ALL INDIA INSTITUTE OF MEDICAL SCIENCES, MANGALAGIRI

PHARMACOLOGY BULLETIN

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FROM THE EDITORIAL DESK….

Dear Friends, Greetings from AIIMS Mangalagiri and Welcome to the 18th issue of ESSENCE.

Mental health has always been a challenge, more so with the prevailing pandemic, growing social and economic inequalities, global conflicts, we are looking at a global crisis with an estimated one in eight people living with a mental disorder. The world celebrated the World Mental Health Day in October and this issue of ESSENCE is dedicated to Mental Health.

Current selection of an appropriate drug and dose of psychiatric medications still relies on psychiatrists' clinical experience as well as possibly lengthy process of trial and error. The current issue covers parameters, guidelines, recommendations and information about how pharmacogenomic variation viz CYP2C19 and CYP2D6 polymorphism should be taken into account while deciding on the choice and dose of psychiatric medications.

Pharmaco-vigilance and monitoring of adverse effects of psychiatric medications comes with its own set of specific challenges and the current issue of ESSENCE covers this important aspect of mental health.

Further, as always, the we have recent updates from the world of medicines, new drug approvals, Drug safety alerts and a crossword quiz on clinical pharmacology of psychiatric medications.

Link to access the crossword quiz is given below. Names of the winners will be declared in the next issue.

https://docs.google.com/forms/d/e/1FAIpQLSc7Hse3zLNKJioEOuQMkqbfOZNt0ALGP9fy8Kz9nuWEIN1xLQ/viewform?vc=0&c=0&w=1&flr=0

Happy Reading, Jai Hind

Feedback and Suggestions may be sent to Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh at email id: pharmacology@aiimsmangalagiri.edu.in

Despite the common use of antipsychotic and antidepressant drugs for the treatment of various psychiatric illnesses, current selection of an appropriate drug and dose still relies on psychiatrists' clinical experience as well as possibly lengthy process of trial and error. There are no biomarkers that can objectively guide dose and treatment selection or alteration and many patients either receive less or more than the required dose leading to under treatment or adverse effects.

A promising approach towards this effort is the use of pharmacogenomics to better identify patients that are likely to have an efficacious or adverse response to psychiatric medications. Candidate gene approaches as well as genome-wide association studies have been conducted to identify genes or loci that influence drug response. It is estimated that roughly one quarter of the total variability in drug response is genetic in origin; In particular, functional polymorphisms in genes encoding the drug metabolizing enzymes CYP2C19 and CYP2D6 which are extremely common. Additionally, they play a key role in the phase I metabolism of more than two thirds of all the available psychiatric medications.

Hence genotyping of these genes encoding for these drug-metabolizing enzymes viz CYP2C19 and CYP2D6 can play a great part in personalizing and individualizing the choice of the drug and its dose improving significantly affect the response and efficacy of medications. Based on these parameters, guidelines, recommendations and information about how pharmacogenomic variation should be taken into account regarding the indication or dosage etc. have been framed.

Anti-Psychotic agents	**CYP2D6**			
	PM	IM	NM	UM
Risperidone	Reduce maximum dose by 33% (to 4 mg/day)	Reduce maximum dose by 33% (to 4 mg/day)	Recd Starting dose	Be alert for sub-therapeutic drug levels (TDM) OR Select alternative drug
Aripiprazole	Reduce maximum dose by 33% (to 20 mg/day)	Reduce maximum dose by 33% (to 20 mg/day)	Recd Starting dose	
Zuclopenthixol	Reduce the dose by 50% OR select alternative drug	Reduce the dose by 25% OR select alternative drug	Recd Starting dose	
Haloperidol	Reduce the dose by 50% OR select alternative drug	Be alert to ADRs OR select alternative drug	Recd Starting dose	

SSRI/SNRI	CYP2C19				CYP2D6			
	PM	IM	NM	UM	PM	IM	NM	UM
Fluvoxamine	Recd Starting dose	Recd Starting dose	Recd Starting dose	Recd Starting dose	25-50 % of starting dose	Recd Starting dose	Recd Starting dose	--
Escitalopram	50 % of starting dose	Recd Starting dose	Recd Starting dose	Use Alternative drug	Recd Starting dose	Recd Starting dose	Recd Starting dose	Recd Starting dose
Sertraline	50 % of starting dose	Recd Starting dose	Recd Starting dose	Recd Starting dose	--	--	--	--
Venlafaxine	--	--	--	--	Use Alternative drug	Use Alternative drug	Recd Starting dose	150 % of starting dose or Use Alternative drug

