schizophrenia

- Psychosocial stressors and family dynamics
- Bio-psycho-social emotion theory suggests that people with bipolar disorder are overtly sensitive to stimuli related to goals and rewards

Neurobiology



- Brain and Behaviour • Neuroimaging and neuropathology • Neurotransmitter dysregulation

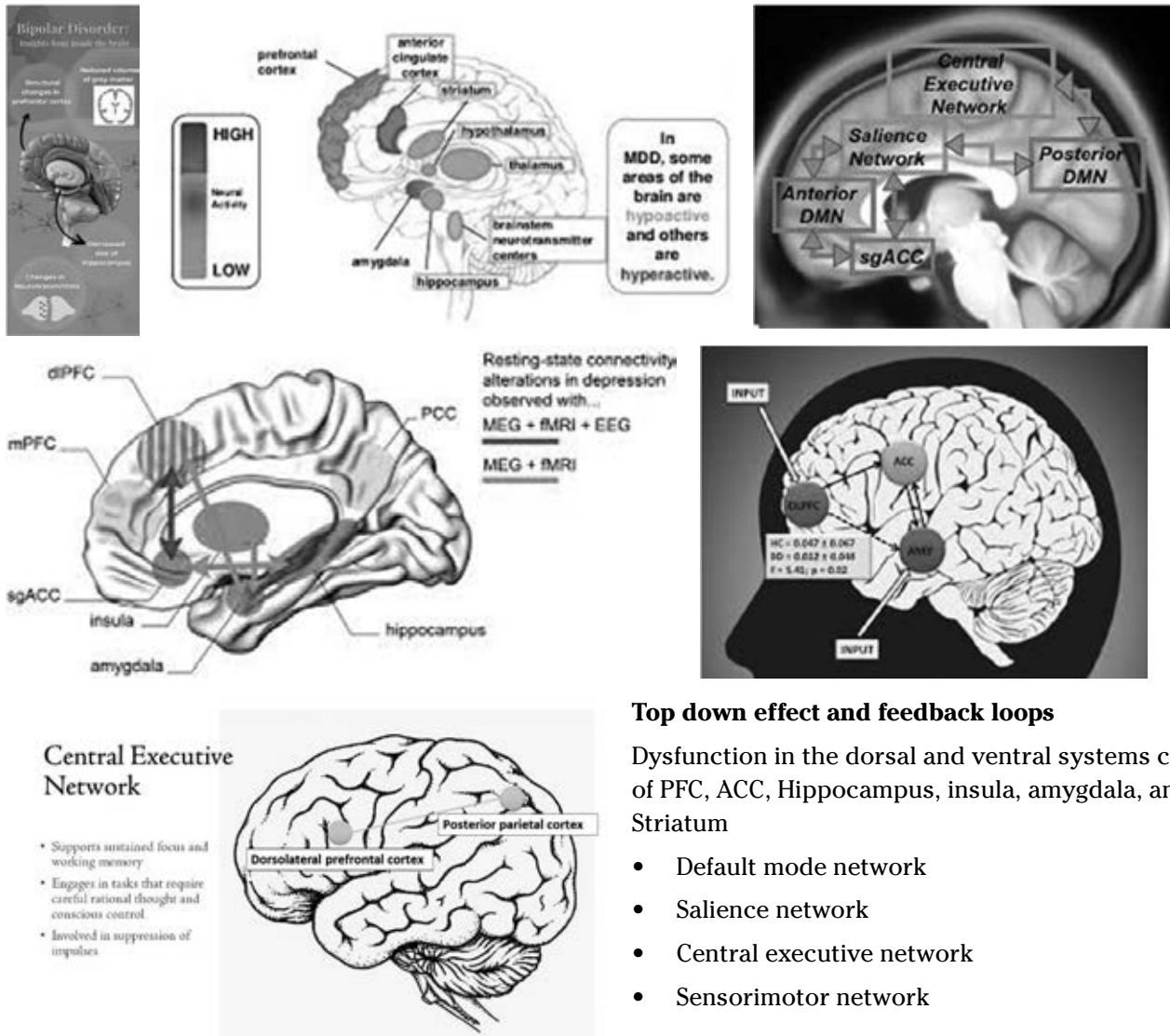
>> Serotonin >> Dopamine >> Norepinephrine

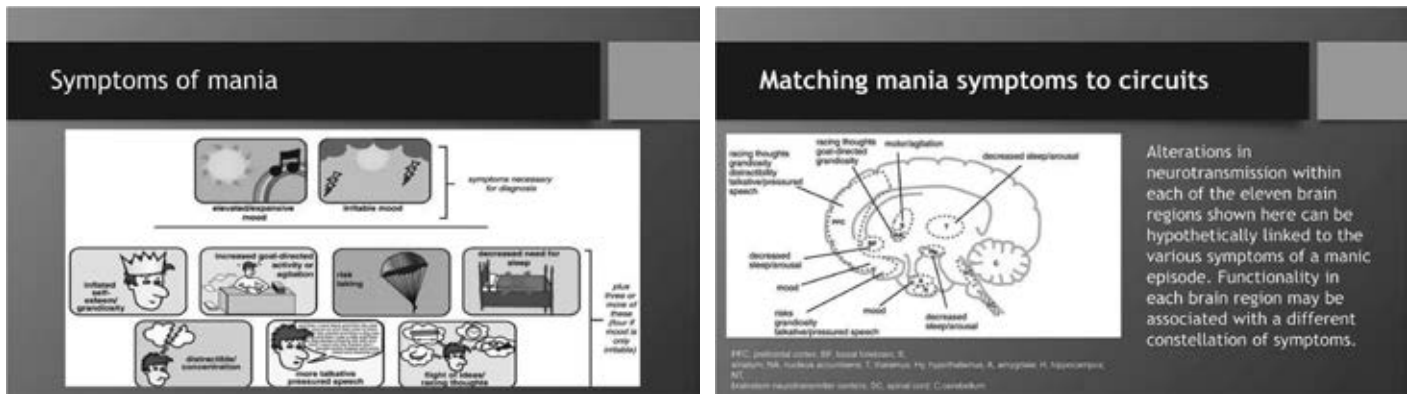
Excess versus deficit or excitatory versus Inhibitory • Neuro-circuit • Hyperactive versus Hypoactive circuits

Interplay of Circuits and Chemicals

- Fronto-limbic network • Sensorimotor network • Salience network • Default mode network
- Central executive network • Basal ganglia-thalamo-cortical motor circuit

