ALL INDIA INSTITUTE OF MEDICAL SCIENCES, MANGALAGIRI

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FROM THE EDITORIAL DESK….

Dear Friends, Greetings from Department of Pharmacology and welcome to the 26th issue of ESSENCE

In the expanding field of therapeutics, Pharmacometabolomics is a new field which stems from metabolomics, the quantification and analysis of metabolites produced by the body. This concept helps to directly measure metabolites in an individual's bodily fluids, in order to predict or evaluate the metabolism of pharmaceutical compounds, and to better understand the pharmacokinetic profile of a drug.

The current issue also discussed on importance of Biosimilars which are biologic medications that are almost identical copies of an original biologic medication, or reference product, that has already been approved by the U.S. Food and Drug Administration (FDA). The current issue also discussed about the different biosimilars available in the market.

The current issue of ESSENCE also has an article on 'Missed Data in Clinical Research' and their applications as important tools in statistical analysis particularly when there are dropouts and lost to follow-up in the study.

Further, as always, the current issue has new drug approvals, interesting news from the world of medicines, crossword puzzle on 'Drugs Causing Orthostatic Hypotension' and the 'cartoon corner'.

We hope you enjoy reading it.

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

Pharmacometabolomics, also known as pharmacometabonomics, is a field which stems from metabolomics, the quantification and analysis of metabolites produced by the body. It refers to the direct measurement of metabolites in an individual's bodily fluids, in order to predict or evaluate the metabolism of pharmaceutical compounds, and to better understand the pharmacokinetic profile of a drug. As an alternative, pharmacometabolomics can be used to track the effects of a pharmacological substance on specific metabolic pathways (pharmacodynamics) by measuring metabolite levels after the compound is administered. This is an extensive representation of how drugs affect metabolism and the pathways connected to the mechanism underlying treatment response variability.

Goals of Pharmacometabolomics

1. Information from other omics, such as transcriptomics, proteomics, and genomes, is believed to be supplemented by pharmacometabolomic. A person's propensity to react to a pharmaceutical component can be predicted with increasing accuracy when looking at their traits at these various degrees of detail. Pharmacometabolomic overarching objective is to more accurately anticipate or evaluate a person's response to a pharmacological substance, enabling ongoing treatment with the appropriate medication or dosage based on individual differences in metabolism and response to therapy.

2. A patient's complete and thorough metabolic profile, or "metabolic fingerprint," can be obtained through pharmacometabolomic analysis using a metabolomics technique. These metabolic profiles offer a thorough summary of specific metabolite or pathway changes, resulting in a more accurate representation of illness phenotypes. The response of a patient with a specific metabolic profile to a pharmacological molecule can then be predicted using this approach. Pharmacogenetics studies are frequently combined with or conducted after pharmacometabolomic evaluations of medication response.

3. Personalized Medicine: Pharmacometabolomics may be seen as a type of personalised medicine because metabolite analyses are carried out at the level of the individual patient. To enable more individualised treatment plans, this field is currently being used predictively to ascertain the possible reactions of medicinal substances in specific patients. Such pharmacometabolomics approaches are expected to improve the prediction of a chemical's efficacy and metabolism as well as potential harmful or off-target effects in the body, as well as an individual's response to the compound.

Current Applications:

1. <u>Metabotype informs about treatment outcomes:</u> When a patient is set to get medication treatment, pharmacometabolomic can be utilised predictively to help decide the best course of action. This entails figuring out a patient's metabolic profile before starting treatment and connecting metabolic fingerprints to how well a pharmaceutical treatment plan works. A patient's metabolic profile can be analysed to identify potential risk factors for medication toxicity that may be different from those seen in the general

population, as well as characteristics that may lead to altered drug metabolism. This information can be used to predict the overall effectiveness of a proposed treatment. This method has been used to find new or previously identified metabolic biomarkers in patients, which can be used to forecast the patient's outcome. One example of the clinical application of pharmacometabolomics are studies that looked to identify a predictive metabolic marker for the treatment of major depressive disorder (MDD).