TCA	CYP2C19				CYP2D6			
	PM	IM	NM	UM	PM	IM	NM	UM
Clomipramine	50% dose reduction	Recd Starting dose	Recd Starting dose	50% dose increase	No TCA or 50% dose reduction	Reduce dose by 25%	Recd Starting dose	No TCA or higher dose
Amitriptyline	50% dose reduction	Recd Starting dose	Recd Starting dose	50% dose increase	No TCA or 50%	Reduce dose by 25%	Recd Starting dose	No TCA or higher dose
Nortriptyline	---	Recd Starting dose	Recd Starting dose	100% dose	No TCA or 60% dose reduction	No TCA or 40% dose reduction	Recd Starting dose	No TCA or 60% dose increase
Doxepine	50% dose reduction	Recd Starting dose	Recd Starting dose	50% dose increase	Reduce dose by 60 %	Reduce dose by 20 %	Recd Starting dose	No TCA or 100% higher dose

Abbreviations: PM: Poor Metabolizer, IM: Intermediate Metabolizer, NM: Normal Metabolizer UM: Ultrarapid Metabolizer

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3. Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Muller DJ, Shimoda K, et al. CPIC guidelines for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharmacol Ther 2017; 102(1):37–44.

Recent new/Update from the world of medicines ….

Best Drugs for Insomnia Identified!! Results of a systematic review and Meta-analysis.

Two drugs have emerged as the optimal medications for treating insomnia based on the "best-available evidence,". In a comprehensive comparative-effectiveness analysis, Lemborexant and Eszopiclone showed the best efficacy, acceptability, and tolerability for acute and long-term insomnia treatment. Short-acting, intermediate-acting, and long-acting benzodiazepines were effective in the acute treatment of insomnia, but they have unfavorable tolerability and safety profiles, and there are no long-term data on these issues. The findings were published online July 16, 2022 in The Lancet. This was a large-scale systematic review and network meta-analysis, the researchers analyzed data from 154 double-blind, randomized controlled trials of medications used for acute and long-term treatment of insomnia. However, it is important to also consider nonpharmacologic treatments for insomnia disorder, as they are supported by "high-quality evidence and recommended as first-line treatment by guidelines.

FDA approves first oral NMDA Antagonist for treatment of Depression

The US Food and Drug Administration (FDA) has approved the first oral *N*-methyl *D*-aspartate (NMDA) receptor antagonist for the treatment of major depressive disorder (MDD) in adults. *Auvelity* (Axsome Therapeutics) is an extended-release oral tablet containing dextromethorphan (45 mg) and bupropion (105 mg). It is the "first and only rapid-acting oral medicine approved for the treatment of MDD with antidepressant action starting in one week," The currently available anti-depressant drugs take almost 6-8 weeks to show response which is a limitation of these drugs. Given the debilitating nature of depression, the efficacy of this rapidly acting drug may have a significant impact on the current treatment paradigm for this condition. The Auvelity is administered orally once daily for the first three days, then twice daily.

Be Cautious…. Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Clozapine	Gastrointestinal hypomotility
2.	COVID-19 vaccine AstraZeneca (ChAdOx1-S)	Tinnitus, paraesthesia and hypoesthesia
3.	Denosumab	Hypercalcaemia in children and adolescents
4.	Dexamethasone	Phaeochromocytoma crisis
5.	Doxycycline	Fixed drug eruption
6.	Mefenamic acid	Fixed drug eruption

Relevance of Pharmacovigilance in the setting of Mental Health

Psychiatric diseases are characterized by biochemical changes in the brain. The drugs used to treat these disorders either act on the concentration of the neurotransmitters of the synaptic cleft or on their capacity to bind to receptors, affecting directly brain functioning and causing undesirable changes in behavior. Pharmacotherapy is commonly used to treat patients with psychiatric problems. Most recommendations advise that the drugs should be taken for several months or years due to the chronic and relapsing character of these disorders.

The main form of treatment for many psychiatric diseases is pharmacotherapy, and psychotropic medications are associated with a wide range of adverse drug effects. The detection of several adverse drug effects brought on by psychotropic medications during the past few decades as a consequence of pharmacovigilance activity led to their removal from the market or restrictions on usage. Drug interactions that are clinically significant may occur with psychotropic medications since they are frequently taken for prolonged periods of time and are frequently recommended in combination with other medications. As a result, patients are at risk of experiencing a variety of adverse drug reactions (ADRs). These ADRs can occasionally be fatal (like neuroleptic malignant syndrome) or incapacitating (such as drug-induced tardive dyskinesia). Especially for novel or unidentified ADRs, it is crucial for psychiatrists to be aware of the procedures involved in recognizing and reporting them.