Important ties between cognitive deficits, the emotional and psychomotor disturbances





Emotional regulation and processing dysfunctions of neural network in BD

Emotional hyper-reactivity and mood instability

- Excessive reactivity to negative events
- Abnormality in fronto-limbic connectivity
- Prefrontal cortex and its divisions and its connections to subcortical regions
- Hyperactive ventral with hypoactive dorsal systems
- Dysregulation of amygdala by PFC

Cognitive alterations of neural network in BD

- Common cognitive deficits
- Cognition – emotion interaction
- DMN and CEN and SN and SMN
- White matter changes and brain network imbalances

Psychomotor alterations of neural network in BD

- Distinct patterns of alterations in the SMN, DMN and CEN
- Cortico-striatopallido-thalamocortical loops

Conclusion

- Better understanding of BD with respect to clinical management
- Core problem lies in fronto-limbic circuit
- SMN, DMN, SN and CEN
- Basal ganglia thalamo-cortical motor circuit
- Biomarkers and Endo-phenotypes
- State versus trait changes
- Better treatment strategies, Neuromodulation

Revisiting Schizophrenia: A Spectrum Concept

Dr. Tirthankar Dasgupta, Consultant Psychiatrist, Email: drtirthankar@moneralo.com

Objectives:

- Understand limitations of categorical diagnosis
- Highlight neurobiological and clinical implications
- Explore schizophrenia as a spectrum
- Discuss shifts in diagnosis and management

Historical Perspective

- Kraepelin's Dementia Praecox vs. Bleuler's Schizophrenias
- DSM/ICD categorical evolution
- Limitations of past models

Phenotypic Continuum

- Continuum of core symptoms
- Subthreshold psychotic symptoms in general population
- Clinical staging perspective

Spectrum Across Time

- From prodrome to residual
- Dimensional severity scales (DSM-5)
- Focus on functional outcomes

Diagnostic System Challenges

- ICD-11 dimensionality
- DSM-5 specifiers
- Debate: is the term obsolete?

Ethical and Sociocultural Perspectives

- Labeling and stigma
- Cultural context of psychosis
- Spectrum view as a destigmatizing tool

Summary Takeaways

- Spectrum concept is evidence-based
- Informs early diagnosis and personalized care
- Urges evolution in psychiatric thinking

The Spectrum Concept

- Dimensional vs. categorical views
- Spectrum includes schizotypal, schizoaffective, and subthreshold psychosis
- Fuzzy diagnostic boundaries

Neurobiological Evidence

- Brain imaging: gradients in gray matter loss
- Shared genetics with bipolar disorder
- Functional connectivity patterns

Clinical Implications

- Importance of early intervention
- Risks of misdiagnosis
- Use of psychosocial and pharmacological strategies

Treatment Reimagined

- Precision psychiatry approach
- Stage-specific psychosocial interventions
- Neurocognitive remediation

The Future: Integrative Psychiatry

- RDoC and network models
- AI and computational psychiatry
- Need for multidimensional diagnosis

Discussion

- Is schizophrenia a valid term?
- How to apply spectrum thinking clinically?
- Impacts on service models?

Cognitive Bibliotherapy as a crucial annex to Psychotherapy in a case of Major Depressive Disorder: A Case Report

Dr. Suddhendu Chakraborty, Consultant Psychiatrist, Dr.BN Bose Subdivisional Hospital, Barrackpur, West Bengal

Abstract: Bibliotherapy has long remained a significant tool in dealing cases with subtle affect disorders as well as dealing with periodic mental illnesses. However its role in dealing with cases of psychiatric disease entities like Major Depressive Disorder is largely restricted. In this case report, an young adult female suffering from multiple self harm attempts, severely depressed receiving antidepressants, mood stabilizers and augmenting antipsychotics with concurrent Cognitive Behaviour Therapy was also encouraged with Bibliotherapy, and in course of time, the intervention seemed to be effective with follow up visits and subsequent observation. The case confirms that Bibliotherapy indeed can be an effective annexure in a few selective cases along with conventional psychopharmacotherapy.

Keywords: Bibliotherapy, Psychotherapy, Major Depressive Disorder

Introduction:

Bibliotherapy and Psychiatry has long been interrelated. It has long remained an adjunct for treating mental illnesses like anxiety, and depression (1). Books have long been referred to as “the medicine of the mind” (2) at Alexandria’s Library. The process of reading books and healing mind is being described as ‘bibliotherapy’ since early 20th Century. Burt (1973) asserts, bibliotherapy acts by achieving insight, verbalizing problems, externalizing problems, identifying with a character or experience towards attainment of an abreaction, and subsequent constructive thinking. (3) Bibliotherapy in synchronisation with cognitive strategies have often been used to treat clinically significant depression as cognitive behaviour therapy. In a Metaanalysis consisting of 29 studies, 17 studies show a strong study design and positive outcome. (4) Further, a systemic study revealed a long term effect of bibliotherapy in treating depression. 1347 subjects were studied, and results revealed positive results in favour of bibliotherapy. (5) In this case report, a young adult woman suffering from Major depressive disorder was studied. Cognitive bibliotherapy was applied and the outcome was found to be significantly satisfactory.

Case:

A 24 year old Hindu unmarried female, appeared in the hospital outpatient department with a long standing history of low mood for 4 years, marginal anxiety, recurrent suicidal thoughts, multiple Deliberate Self Harm (DSH) attempts, the last of which had been 3 weeks back. She was into multiple relationship since the age of 16 years. Her first sexual exposure was at the age of 17 years, which was not consensual, and had incestual connections, which remained unreported, following which she lapsed into a deep state of morose. However, she cleared boards, and entered college following which she entered into a relationship that lasted 2 years. After breakup, she had a brief psychotic episode lasting 13 days with her first DSH attempt following which she was taken to a psychiatrist and put on venlafaxine, lithium and aripiprazole. The psychotic breakdown subsided, but the depressive symptoms continued to persist.