2. <u>Monitoring drug-related alterations in metabolic pathways:</u> Analysing a patient's metabolic profile after receiving a particular therapy is the second major application of pharmacometabolomics. In order to compare the concentrations of metabolites before and after therapy, this procedure is frequently secondary to a pre-treatment metabolic analysis. This makes it possible to identify the metabolic pathways and processes that the medication is changing—either purposefully as the compound's intended target or inadvertently as a side effect. Moreover, it is possible to determine the quantity and range of metabolites that the molecule itself produces. This information can be used to determine the pace of metabolism and may even inspire the development of a related compound with better effects or fewer adverse effects. An instance of this methodology was employed to examine the impact of multiple antipsychotic medications on lipid metabolism in individuals undergoing treatment for schizophrenia. Researchers discovered drug- and lipid-class-specific correlations between antipsychotic medication treatment and lipid metabolism, laying new groundwork for the idea that pharmacometabolomics offers potent tools for enabling thorough mapping of drug effects.

3. <u>Metabolite Quantification and Analysis:</u> Different detection techniques have been used to locate and measure the metabolites that the body produces. These most frequently entail the use of mass spectrometry (MS) or nuclear magnetic resonance (NMR) spectroscopy, which offer universal metabolite detection, identification, and quantification in individual patient samples. While pharmacometabolomic analyses employ both procedures, there are benefits and drawbacks to employing mass spectrometry (MS) or nuclear magnetic resonance (NMR) spectroscopy-based platforms in this context.

Limitations:

1. There is little dispute about the validity of measuring metabolites to ascertain a person's physiological condition, but the tremendous heterogeneity caused by factors such as age, diet, and commensal organisms raises concerns about the creation of generalised pharmacometabolomes for patient populations.
2. There are arguments for and against NMR and mass spectrometry (MS), and problems with metabolite detection methodology can also relate to the measurement of metabolites in an individual.
3. Correct sample handling and processing, as well as the upkeep and calibration of analytical and computational equipment, are additional constraints associated with metabolite analysis. These jobs call for knowledgeable and experienced specialists, and since continuous sample processing might result in expensive instrument repair costs. Pharmacometabolomics-based therapy analyses are challenging for many facilities to afford due to the high cost of the analytical platforms and processing alone.

Conclusion:

By more accurately determining the best therapy drug and dosage to maximise a patient's reaction to a treatment, pharmacometabolomics may lessen the strain on the healthcare system. In the end, hopefully, this strategy will also reduce the amount of adverse drug reactions (ADRs) connected to numerous treatment plans. In general, doctors would be more equipped to provide their patients with more individualized—and possibly more successful—treatments. But it's crucial to remember that patient samples must be processed and analysed, which adds time to the healing process.

Recent new/Update from the world of medicines ….

New Oral Antibiotic Works Against Drug-Resistant Gonorrhea

A first-in-class antibiotic Zoliflodacin is non-inferior to standard of care (SOC) in the treatment of uncomplicated gonorrhea and also shows activity against resistant forms of the infection, a phase 3 clinical trial has shown. Zoliflodacin is the first new class of antibiotics for *Neisseria gonorrhoeae* — a World Health Organization [WHO] high-priority pathogen — for 25 years, and this is the largest ever trial conducted in gonorrhea. The single-dose oral suspension also had a high microbiological cure rate at urogenital and extragenital sites of infection, and safety was comparable with the standard treatment of ceftriaxone plus azithromycin. There was no resistance to Zoliflodacin detected in the trial. The study was carried out by the nonprofit Global Antibiotic Research and Development Partnership (GARDP), in collaboration with Innoviva Specialty Therapeutics, providing the first example of a successful public-private partnership in the development of a critically needed antibiotic.

FDA Approves Expansion of Treatment Area for Actinic Keratosis Treatment

The US Food and Drug Administration has approved a supplemental new drug application for Tirbanibulin topical ointment, allowing the expansion of the surface area treated for actinic keratosis (AK) of the face or scalp from 25 cm^2 to 100 cm^2. Tirbanibulin is a microtubule inhibitor, approved for the topical treatment of AK of the face and scalp in 2020. based on results from a phase 3, multicentre, open-label, clinical safety study in the United States, which evaluated the safety and tolerability of applying Tirbanibulin to a field of approximately 100 cm^2 on the face or balding scalp of adults with AK. Results were consistent with the results in the original pivotal trials that were conducted on an area of 25 cm^2. Tirbanibulin will be available in two package sizes: 250 mg for the treatment of up to 25 cm^2 and 350 mg for up to 100 cm^2.