Clinical trials are the primary source of information on the safety and tolerability of psychiatric medications, although this has a number of drawbacks. Pharmacovigilance initiatives are created to obtain data on drug effects outside of clinical trial populations that have been properly chosen. For the reasons listed above, it is crucial that psychiatrists learn the principles and techniques of pharmacovigilance since they play a crucial part in finding and disclosing novel or severe adverse medication effects.

Pharmacovigilance activities are an important part of medical practice in general. Four factors, though, make this area particularly important to psychiatrists. First, the majority of psychiatric medications regularly cause adverse drug reactions. Patients frequently may not respond to the initial dose of the pharmacological therapy and may need to try multiple different drugs. Thus, the use of many medications on trial basis (polypharmacy) might increase the risk of side effects or drug interactions. Second, the majority of psychotropic drug clinical trials are carried out under "perfect" circumstances; individuals are chosen based on strict standards, and coexisting medical disorders are typically eliminated. Additionally, these trials often only last a few weeks or months. In contrast, the patients we treat in practice frequently have more complicated diagnoses and co-occurring medical conditions, and thus require more ongoing attention. In this situation, ADRs that went unnoticed during a trial are more obvious, and the psychiatrist is responsible for managing them.

Third, clinical trials—especially those in psychiatry—have a publishing bias. Even in published studies, ADRs are not always accurately documented, and it is possible that in some instances, essential data may be falsified. Therefore, it is the responsibility of treating psychiatrists to recognise and report such responses, especially those connected to more recent medications. Fourth, psychotropic drugs have a direct impact on how the brain works and may cause unfavourable behavior changes. These alterations can occasionally be fatal, as in the case of antidepressant-induced suicidal behavior in youngsters. Other times, long-term behavioral changes might be observed, such as the return of symptoms. This condition, known as "tardive dysphoria," has been linked to antidepressants. For each of these reasons, it is crucial that psychiatrists familiarize themselves with pharmacovigilance principles and procedures. Finding probable ADRs is the initial stage in this approach.

Benefit of Pharmacovigilance in Mental Health

The four major categories into which the beneficial impacts of pharmacovigilance in mental health can be classified:

Patient: Even when adverse drug reactions are not life-threatening, patients might nevertheless find them upsetting and inconvenient. Reporting these occurrences might promote greater patient-physician confidence. Regular reporting can also result in earlier problem detection, which can enhance patient compliance and quality of life.

Doctor: Pharmacovigilance can assist psychiatrists in spotting and handling probable ADRs. In a number of situations, doctors may have discovered a specific ADR and are rewarded for doing so. This is especially true for events like behavioral toxicity (drug-induced mania, drug-induced suicidality), which are easiest for practitioners who work closely with patients to notice.

Pharmaceutical industry: With stories of major adverse drug reactions (ADRs) being omitted or concealed during clinical trials, the pharmaceutical industry's role in psychiatry has recently come under question. The "culture of pharmacovigilance" that the lead investigators in these studies cultivate will enable them to detect such ADRs as early as feasible and take the appropriate action before the medicine is commercialized.

Regulatory agencies: As was already indicated, the majority of published trials for psychotropic drugs are short-term studies. Although these statistics may be used by regulatory bodies to approve a product, long-term adverse drug reactions could take much longer to manifest. Early "signal detection" of such occurrences could aid in the drug's removal or use restriction by the authorities.

As a result, it's critical to identify ADRs early and be aware of them so that medical practitioners can modify the medication they've prescribed to lessen or eliminate side effects brought on by psychotropic medicines. This will advance sane drug use while also improving patient care and safety.

Reference:

1. Rajkumar RP, Melvin G. Pharmacovigilance for psychiatrists: An introduction. Indian J Psychiatry. 2014 Apr;56(2):176-81.

2. Healy D. Are selective serotonin reuptake inhibitors a risk factor for adolescent suicide? Can J Psychiatry 2009;54:69-71.

