ESSENCE

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 14th issue of ESSENCE.

Circadian rhythm controls most of the physiological functions of the body and giving a drug at the right time can greatly increase the effectiveness of drug therapy. The current issue talks about the field of Chronopharmacology and use of knowledge of biological rhythms to develop an optimal time when the drug would be most effective.

With everything becoming virtual, it's no surprise that clinical trials have also gone the virtual mode. These Virtual Clinical Trials (VCTs) are a relatively new and underutilised technique of conducting clinical research that makes use of technology (apps, electronic monitoring devices, and so on) and online social interaction platforms. VCTs are cost-effective, time-saving, user-friendly. They are able to recruit more quickly, enhance retention, and expand participant diversity and representation by utilising digital health technology. We have an interesting write-up on Virtual Clinical Trials in the current issue.

With multiple groups of drugs approved for treatment of any clinical condition, it is important to know the treatment algorithm followed and the role/place of each drug in the management of a patient. From this issue onwards, we are starting a guest column giving us the clinicians perspective on pharmacotherapy of a given condition. The current issue has clear, concise and updated outline of pharmacological management of Type II Diabetes Mellitus.

Further, like always, we have new drug approvals, recent updates and crossword.

Happy Reading.

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

Circadian rhythm and its impact on body physiology and chronopharmacology

The suprachiasmatic nucleus (SCN) in the hypothalamus is one of the major regulators of the circadian clock as it receives afferent input from retina through the retinohypothalamic tract. The efferent from SCN traverses to different organ systems e.g., autonomic, endocrine (including HPA axis), and immune systems to carry out modulation of the functioning of other body systems practically affecting body physiology at all levels e.g., at individual level (e.g., sleep-awake cycle), at cellular level, at the genetic and epigenetic level.

Chronopharmacology basically deals with the impact of biological rhythms on pharmacotherapy and uses the knowledge of biological rhythms to develop an optimal time when the drug would be most effective.

Pharmacokinetics and Circadian rhythm:

The Pharmacokinetics incl absorption, distribution, metabolism and excretion can be deeply influenced by the time of the day having implications on the effectiveness of pharmacotherapy. Chrono-pharmacokinetics evaluates the impact of the circadian rhythms on the pharmacokinetics of drugs. Many factors which govern drug absorption remains under the control of circadian rhythm e.g., gastric acid (highest acid secretion just before midnight). The expressions of different types of transporters (e.g., Pept1, Mrp2, Mdr1, Mct1 and Bcrp1) are also under circadian control. Plasma protein concentrations (α1 acid glycoprotein and albumin) are lower at night influencing the bound and unbound fractions of the drugs. Distribution of drugs, hepatic and renal clearance depends upon the blood flow to the respective organs, and circadian variation in blood flow is well established. Even the hepatic intrinsic clearance parameters e.g., hepatic enzyme activity changes over the 24 hours in a timely manner. Phase 1 oxidations reactions are accentuated during daytime and the activity of sulfation reactions are maximum at night. Highest GFR is observed during the day. Thus, it can lead to fluctuations in drug levels at different times of the day.

Chrono-pharmacology in day-to-day practice: few common examples:

The most common example for illustration of Chronopharmacology comes from the management of insomnia. The level of melatonin (sleep hormone) is highest in the evening and peaks at bedtime. Using this principle, melatonin agonists are given at a fixed time at night.

Effect of circadian rhythm is easily noticeable in the cardiovascular system. Blood pressure and heart rate decrease at night and increase in the morning hours. Again, plasma fibrinolytic activity is decreased in morning. All these findings correlated with increased risk of cardiovascular events in the early hours of the morning. Interestingly, hypertension represents an excellent condition to be treated by chronopharmacotherapy principles. As the level of BP is generally higher in the morning, a common general principle is that the antihypertensive medications are to be administered at higher doses in in the morning and the midnight concentration of the drug should be low (at that time BP level generally remains low). On the basis of the pattern of diurnal variation, hypertensives can be further categorized into morning surge, dipper or non-dippers. However, the principles can't be generalized to all class of antihypertensive drugs.