After 3 months of medication, she stopped taking the medicines on her own without any definite cause. Meanwhile her parents got separated. Her mother reportedly got involved with someone following which there were frequent quarrels at home. After separation, her father became an alcoholic and repeatedly started abusing her verbally. However she got involved in a new relationship with a married man, much older to her age. The relationship lasted 8 months. During the later half, she was repeatedly abused, both verbally and physically. But she accepted the abuse with the saying “it reminded me of my father’s torture”. After the relation ended abruptly, she tried to slash her

wrist, hospitalised, later released, but started staying extremely withdrawn, with no appetite and sleep. She used to be a regular columnist in a few little magazines, and also a poet. But after the last breakup she stopped each one of those. She was again brought back to a psychiatrist, who restarted psychotropics, this time mirtazapine, vortioxetine, lithium and amisulpiride. The dose was escalated, leading to extreme sedation, lethargy, tremor. She was checked for haemodynamics, glycemic control, hypertension and thyroid status, all of which came out to be normal. She came to my clinic at this stage. A written informed consent was taken prior to the interview. Mental Status Examination showed flattened affect, with a profound loss of prosody, nihilistic ideations, self harm thoughts, feeling of a generalized hopelessness and numbness; there were no hallucination, but occasional mood congruent delusions; her insight was fairly poor ranging in between grade 2 and 3. Her initial Beck Depressive Inventory II (BDI-II) score was 48. Dosage of her psychotropics were optimised. She was started on concurrent Cognitive Behaviour Therapy (CBT). After 4 initial sessions and her refusal to respond to Thought Affect Diary writing, I suggested her to read Viktor E Frankl's 'Man's Search for Meaning'. To encourage her reading, there was a small group narrative session where parts of the book were read out. After 3 sessions, she admitted she has started reading the book, but her negative feelings are persisting. After 6 sessions over a period of 3 weeks, she reported an improvement. BDI II Score at that stage was still 35. After 3 months, she came back with her father. She had joined her studies, which she had quit after her last breakup. She was gaining energy and was thinking of writing a novel with a young adult girl as the protagonist. The BDI II score was 30. After 9 months of combined pharmacotherapy, CBT and Cognitive Bibliotherapy sessions, she showed substantial improvement at BDI II 23. Her provisional diagnosis was Major Depressive Disorder with predominant suicidal ideations in a case of adult female with prominent Cluster B traits and Multiple social stressors, poor peer and family support and absence of any Substance Abuse.

Discussion

BDI II is a reasonable tool to measure Clinically Significant depression in a person. (6) The score in this case changed from 48, which indicated Severe Depression to 23 which fell into the Moderate Depression Category. The patient did not show improvement while on medicines and CBT alone for 8-12 weeks. Her BDI II Score remained static. The choice of books in Cognitive Bibliotherapy is crucial. It should match the patient's interest, and preferences. Also the book should be able to deliver a positive message towards attaining a goal in the therapy. Choosing self-help books and preferring hard copies rather than soft ones have been strongly suggested by studies. (7) The rationale behind choosing Viktor Frankl's 'Man's Search for Meaning' was also because the book masterminded the author's legendary story of survival, resilience and come back from a World War nightmare in an autobiographical note. The book also encompasses Frankl's own idea of a separate genre of psychotherapy namely 'logotherapy'. Logotherapy is defined as a therapy that concentrates towards finding the 'meaning of life'. The inner philosophy of the chosen book revolves around an existential analysis of different lifetime crises. Studies suggest that logotherapy itself can reduce anxiety, promote hope and reduce clinical depression. (8) Also Studies suggest that Logotherapy can be a bridge between CBT and positive Psychology. (9) The client in discussion was a perfect candidate for bibliotherapy as she was once herself an author. Further Frankl's book on Logotherapy opened avenues of hope and newer opportunities in her situation that triggered an improved response to an already undergoing CBT and Pharmacotherapy.

The case is unique because firstly in this case cognitive Bibliotherapy proved to be an effective intervention in treating a difficult case of depression. Also follow up assessment showed a substantial decrease in suicidal thoughts in the patient, feeling of hatred towards parents and opposite gender and impulsivity was substantially reduced. This proves the role of bibliotherapy as an augmenting agent to conventional psychotherapeutic tools. The fact that client restarted writing a novel with supposedly her projected self as a protagonist also opens avenues of discussion as to whether bibliotherapy can also annex different forms of Expressive Behaviour Therapy. Bibliotherapy as study suggests is particularly effective in inducing expressive writing in paediatric age group. (10) Expressive writing in turn addresses many areas of cognitive, social and executive brain functioning. (11) The approach may also open further scope to start a creative writing group, which increases attention, goal direction. (12)

Conclusion:

The case discussion bridges the research gap that is created exploring possible use of cognitive bibliotherapy in treating mental illness like depression especially in an Indian scenario. Scattered research suggests bibliotherapy can

be an effective intervention in tackling anxiety and clinical depression.(13,14,15) Further enumeration of similar cases may actually open avenues for further research and more in depth statistical analysis, which remains future prospects in this case.

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NEWER treatment Approaches in Obesity management ... (Pharmacological)

Dr Utpal Bora, ASSOCIATE PROFESSOR, Dept. Of Psychiatry; Pragjyotishpur Medical College and Hospital; Guwahati, Assam.

OBESITY

Defined as an excess accumulation of fat in the Body.

- 25% or greater total body fat- Men
- 35% or greater- Women

Definition

Obesity may be defined as an abnormal growth of the adipose tissue due to an enlargement of fat cell size {hypertrophic obesity} or an increase in fat cell number {hyperplastic obesity} or a combination of both

Epidemiology

Obesity > “Global public health threat.”

According to WHO, 2 billion people (44% of global adult population) classified overweight worldwide, 3% of Indian population- obese

India is just behind US and China among top 10 countries with highest number of obese.



40% in women and 12% in men.

5–6 out of 10 women between the ages of 30–49 are abdominally obese.

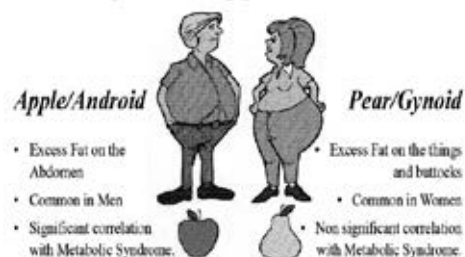
More obesity urban residents, wealthier sections, and non-vegetarians. On the rise in rural areas.

(NFHS 5; 2019-21)

Measurement of Obesity:

- Height-weight chart • Body Mass Index (BMI)
- Waist Circumferences
- Waist to Hip ratio • Skinfold thickness
- Bodyline Method.

TYPES OF OBESITY – Are you an Apple or a Pear ??