New Drug Approvals…

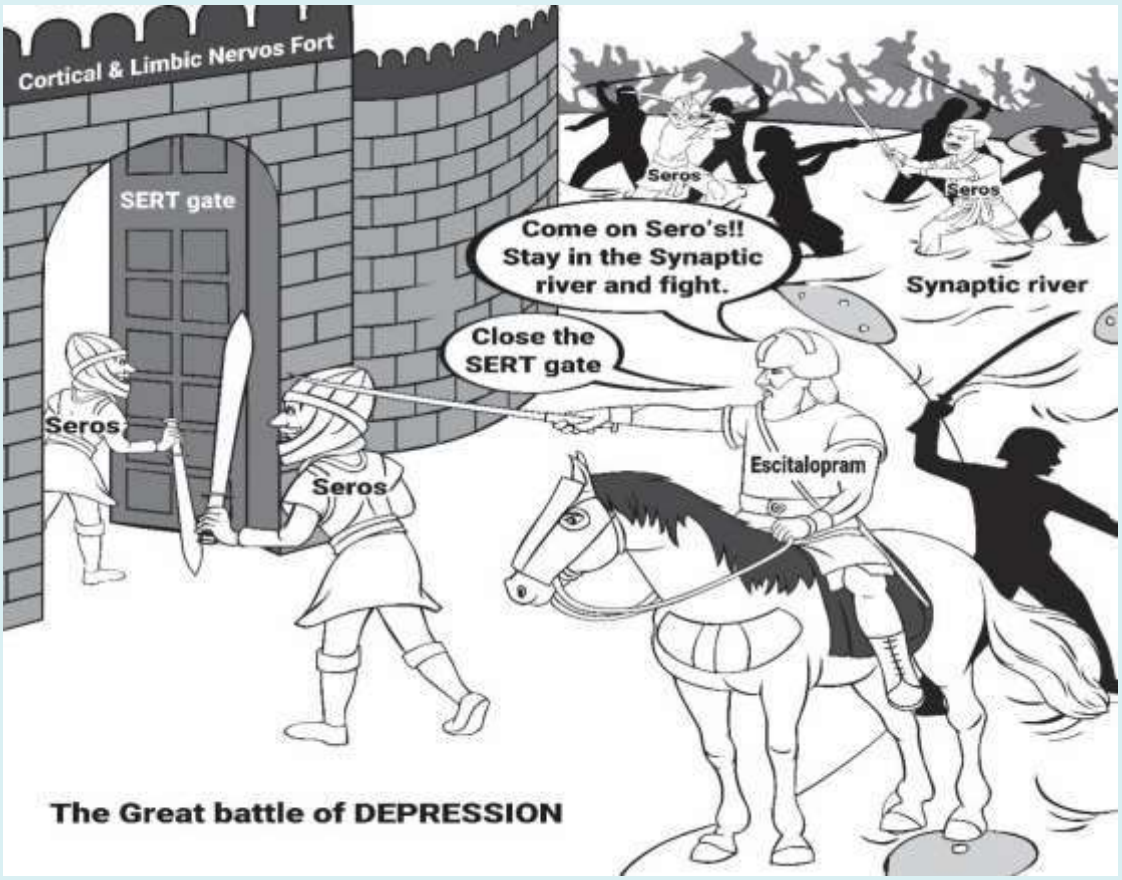
Spesolimab is a humanized anti–interleukin-36 receptor antagonist monoclonal antibody approved for the treatment of generalized pustular psoriasis flares in adults. The recommended dose is 900 mg single dose by intravenous infusion over 90 minutes.

Futibatinib is an irreversible tyrosine kinase inhibitor of FGFR1, 2, 3 and 4 approved for the treatment of intrahepatic cholangiocarcinoma. The recommended dose is s 20 mg orally once daily until disease progression.

Deucravacitinib is a tyrosine kinase 2 (TYK2) inhibitor approved for the treatment of moderate-to-severe plaque psoriasis. The recommended dose is 6 mg orally once daily.

Olipudase alfa is a hydrolytic lysosomal sphingomyelin-specific enzyme approved for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD). The recommended starting dose is 0.1 mg/kg administered as an intravenous infusion.

Cartoon Corner…



Excerpt from "Drug Autobiographies in Pharmacology" by Dr. Sushil Sharma

1. CARIPRAZINE:

Cariprazine is a piperazine derivative that is a partial agonist at dopamine D3 and D2, serotonin 5HT1A receptors and antagonist at 5HT2B and 5HT2A receptors.

Cariprazine's D3-preferring propensity might be responsible for its pro-cognitive, antidepressant effects and efficacy in improving negative symptoms. It has been surmised that its higher affinity to alpha 1B receptor could lead to a reduced occurrence of extrapyramidal symptoms and akathisia.