Be Cautious…. Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Dabigatran etexilate methanesulfonate	Risk of oesophageal ulcer, oesophagitis
2.	Domperidone	Potential risk of psychiatric withdrawal events when used for lactation stimulation
3.	Atorvastatin	Risk of erectile dysfunction
4.	Clomiphene citrate	Risk of serious visual disturbance (blindness)
5.	Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	Risk of pemphigoid
6.	Etoposide	Risk of electrolyte imbalance

Biosimilars are highly similar to biologics that are already FDA-approved reference products, in terms of their structure, functional characteristics, potency, efficacy and safety. Biologics are one of the costliest therapeutic interventions in the patient care, most of them are limited to the access of such therapies due to economic constraints. In such situations, the introduction of biosimilars (named in Europe), follow-on biologics (in the USA) was of paramount use to cater the needs of such population with limited access. Many companies are developing biosimilars due to the higher expense and loss of patency in upcoming years for the already available biologics therapy. After the initial approval of somatropin (Omnitrope) biosimilar in the year 2006 by the EMA (European Medicines Agency) paved the way for many such biosimilars in the recent past.

Some of the most often utilized biologics include human growth factors, Interferons, erythropoietin and human insulin. Biosimilars for monoclonal antibodies have been increasingly developed in recent years. Moreover, it is also one of the profitable businesses for various biotechnological companies such that these biosimilars may contribute to the considerable amount of its shares in global pharmaceutical market. Biosimilars undergo a smaller number of clinical trials compared to their reference biologics, despite the fact that manufacture still requires production within living cells. This lowers the production cost and final price of the biosimilars in comparison to the reference biologics. (Table 1)

More than thirty biosimilar agents have been approved so far, with ten biological compounds serving as reference products. A number of diseases can be managed with biosimilars. These include diabetes mellitus (DM), various cancers like colorectal, non-small cell lung, cervical, and renal cell carcinoma etc, and various inflammatory disorders such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, inflammatory bowel disease (IBD), ulcerative colitis, and adult Crohn's disease. (Table 2)

Conclusion:

Biosimilars are a game-changer in the pharmaceutical sector because they solve the critical shortage of accessible and reasonably priced biologic treatments. Biosimilars are becoming an essential part of contemporary healthcare due to developments in regulatory frameworks, production methods, and market dynamics. The most recent recommendations or guidelines, developments, and FDA-approved indications for the use of biosimilars should be known by the physicians. The Food and Drug Administration has determined that biosimilars are clinically indistinguishable from their reference biologic drugs with respect to safety, purity, potency, and efficacy; thus, patients should be informed about biosimilars and their comparison to reference biologics.

References:

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2. Ditani AS, Mallick PP, Anup N, Tambe V, Polaka S, Sengupta P, Rajpoot K, Tekade RK. Biosimilars accessible in the market for the treatment of cancer. J Control Release. 2021;336:112-129

Aspects	Biosimilars	Biologics	Generics
Synthesis	Synthesized from living cells	Derived from living cells	Chemically synthesized
Structural comparison to reference Drugs	There may be differences in minor parts of the structure but highly similar to reference biologics in terms of quality, safety and efficacy.	Complex structures	Structurally identical to branded drugs.
Cost	100-300 million 10-20% less cost than reference biologics but more than generics.	80-1000 million Most expensive drug category	2-3 million 80-85% less cost than branded drug
Duration	7-8 years	8-10 years	2-3 years
Drug Development	Comparability studies between the biosimilars and reference biologics Preclinical and Clinical trials Phase I, III and IV	Drug discovery - development Preclinical and clinical trials Phase I, II, III and IV	Only Bioequivalence studies between generics and branded drugs
Regulation	Undergoes more rigorous approval process than generics by FDA and EMA with additional requirements to demonstrate similarity	Heavily regulated by FDA and EMA, with strict guidelines for manufacturing and quality control.	Less regulatory oversight as they only need to demonstrate bioequivalence to the branded drugs