Assessment of obesity

- BMI grading: internationally comparable

Classification	BMI	RISK of comorbidities
underweight	<18.5	Low, but risk of other clinical problems increased
Normal	18.5 – 24.99	Average
Overweight	>_ 25	
Pre - obese	25 - 29.9	Increased
Obese class I	30 – 34.9	Moderate
Obese class II	35 - 39.9	Severe
Obese class III	>40	Very severe



WHAT CAUSES OBESITY???

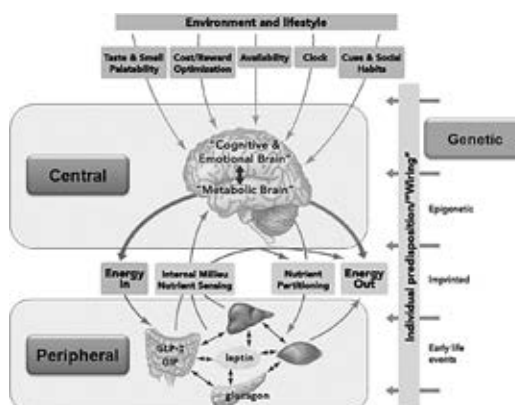
Pathophysiology

Long-term sedentary lifestyle and/or > calorie intake > Imbalance between energy expenditure & energy intake

- > Adipocyte hypertrophy > Increases adipocyte volume & increases lipid storage
- > Visceral & subcutaneous fat accumulation > Alterations of adipokines (Lipase)
- > Overweight or Obesity

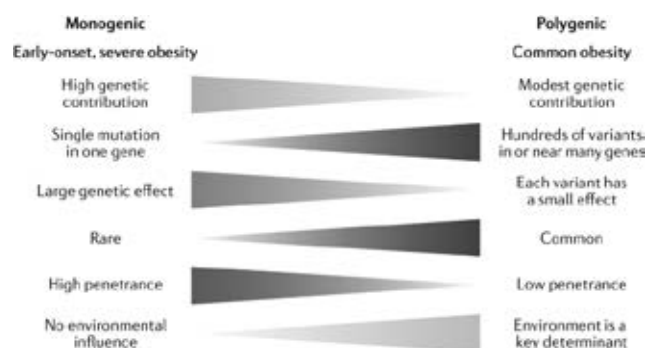
Energy regulation and obesity pathophysiology

Figure Adapted from Zheng & Berthoud et al. Physiology. 2008;23 75-83



Obesity And Genetics

- 20-25%
- How genes contribute to obesity???
 - One/ more abnormality of pathway regulating feeding center
 - Abnormality of energy expenditure and fat storage

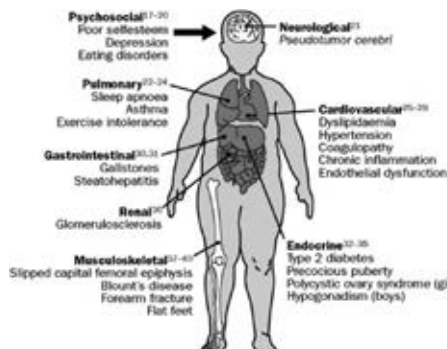
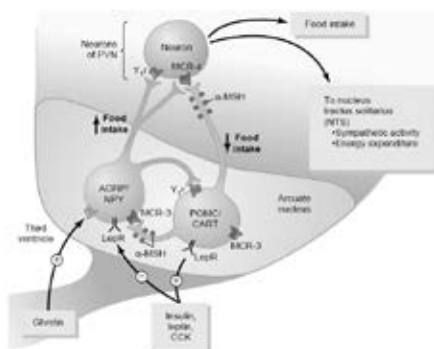


Decrease Feeding (Anorexigenic)

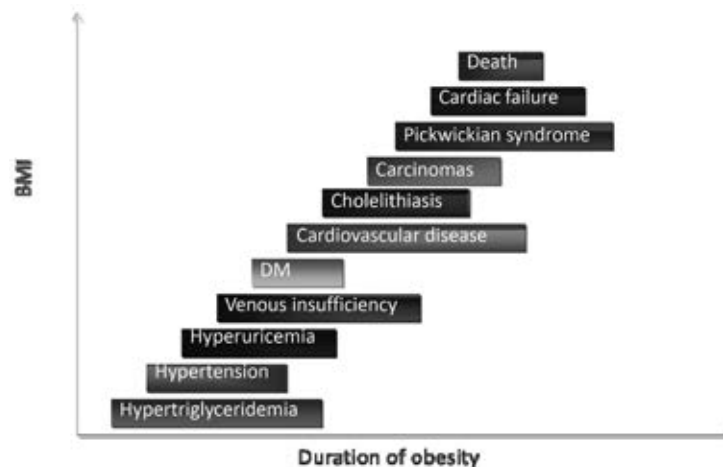
α -Melanocyte-stimulating hormone (α -MSH)
 Leptin
 Serotonin
 Norepinephrine
 Corticotropin-releasing hormone
 Insulin
 Cholecystokinin (CCK)
 Glucagon-like peptide (GLP)
 Cocaine- and amphetamine-regulated transcript (CART)
 Peptide YY (PYY)

Increase Feeding (Orexigenic)

Neuropeptide Y (NPY)
 Agouti-related protein (AGRP)
 Melanin-concentrating hormone (MCH)
 Orexins A and B
 Endorphins
 Galanin (GAL)
 Amino acids (glutamate and γ -aminobutyric acid)
 Cortisol
 Ghrelin



Complications associated with Obesity



Evaluation and Management of Obesity

The Obesity-Focused History

- What factors contribute to the patient's obesity?
- How is the obesity affecting the patient's health?
- What is the patient's level of risk from obesity?
- What does the patient find difficult about managing weight?
- What are the patient's goals and expectations?
- Is the patient motivated to begin a weight management program?
- What kind of help does the patient need?