Cariprazine has been approved by the FDA in 2015 for the treatment of schizophrenia and bipolar disorder. Ii is administered as 1.5-6 mg, once daily dosing.

In bipolar disorder, the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guidelines recommend cariprazine as first-line monotherapy for acute mania (Level-1 evidence) and bipolar depression.

Black Box Warning has been issued for Cariprazine for causing increased mortality in elderly patients with dementia and also has increased risk of suicidal thoughts.

2. ENDOXIFEN

Endoxifen is a novel potent PKC inhibitor, which belongs to the class of Selective Estrogen Receptor Modulators (SERM). It has a longer half-life of 50 hours and does not require hepatic enzymes for conversion in active metabolite.

It has been approved by the Drug Controller General of India (DCGI) for the acute treatment of manic episodes with or without mixed features of bipolar 1 disorder.

It was concluded that given as 8 mg once daily orally for 21 days, Endoxifen 8 mg is as effective as Divalproex sodium extended release 1000 mg in the treatment of bipolar disorder with concurrent manic or mixed episode. An earlier response with better safety and tolerability was found with Endoxifen when compared to divalproex.

Endoxifen should not be administered to women who are pregnant or nursing as it belongs to category D group of drugs. Similar to other SERMs, Endoxifen enhances the risk for uterine malignancies.

3. LUMATEPERONE

Lumateperone is an atypical antipsychotic (serotonin-dopamine antagonist) and also a mood stabilizer. It acts as an antagonist of 5-HT2A and D2 (post synaptic) receptors but partial agonist at D2 (pre-synaptic) receptors.

Lumateperone was FDA Approved in 2019 for the treatment of schizophrenia. It can also be used for the management of acute mania and bipolar depression.

The usual dosage is 42 mg, used once daily for treatment of schizophrenia. Lumateperone exhibits a favorable safety profile with body weight, motor side effects, metabolic and endocrine parameters.

4. VORTIOXETINE

Vortioxetine has a unique multimodal mechanism of action as serotonin modulator and stimulator. Therefore, patients who do not respond to antidepressants with other mechanisms of action may respond to vortioxetine. It acts as an antagonist of SERT pump, 5HT3, 5HT7 receptors and partial agonist at 5HT1A and 1B receptors.

Multiple studies show pro-cognitive effects with Vortioxetine when compared with other antidepressants in patients with major depressive episodes. It has been effective specifically in elderly patients with depression, with a positive trial showing improvement in cognition as well as mood.

Vortioxetine has been approved by FDA Approval in 2013 for the management of Major depressive disorder. It is usually administered in the dosage range of 5–20 mg/day.

5. BREXANOLONE

Brexanolone is a positive allosteric modulator at neuroactive steroid sites on both gamma-aminobutyric acid (GABA-A) benzodiazepine-sensitive and benzodiazepine-insensitive ligand-gated ion channels.

It is available as an Injection of 100 mg/20 mL (5 mg/mL) single-dose vial. FDA approval was given for Brexanolone in 2019 for the treatment of Postpartum Depression.

Zheng et al., 2019 observed that a single brexanolone infusion appears to have ultra-rapid antidepressant effect for PPD, lasting for up to 1 week.

References:

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2. Ahmad A, Sheikh S, Khan MA, Chaturvedi A, Patel P, Patel R, Buch BC, Anand RS, Shah TC, Vora VN, Ramasubramanian V. Endoxifen: A new, protein kinase C inhibitor to treat acute and mixed mania associated with bipolar I disorder. Bipolar disorders. 2021 Sep; 23(6):595-603.
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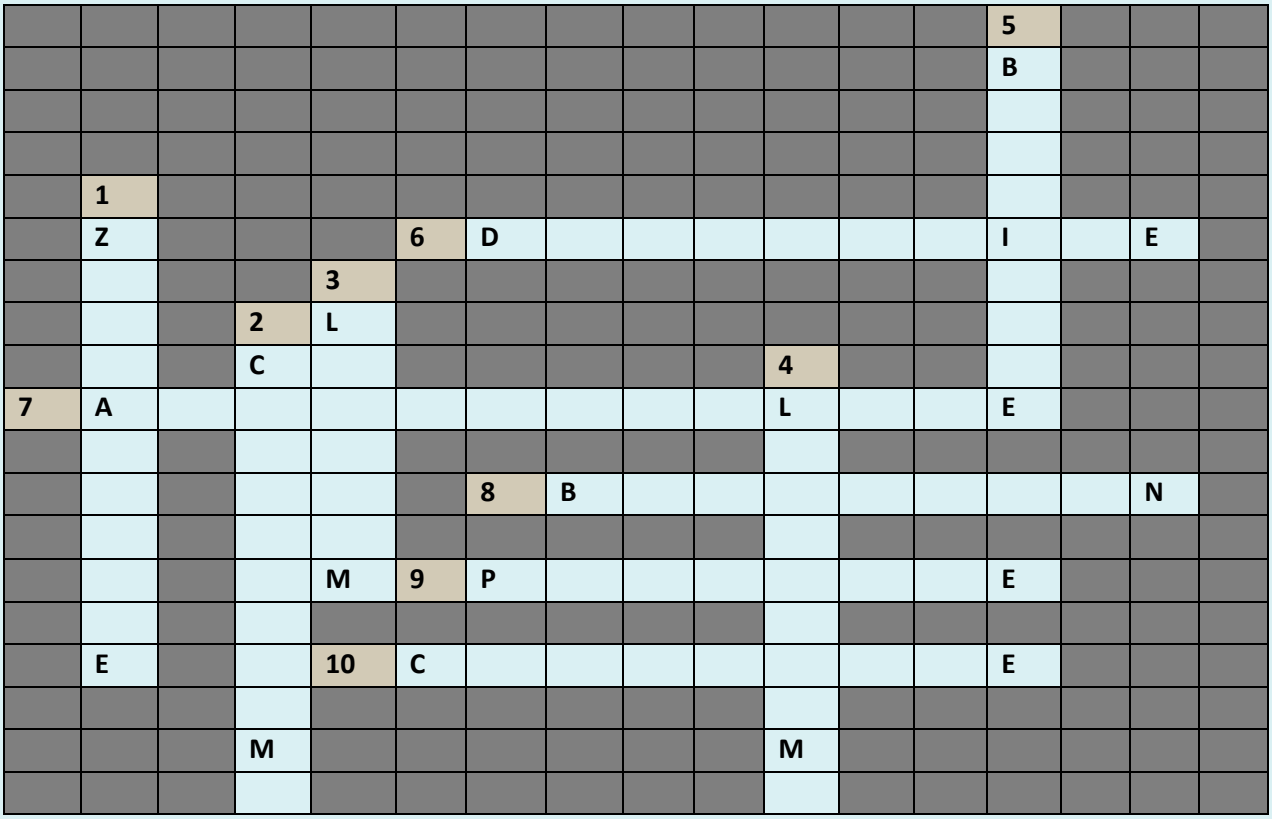

Downward	Across
1. Atypical antipsychotic drug associated with prolongation of Q-T interval (*11*) 2. SSRI preferred in Premenstrual Dysphoric Disorder [PMDD] (*10*) 3. Antimanic drug with narrow therapeutic index (*7*) 4. Sedative hypnotic drug acts by facilitation of $GABA_A$ receptor (*9*) 5. Antianxiety drug acts by stimulation of presynaptic 5-HT_{1A} autoreceptors (*9*)	6. Serotonin and Noradrenaline Reuptake Inhibitor [SNRI] (*10*) 7. Tricyclic Antidepressant [TCA] associated with anticholinergic side effects *(13)* 8. Atypical antidepressant acts by inhibition of DA and NA reuptake *(9)* 9. Antipsychotic drug with selective DA antagonism and associated with the risk of arrhythmias *(8)* 10. Atypical antipsychotic drug reserved in refractory schizophrenia and associated with risk of agranulocytosis *(9)*

Click on the link below to access the quiz:
https://docs.google.com/forms/d/e/1FAIpQLSc7Hse3zLNKJioEOuQMkqbfOZNt0ALGP9fy8Kz9nuWEIN1xLQ/viewform?vc=0&c=0&w=1&flr=0

(Results and Winners of the Quiz will be announced in the next issue)

Winners of Previous Crossword PUZZLE [17th Issue]

Dr. Srikanth Marthandam, AIIMS Mangalagiri and Dr. G Shwetha, KAMSRC

Answer to the previous Crossword Puzzle (17th Issue) is given in the link below:
https://docs.google.com/forms/d/e/1FAIpQLSeXJL1kuwDplzXshMm5FG4EL_5ZoXd1j23U-PvpCwoF18vcgg/viewform?vc=0&c=0&w=1&flr=0