Table 1: The differences between biosimilars, biologics, and generics across various aspects

FDA approved Reference biologics	Biosimilars	Uses
Bevacizumab	Bevacizumab-bvzr bevacizumab-awwb	Colorectal cancer, non-small cell lung cancers, cervical cancer, glioblastoma multiforme, and renal cell carcinoma
Trastuzumab	Trastuzumab-pkrb Trastuzumab-qyyp Trastuzumab-anns Trastuzumab-dttb Trastuzumab-dkst	HER 2- Positive breast cancer
Rituximab	Rituximab-arrx Rituximab-pvvr Rituximab-abb	Granulomatosis with Polyangiitis (GPA), Microscopic polyangiitis (MPA), Chronic lymphocytic leukemia (CLL) and CD20-positive B-cell Non-Hodgkin Lymphoma (NHL)
Filgrastim	Filgrastim-aafi, Filgrastim-sndz	Reduction in febrile neutropenia in cancer patients undergoing chemotherapy
Pegfilgrastim	Pegfilgrastim-bmez, Pegfilgrastim-cbqv Pegfilgrastim-apg, Pegfilgrastim-jmdb	
Insulin glargine	Insulin glargine-yfgn	Diabetes Mellitus
Epoetin alfa	Epoetin alfa-epbx	Anemia
Etanercept	Etanercept-ykro , Etanercept-szzs	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis etc.,
Infliximab	Infliximab-axxq, Infliximab -qbtx, Infliximab -abda, Infliximab dyyb.	
Adalimumab	Adalimumab-fkjp, Adalimumab-adbm, Adalimumab-bwwd, Adalimumab-adaz Adalimumab-afzb Adalimumab-atto	

Table 2: Biosimilars to their USFDA approved reference biologics

New Drug Approvals…

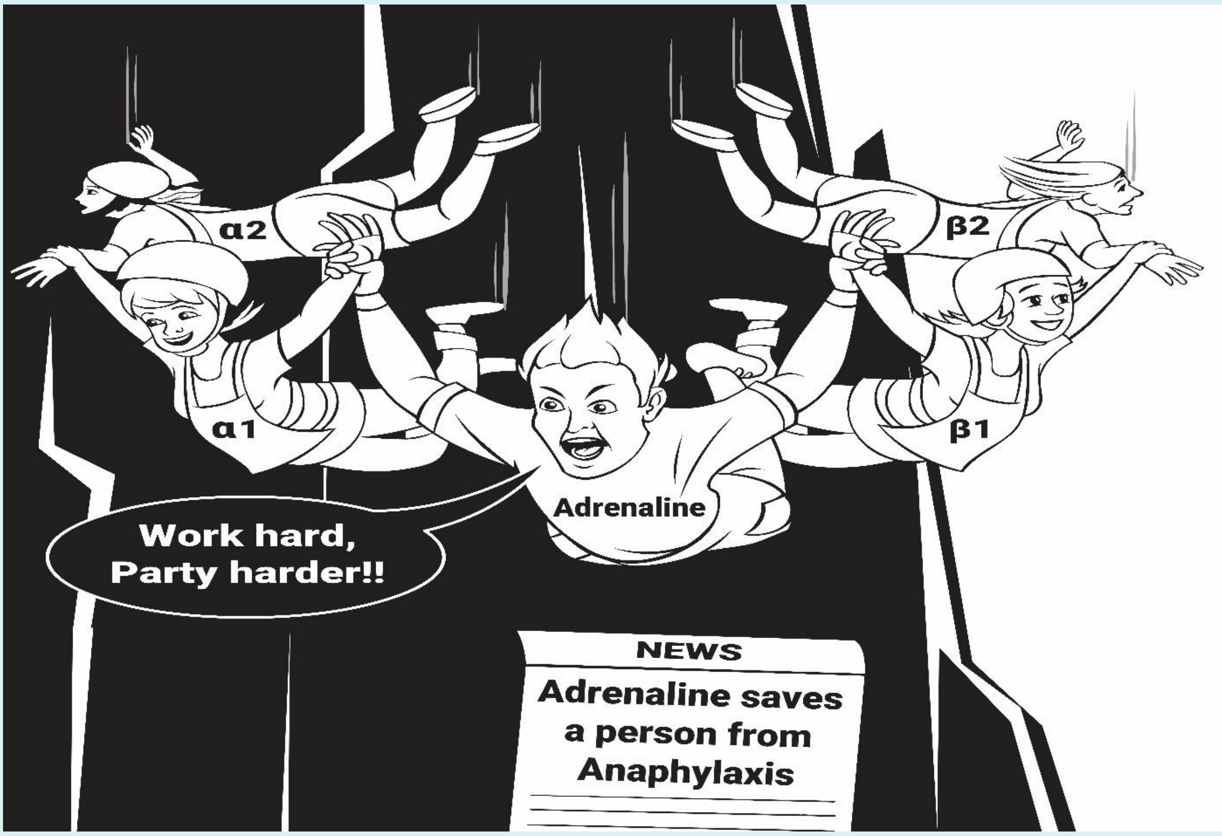
Imetelstat is an oligonucleotide telomerase inhibitor approved for the treatment of adult patients with low-to intermediate-1 risk myelodysplastic syndromes (MDS). The recommended dose is 7.1 mg/kg administered as an intravenous infusion over 2 hours every 4 weeks.