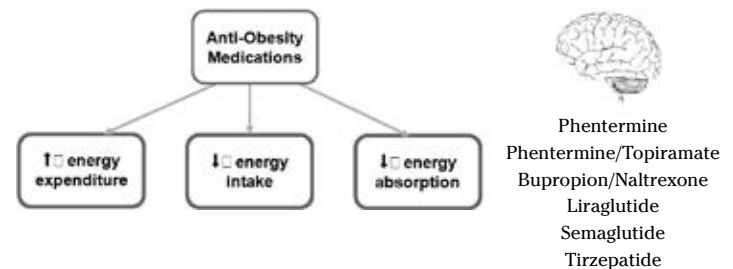
Treatment

- Prevention • Diet • Increased physical activity • Behavior modification • Medicines • Surgery

Guide To Treatment Options

Treatment	BMI Category (kg/m ²)				
	25-26.9	27-29.9	30-34.9	35-39.9	≥40
Diet, exercise, behavioral therapy	With comorbidities	With comorbidities	+	+	+
Pharmacotherapy	—	With comorbidities	+	+	+
Surgery	—	—	—	With comorbidities	+

Mechanisms of anti-obesity medications



Recommended if BMI ≥ 27 with comorbidities **or** BMI ≥ 30

FDA-Approved Medications for Weight Management

Name	Year of approval	Mechanism of action
Phentermine	1959	Sympathomimetic/suppresses appetite
Diethylpropion	1979	Sympathomimetic/suppresses appetite
Orlistat	1999	Intestinal lipase inhibitor/ reduces fat absorption
Phentermine-Topiramate	2012	sympathomimetic + Carbonic Anhydrase inhibitor/ decreases appetite and binge eating behaviour.

Name	Year of approval	Mechanism of action
Bupropio-Naltrexone	2014	DA and NE Reuptake inhibitor + mu opioid receptor antagonist/decreases appetite and cravings
Lirglutide 3.0	2014	GLP 1receptor Agonist/ decreases appetite, increases fullness, increases satiety
Gelesis	2019	Superabsorbent hydrogel particles of a cellulose-citric matrix/Increases fullness. A medical device rather than functions as a medication
Setmelanotide	2020	Melanocortin 4 receptor agonist/ decreases appetite
Semaglutide 2.4	2021	GLP 1receptor Agonist/ decreases appetite, increases fullness, increases satiety
Tirzepatide	2023	GLP 1 and GIP receptor agonist/ Decrease appetite,increases fullness, increases satiety

Pharmacotherapy

Centrally Acting Anorexiant Medication

- Anorexiants increases satiety and decreases hunger, these agents help patients reduce caloric intake without a sense of deprivation.
- Targets the ventromedial and lateral hypothalamus

Peripherally acting Anorexiant Medication

(Gastrointestinal fat blockers): Blocks the digestion and absorption of Dietary fat.

Phentermine and Diethylpropion

Approved short-term drug for treating obesity

First FDA-approved short-term medications for weight loss and remains available today

Phentermine is a sympathomimetic anorexigenic agent

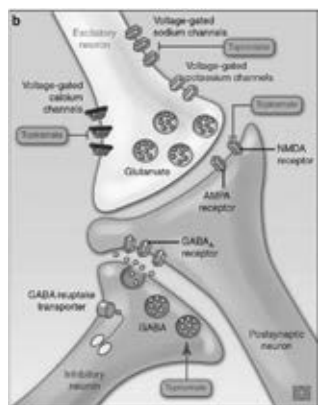
Increases NE release; Decreases its Uptake at Hypothalamus

Decrease in food intake (Dose:30 mg OD)

Diethyl Propion: another sympathomimetic and derivative of Bupropion (Dose: 50 mg BD)

SIDE EFFECTS: Raised BP Tachycardia Insomnia Constipation dry mouth	CONTRADICTED IN: UNCONTROLLED HYPERTENSION KNOWN CVD HYPERTHYROIDISM GLAUCOMA
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Phentermine/ Topiramate



Sympathomimetic amine (phentermine)

GABA-receptor modulation (topiramate)

- inhibitory effect of NPY/AGRP

Topiramate reduce body weight by causing taste aversion and decreasing calorie intake

Available in doses of:

P/T: 3.75/23 mg

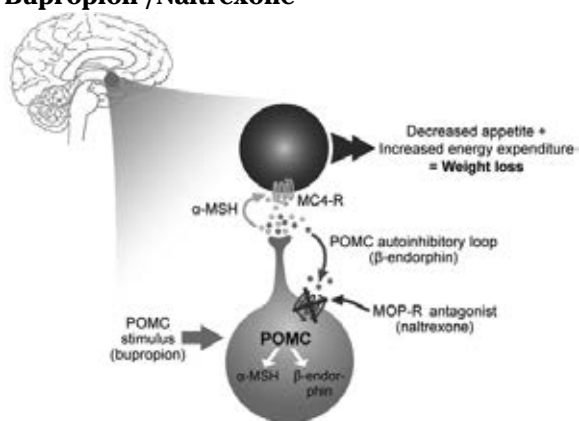
7.5/46 mg (Lowest Rx Dose)

11.25/69 mg

15/92 mg (Max Dose)

Common Side Effects: • Paresthesias • Dry Mouth • Dysgeusia • Anxiety • Dizziness • Constipation • Insomnia	Contraindication: • Hyperthyroidism • Glaucoma • Significant Cardiac Illness
Topiramate can increase the risk of acidosis and renal stones	
Discontinuation should be performed gradually because rapid withdrawal of topiramate may provoke seizures	

Bupropion /Naltrexone



Formulation of Tablet:

Bupropion 90mg and Naltrexone 8mg

Reuptake inhibitor of DA and NE (bupropion)

- activates POMC neurons

Opioid antagonist (naltrexone)

- blocks the feedback inhibition of by β -endorphin

Dose:

initially 1 tab OD

Increase by 1 tab every week until

maximum dose of Bupropion 360 & Naltrexone 32mg

Side effects of Bupropion/ Naltrexone

Nausea/ vomiting

Constipation

Headache

Dizziness, insomnia

Dry mouth

SHOULD BE AVOIDED :

Uncontrolled hypertension

h/o Seizure

h/o Bulimia/ Anorexia Nervosa

Patients taking narcotics for pain control

FDA recommends for Monitoring patients for worsening or emergence of suicidal thoughts or behavior.

Liraglutide: Glucagon-like peptide-1 (GLP-1) analogue with 97% homology to human GLP-1 that activates GLP-1 receptor.

FDA approval 2014 for Adult Obesity

Previously approved for the treatment of Type 2DM at doses up to 1.8 mg once daily.