Elafibranor is a peroxisome proliferator-activated receptor (PPAR) agonist approved for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid. The recommended dose is 80 mg orally once daily.

Ensifentrine is a selective dual inhibitor of the phosphodiesterase 3 (PDE3) and phosphodiesterase 4 (PDE4) enzymes approved for the treatment of chronic obstructive pulmonary disease (COPD). The recommended dose is 3 mg inhaled orally BID via standard jet nebulizer with a mouthpiece.

Donanemab is s an amyloid beta-directed antibody approved for the treatment of Alzheimer's disease. The recommended dose is 700 mg administered as an intravenous infusion over approximately 30 minutes every four weeks for the first three doses, followed by 1400 mg every four weeks.

Cartoon Corner…



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

Clinical trials are fundamental in evaluating the efficacy and safety of medical treatments, procedures, and interventions. However, one of the significant challenges faced by researchers in this field is missing data. Missing data can compromise the integrity of trial results, potentially leading to biased conclusions and jeopardizing the reliability of study outcomes. This information delves into the phenomenon of missing data in clinical trials, examining its types, causes, impacts, and strategies for effective management. It underscores the critical importance of addressing missing data to maintain the robustness and validity of clinical research.

Types of Missing Data

Understanding the types of missing data is crucial for developing appropriate strategies to handle them. Missing data in clinical trials can be categorized into three main types:

1. **Missing Completely at Random (MCAR):** Data are considered MCAR when the likelihood of data being missing is independent of both observed and unobserved data. For instance, if laboratory samples are randomly lost due to a shipping error, the missingness is unrelated to patient characteristics or outcomes.
2. **Missing at Random (MAR):** Data are MAR when the missingness is related to observed data but not to the unobserved data. An example is if younger patients are less likely to report their smoking status, and age is recorded in the dataset, the data is MAR.
3. **Missing Not at Random (MNAR):** Data are MNAR when the missingness is related to the unobserved data itself. For instance, patients experiencing severe side effects might be less likely to complete follow-up visits, leading to MNAR data.

Several factors contribute to missing data in clinical trials:

1**. Patient Dropout**: Patients may withdraw from the study due to adverse effects, lack of perceived benefit, or logistical difficulties. This is a common cause of missing data, particularly in long-term trials.
2. **Nonresponse**: Participants may skip specific questions or assessments due to discomfort, misunderstanding, or time constraints. This often leads to partial data within otherwise complete records.
3. **Technical Issues:** Equipment malfunctions, data entry errors, or software glitches can result in missing values. These technical problems can occur at any stage of data collection and processing.
4. **Protocol Deviations:** Inconsistencies in how study protocols are implemented can lead to variations in data collection. This may result in missing data if certain assessments are not consistently administered.
5. **Loss to Follow-Up:** In longitudinal studies, patients may be lost to follow-up, leading to incomplete data over time. This is particularly challenging in studies requiring long-term monitoring.

Implications of Missing Data

1. **Biased Estimates:** Missing data, particularly if MNAR, can bias the results, leading to incorrect conclusions. For instance, if patients experiencing severe side effects are more likely to drop out, the remaining data may underestimate the true incidence of these effects.
2. **Reduced Statistical Power:** Missing data reduces the effective sample size, making it harder to detect true effects. This can result in a loss of statistical power and an increased risk of Type II errors.
3. **Invalid Conclusions:** Incomplete data can lead to false positives or negatives, potentially affecting clinical decisions and policy. This compromises the reliability of the study findings and can misinform clinical practice.
4. **Ethical Concerns**: Poor handling of missing data can compromise patient trust and the ethical integrity of the research.

Strategies to Handle Missing Data

Prevention Strategies:

Study Design: Careful planning can minimize the likelihood of missing data. This includes clear protocols, thorough training of staff, and robust data collection methods.

Patient Engagement: Keeping patients informed and engaged can reduce dropout rates. Regular follow-ups and addressing patient concerns promptly can help maintain participation.

Monitoring and Early Intervention: Regularly monitoring data collection and addressing issues as they arise can prevent data loss.

Handling Missing Data:

Deletion Methods:

Listwise Deletion: Excludes entire cases with any missing value. This is simple but can lead to significant data loss if missingness is high.

Pairwise Deletion: Uses all available data points for each analysis. This retains more data but can lead to inconsistencies because different analyses might use different subsets of data.

Imputation Methods:

Mean/Median/Mode Imputation: Replaces missing values with the mean, median, or mode of the observed values. This is easy to implement but can underestimate variability and distort distributions.

Regression Imputation: Uses regression models to predict and fill in missing values based on observed data. This maintains relationships between variables but can underestimate variability.

Multiple Imputation: Creates several imputed datasets, analyses each one, and combines the results. This accounts for the uncertainty associated with missing data and generally provides more accurate estimates.

Model-Based Methods:

Maximum Likelihood (ML): Estimates model parameters by maximizing the likelihood function based on available data. This provides unbiased estimates under MAR conditions but requires complex computations.

Bayesian Methods: Incorporates prior distributions and observed data to estimate missing values. This is flexible and can handle different types of missing data mechanisms.

Advanced Techniques:

Machine Learning Approaches: Algorithms like k-Nearest Neighbours (k-NN), Random Forest, and neural networks can be used for imputation. These methods can capture complex relationships in the data but may require substantial computational resources.

Expectation-Maximization (EM) Algorithm: Iteratively estimates missing values and model parameters, suitable for complex models and datasets.

Conclusion:

Missing data is an inevitable challenge in clinical trials, with significant implications for the validity and reliability of research findings. By understanding the types, causes, and impacts of missing data, researchers can develop and implement effective strategies to manage it. Advanced methods such as multiple imputation, machine learning approaches, and Bayesian methods offer robust solutions for handling missing data. However, prevention through careful study design and patient engagement remains critical. Ethical considerations and adherence to guidelines are essential to ensure the integrity of clinical trials. As the field continues to evolve, ongoing research and innovation will further enhance our ability to manage missing data, ultimately improving the quality and reliability of clinical research.