Also Approved for Secondary CV prevention in adults with T2DM.(1.8mg)

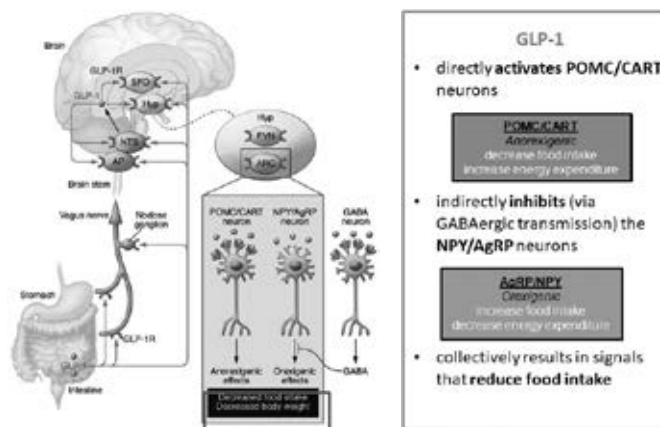
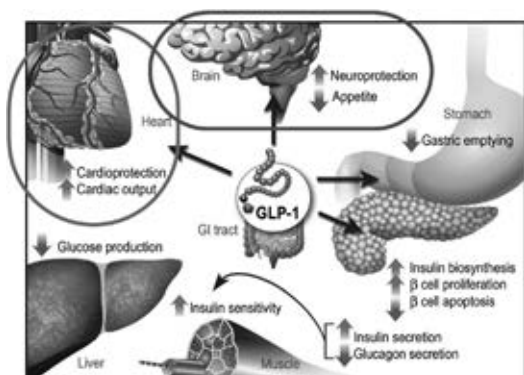
Semaglutide 2.4:

- Long Acting GLP -1 Analogue
- Weekly SC Injection

FDA approved in :

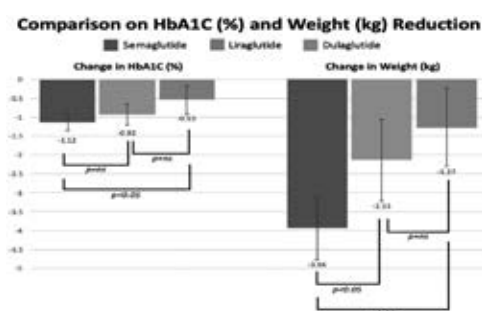
1. To reduce the risk of MACE in adults with established CVD and either obesity or overweight
2. To reduce excess body weight and maintain weight reduction long term (Both Adults and Children above 12 years with obesity)

GLP-1 analogues: mechanism of action



J Clin Invest DOI: 10.1172/JCI78371

Clinical effects (GLP1 analogues)



Comparative analysis of A1c and weight reduction potential of subcutaneous GLP-1 receptor agonists in a real-world setting- CJD 2020

GLP-1 Analogue: Side effects

- M/C: GI- Nausea (20 to 60%) and vomiting (5-15%)
- Start treatment at low dose.
- Diarrhoea (10 - 20%)
- Increased risk of thyroid C-cell tumours in rodents (Contraindicated in patients with family h/o medullary Ca of Thyroid and MEN)
- Gallbladder disease including cholelithiasis and cholecystitis
- Increased risk of diabetic retinopathy related complications with semaglutide.
- Mild Acute Pancreatitis (0.2% Vs Placebo)
- Injection site reactions
- COST

Pharmacotherapy

- Orlistat is a synthetic hydrogenated derivative of a naturally occurring lipase inhibitor lipostatin
- Lipostatin Acts in the lumen of the stomach and small intestine
- This drug is a potent, slowly reversible inhibitor of pancreatic, gastric, and carboxylester lipases and phospholipase A2 , which are required for the hydrolysis of dietary fat into fatty acids and monoacylglycerols
- Blocks the digestion and absorption of ~30% of dietary fat
- Weight loss of ~9–10%

Orlistat

- Dose: 120mg TDS
- Orlistat intake causes significantly lower serum levels of vitamins D, E, and B-carotene.
- Positive effects in Metabolic Profile.
- GI side effects Significant cause of Non Compliance:
(fatty/oily stool, fecal urgency, oily spotting, increased defecation, fecal incontinence, flatulence with discharge, and oily evacuation)
- Administration of psyllium mucilloid reduced the incidence of GI side effects

SETMELANOTIDE: Melanocortin-4-receptor (MC4R) agonist

POMC deficiency, Mean weight loss: 70 lbs (25% TBW)

July 2020 - FDA granted, rare pediatric disease designations for the treatment of POMC deficiency obesity and leptin receptor (LEPR) deficiency obesity

1mg SC injection daily : 6 to 12 years

2mg SC injection daily : 12 years and above



Obesity
High growth
velocity
Tall stature
Insulin resistance



Early-onset obesity
Hyperphagia
Hypopigmentation,
red hair
ACTH deficiency
adrenal crisis as
neonates

S/E: Injection site reaction,
hyperpigmentation,
nausea, penile erections,
depression

Incretins based therapy

Enteroendocrine (peptide) hormones:

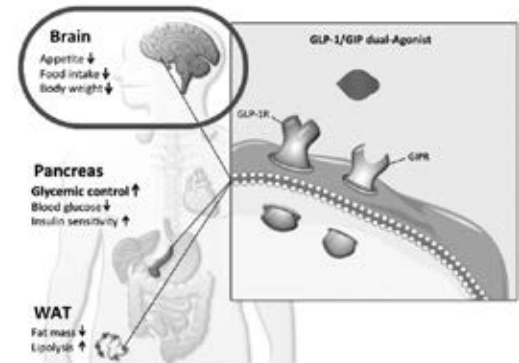
Incretins are GI hormones that are released after meals and stimulate insulin secretion.

Currently established incretins are:

GLP-1 – Glucagon-Like Peptide 1

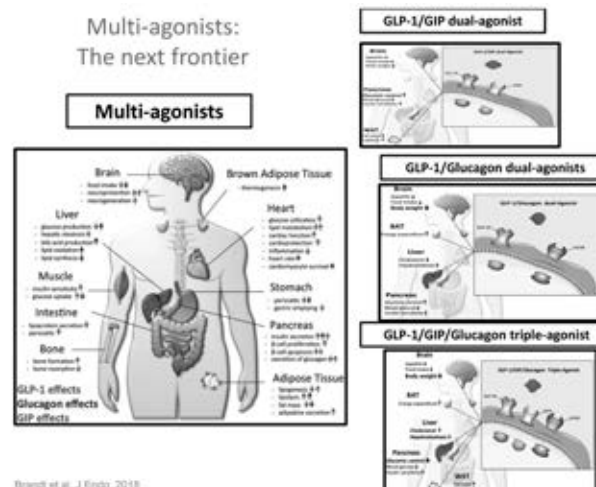
GIP – Glucose-dependent Insulinotropic Polypeptide

Both act through specific receptors on β cells to stimulate insulin secretion.



Tirzepatide

- Dual action: GIP +GLP1 receptor agonism
- (GIP > GLP1)
- Mechanism – peripheral Inhibition of gastric emptying and glucagon secretion and centrally stimulates GLP-1 R in the arcuate nucleus to reduce feeding.
- Long Acting
- Starting dose 2.5 mg s/c weekly
- Max dose: 15 mg weekly
- Approved in 2022
- Average weight Loss: Greater than 20% .
- Significant effect on Metabolic profile.





RETATRUTIDE

- A triple hormone receptor agonist at GIP, GLP-1R and glucagon receptors.
- Less potent at GLP-1 and GCG receptors
- More potent at GIP R
- T1/2-6 days,
- Dosing range 1 mg-12 mg S/c /week



Orforglipron

- An oral once daily nonpeptide GLP-1R agonist.
- T1/2-29/49 hrs
- Dose -12-45 mg OD
- S/E-predominantly GI

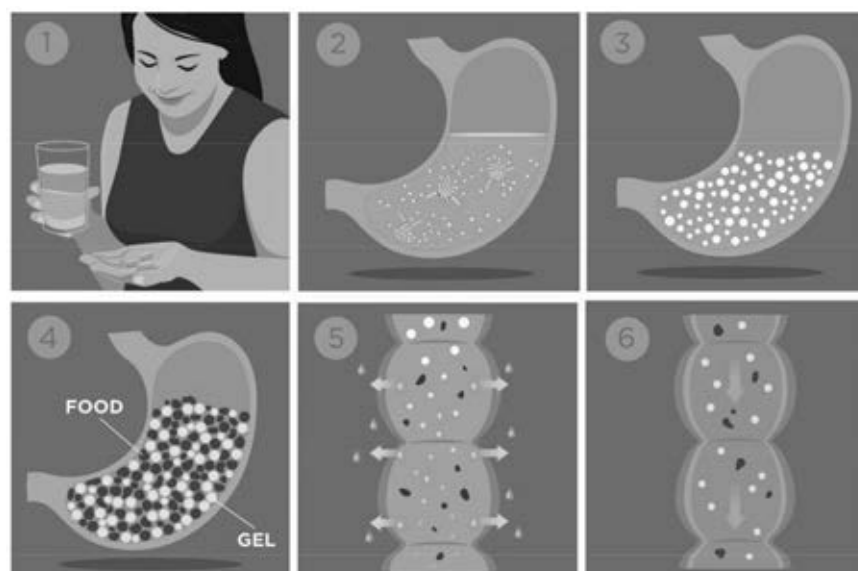


GELESIS

- Gelesis100 is a hydrogel matrix composed of modified cellulose cross-linked with citric acid.
- MOA: is to absorb water to occupy about one-fourth of the average stomach volume, promoting fullness
- mechanical mode of action
- A device rather than a drug and has no systemic effects
- One dose is three oral capsules (2.25 g/dose) that is ingested with 500 ml of water 20-30 min prior to lunch and dinner.

Side Effect/ Caution:

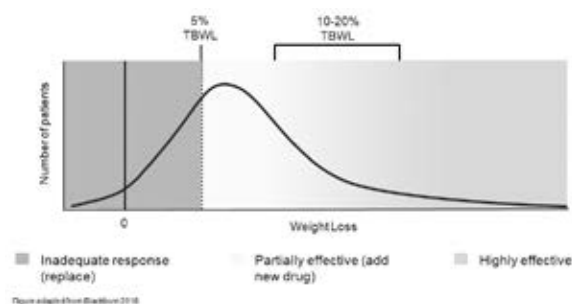
- Gastrointestinal, including abdominal distension, infrequent bowel movements, or dyspepsia.
- Gelesis100 is contraindicated in pregnancy
- caution in patients with active GI reflux diseases; GI surgery
- No effect on Metabolic profiles
-



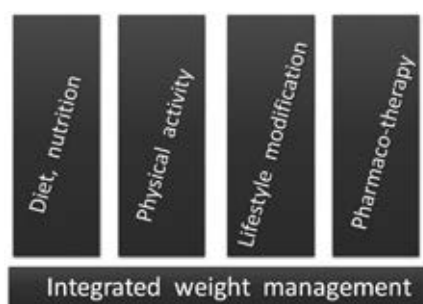
Key clinical concepts in treating obesity pharmacotherapy



Key clinical concepts in treating obesity with obesity anti-obesity with anti-pharmacotherapy



WEIGHT LOSS & WEIGHT MAINTENANCE



Surgery

Indications

- BMI > 35 with an associated comorbidity or a BMI > 40 (irrespective)
- Repeated failures of other therapeutic approaches
- Capability of tolerating surgery

Surgery

Indications

Restrictive surgeries limit the amount of food the stomach can hold and slow the rate of gastric emptying.

Malabsorptive surgeries reduce the amount of absorption

Laparoscopic gastric band (LAGB)

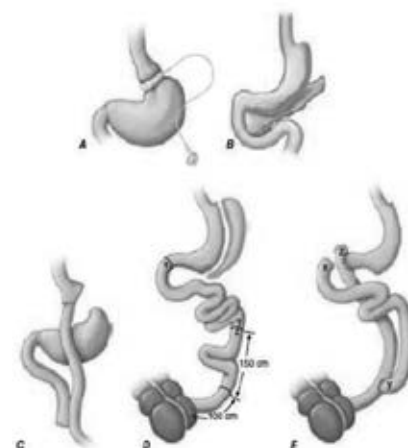
The Roux-en-Y gastric bypass.

Biliopancreatic diversion with duodenal switch.

Biliopancreatic diversion. vertical-banded

gastroplasty

Biliopancreatic diversion



Prevention and control

- Dietary changes
- Increased physical activity
- Others: appetite suppressing drugs, gastric bypass, gastroplasty, jaw wiring.. Not effective
- Health education is the most common effective measure

ESLICARBAZEPINE

Dr. Ambarish Ghosh, Professor, Department of Psychiatry

Case I

A 29 year male actor by profession has come in the OPD with c/o Euphoric Mood, over familiarity, aggression, decreased sleep and appetite since last 20 days.

Patient is under treatment since 5 years with 3 prior

Positive family history for similar symptoms in paternal grandfather.

No history of any substance use

- What is your probable diagnosis?
- How will you approach the patient?