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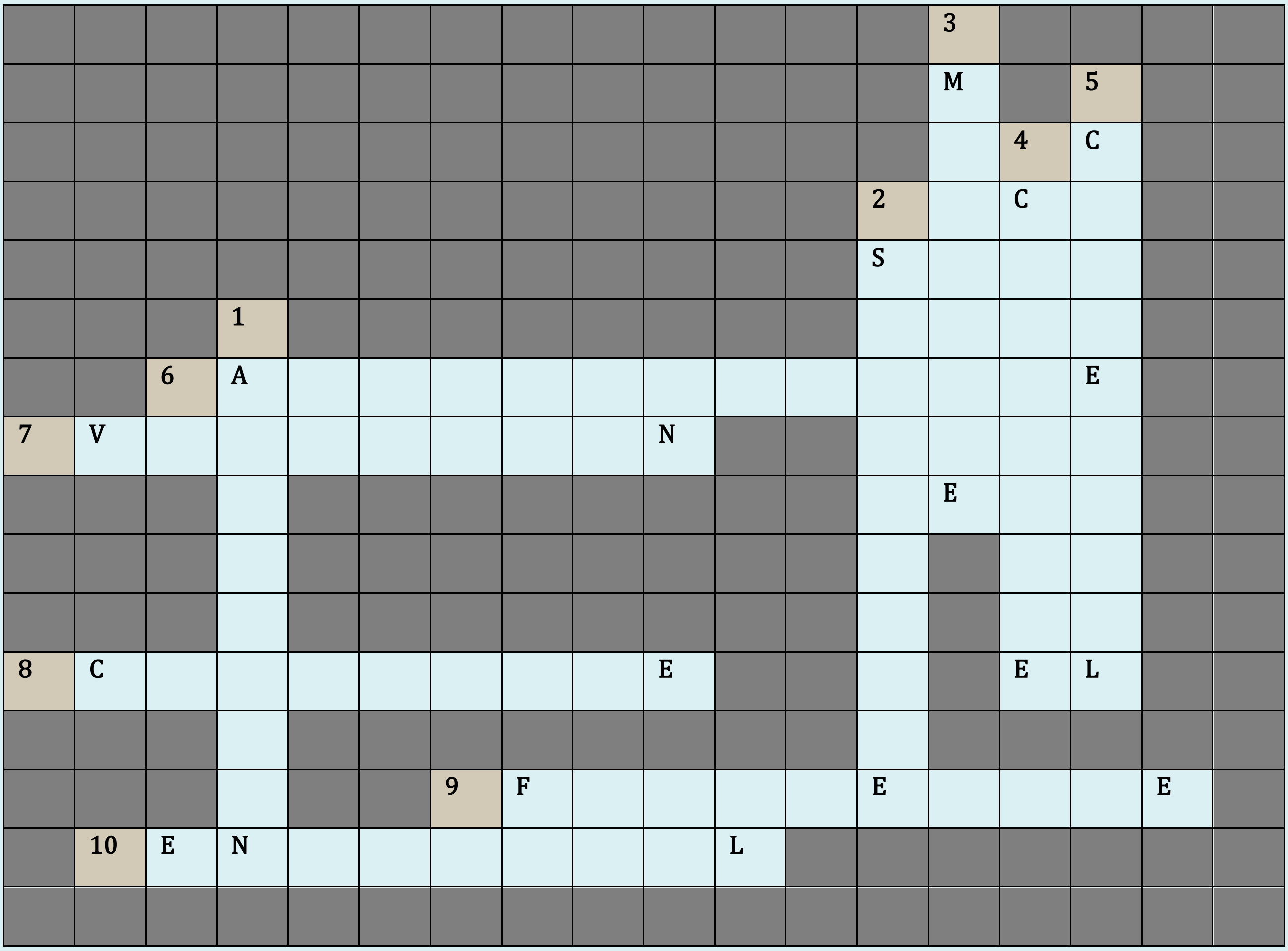

Downward	***Across***
1. Selective α_1 Receptor antagonist (*9*)	6. Tricyclic antidepressant which acts by inhibition of reuptake of 5-HT & NA (*13*)
2. Drug used in Parkinson's disease acts by inhibition of MAO -B enzyme (*10*)	7. AT_1 Receptor antagonist used in treatment of hypertension *(9)*
3. Alkaloid obtained from plant *Papaver somniferum* (*8*)	8. Atypical antipsychotic drug reserved for cases of refractory schizophrenia *(9)*
4. Central sympatholytic drug acts selectively as agonist at α_{2A} receptor in the brain (*9*)	9. High Ceiling (Loop) Diuretic acts by Inhibition of Na^+-K^+-$2Cl^-$ Cotransport mechanism *(10)*
5. Drug which blocks both α and β receptors (*10*)	10. Angiotensin Converting Enzyme (ACE) inhibitor used in hypertensive disorders *(9)*

Answer to the Crossword Puzzle is given below:

Downward

1. Alfuzosin 2. Selegiline 3. Morphine
4. Clonidine 5. Carvedilol

Across

6. Amitriptyline 7. Valsartan 8. Clozapine
9. Furosemide 10. Enalapril