More Information

Drugs Prescribed

Lithium 1200mg/day for 6 weeks with minimum response, and then stopped due to Polyuria

Sodium valproate was given upto 2000 mg/day for 4 weeks but stopped due to poor response

Olanzapine was administered upto 15 mg/day with good response but withdrawn due to excessive sedation and weight gain

Risperidone was administered to 4 mg/ day and partial improvement but withdrawn due to increased prolactin level

Quetiapine was used up to 200 mg but withdrawn due to excessive sedation

- What will be your line of treatment?
- Can we consider Eslicarbazepine as an alternative drug?

Eslicarbazepine was started with the YMRS score at 35 on admission.

On Week 1 YMRS score decreased to 27 with reduction in aggressive behaviour

On Week 2 YMRS score came down to 20 with improved sleep, more reduction in aggression

On Week 4 YMRS score decreased to 12 with decreased over familiarity, delusion of grandiosity along with Euthymic mood

Patient as discharged after a month of stay in the IPD

On follow up after a month patient had resumed his acting schedule and maintaining well.

Case II

A 20 year old female has come to the OPD with diagnosed case of focal epilepsy since last 3 years with right temporal interictal spikes in her EEG

Patient is on Levetiracetam 500 mg BD

Last episode of convulsion was the previous night

- Which drug can be used as an add-on therapy?
- Can Eslicarbazepine be used as an add on therapy?

More Information**Drugs Prescribed**

ESL initiated at 400mg/day and Titrated to 800mg/day over 2 weeks

Continued Levetiracetam at 1000 mg/day

No other AEDs or medication used

Follow-up conducted at 0, 4, 12 and 24 weeks post ESL initiation

Follow-Up

Follow-Up (Weeks)	Seizures / Month	Adverse Effects	Clinical Status
Week 0 (Baseline)	1-2	Irritability (Levetiracetam)	Employed, Partial Controlled
Week 4	0-1	Mild Dizziness (Resolved)	Improved Energy and Sleep
Week 12	0	None	Seizure Free, Fully Functional
Week 24	0	None	Maintained Seizure Freedom, Stable

Parameter	Week 0	Week 4	Week 12	Week 24
Sodium (Na+) (mEq/L)	139	137	138	139
Potassium (K+) (mEq/L)	4.2	4.0	4.1	4.1
Creatinine (mg/dL)	0.8	0.8	0.9	0.8
AST (U/L)	22	24	23	21
ALT (U/L)	25	26	24	23
Total Bilirubin (mg/dL)	0.6	0.7	0.6	0.6

Quiz

Compiled by Dr. Pinaki Sarkar, Consultant Psychiatrist

1. A short introduction to this therapy is given in Viktor Frankl's most famous book, *Man's Search for Meaning* (1946), in which he outlines how his theories helped him to survive his Holocaust experience and how that experience further developed and reinforced his theories. Which therapy?
2. This journal was established in 1853 as the *Asylum Journal*, changing title in 1855 to the *Asylum Journal of Mental Science* and changing title again to *Journal of Mental Science* from 1858 to 1963, when it obtained its present name. Which journal?
3. What is a cognitive bias in which people with limited competence in a particular domain overestimate their abilities? In popular culture, this is often misunderstood as a claim about general overconfidence of people with low intelligence instead of specific overconfidence of people unskilled at a particular task.
4. This psychological test is a standardized tool developed by the National Institute for the Mentally Handicapped (NIMH), India. It is primarily used for diagnosing and certifying for disability certification and clinical assessment.
5. Which book is often called the first true psychiatric textbook? John Haslam at Bethlem Hospital documented detailed case studies of mental disorders, distinguishing symptoms and treatments.
6. Identify the Clinical Condition where a person showing disinterest in his or her physical complaint. It occurs in conversion disorder.
7. What was discovered in 1998 almost simultaneously by two independent groups of researchers working on the rat brain? One group named it X, meaning "appetite" in Greek; the other group named it hypocretin, because it is produced in the hypothalamus and bears a weak resemblance to secretin. X?
8. This test is an experimental method used in scientific research to measure stress in rodents. It is based on the observation that if a mouse is subjected to short term inescapable stress then the mouse will become immobile. It is used to measure the effectiveness of antidepressant-like agents but there is significant controversy over its interpretation and usefulness.
9. Otto Loewi, a German-born pharmacologist and psychobiologist who discovered the role of X. For this discovery, he was awarded the Nobel Prize in Physiology or Medicine in 1936. X?
10. What was developed by Marsha M. Linehan, a psychology researcher at the University of Washington? She defines it as "a synthesis or integration of opposites".
11. This 40-year Study was a major violation of ethical standards and has been cited as "arguably the most infamous biomedical research study in U.S. history." Its revelation led to the 1979 Belmont Report and to the establishment of the Office for Human Research Protections (OHRP) and federal laws and regulations requiring institutional review boards for the protection of human subjects in studies. Name the study.
12. Which test involves presenting individuals with a series of ambiguous pictures, and then asking them to tell a story about what is happening in the picture? The stories people create often reflect their underlying motives, concerns, and personality traits.
13. X involved a national consortium of 14 university-based regional centers, which oversaw a total of 23 participating psychiatric and 18 primary care clinics. Enrollment began in 2000, with follow-up completed in 2004. X evaluated feasible treatment strategies to improve clinical outcomes for real-world patients with treatment-resistant depression. Although the study found no clear-cut "winner," it does provide guidance on how to start therapy and how to proceed if initial treatment fails.
14. This therapy is a humanistic and experiential form of psychotherapy that emphasizes personal responsibility, present-moment awareness, and the holistic integration of mind, body, and emotions. Fritz Perls, Laura Perls, and Paul Goodman made significant contribution to this therapy. Which therapy?
15. This Institute was founded in 1984 by a group of mental health professionals and philanthropists headed by Padma Bhushan Dr M Sarada Menon. It has been a WHO Collaborating Center since 1996. Which institute?

Answers of Quiz:

1. Logotherapy
2. British journal of Psychiatry
3. Dunning–Kruger effect
4. ISAA
5. Observations on Madness and Melancholy
6. Belle Indifference
7. Orexin
8. Tail Suspension Test
9. Acetylcholine
10. DBT
11. Tuskegee Syphilis Study
12. TAT
13. STAR*D
14. Gestalt Therapy
15. SCARF

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A circular seal with a yellow smiley face at the top, a blue circle with the number "1" in the center, and the text "No. 1 Prescribed" and "Sertraline in Indian patients" around the bottom.

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Feliz S
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Arip MT
Aripiprazole