Drug name	Impact of circadian rhythm
Aminoglycosides	Higher nephrotoxicty is noted with night-time administration (owing to decreased night-time renal elimination).
NSAIDs	Concentration (Cmax) higher after morning administration. Among patients with rheumatoid arthritis, (as there is morning stiffness), starting NSAIDs early in the morning before starting of daily activities is advised.
Statins	To be prescribed as evening dose as the activity of HMG-CoA reductase activity is highest at night.
Beta blockers	Sympathetic activity is highest in the morning. So, preferably to be administered in the morning hours.
H2 antihistamines	To be administered at bedtime in peptic ulcer disease as there is an increase in gastric secretion in the evening and at night.
Anti-epileptic drugs	Preferably to be given in the early morning hours, before getting out of bed as there is higher seizure occurrence risk between 6-7 AM. Also, better absorption of these drugs in morning.
Antihypertensive drug	Dippers: Anti-hypertensives to be prescribed in morning. Non dippers: Give antihypertensive drugs in the evening or divide the total dose into morning and evening dose.
5 Fluorouracil	Significant diurnal variation, owing to circadian control of the activity of metabolizing enzyme dihydropyrimidone dehydrogenase.
Rivaroxaban	In animal model, factor X activity peaks in the middle of the light phase and the factor X inhibitory action of rivaroxaban was better when it was administered at the beginning of the light phase.
Corticosteroids	Early morning dose of corticosteroids is advised as it mimics the timing of the body's own endogenous production of this hormone.

Conclusion:

To conclude, circadian rhythm has a crucial control on the pharmacokinetics and pharmacodynamics of many drugs. Complying with principles of Chronopharmacology can aid to better patient management by enhancing kinetic profiles, enhancing efficacy and decreasing toxicity.

Reference:

1. Dallmann R, Brown SA, Gachon F. Chronopharmacology: New Insights and Therapeutic Implications. Annu Rev Pharmacol Toxicol. 2014 Jan 6;54:10.1146/annurev-pharmtox-011613–135923.

2. Dobrek L. Chronopharmacology in Therapeutic Drug Monitoring—Dependencies between the Rhythmics of Pharmacokinetic Processes and Drug Concentration in Blood. Pharmaceutics. 2021 Nov;13(11):1915.

Recent new/Update from the world of medicines ….

Enzyme inducing anti-seizure medicines (eiASM) associated with increased risk of long-term cardio-vascular diseases. Is it now time to retire eiASM?

Long-term use of eiASMs in patients with epilepsy is linked to a significant increase in cardiovascular disease namely IHD, Ischemic stroke, TIA, or haemorrhagic stroke. Medications classified as enzyme-inducing include Carbamazepine, Eslicarbazepine, Oxcarbazepine, Phenobarbitone, Phenytoin, Primidone, Rufinamide, and Topiramate. Compared with patients who used non-enzyme-inducing medication, eiASM users with persistent exposure to more than four prescriptions had a median risk increase from 1.54 (95% CI, 1.28 - 1.79). Results from the study showed that even short-term exposure to eiASMs was significantly associated with an increased risk for IHD, or ischemic or hemorrhagic stroke. For patients who used eiASMs for 10 years or longer, especially those with high-dose prescriptions, the risk increased exponentially with each passing year.

Statin Intolerance 'Overestimated and Overdiagnosed

Statin intolerance is far less common than previously reported, according to a new meta-analysis of more than 4 million patients worldwide from 176 studies: 112 RCTs and 64 cohort studies. The study puts the prevalence of statin intolerance at 6% to 10%, which is much lower than the reported prevalence of 10-50%. The main factors associated with an increased risk for statin intolerance were found to be female gender, hypothyroidism, high statin dose, advanced age, concomitant use of anti-arrhythmic drugs, and obesity.

In many cases, when a patient complains of muscle pain, or have elevated alanine aminotransferase (ALT), many physicians attribute them to statin intolerance and immediately discontinue statins, without any further investigations. The authors suggest that we should evaluate patients' symptoms very carefully, firstly to see whether symptoms are indeed caused by statins, and secondly to evaluate whether it might be patients' perceptions that statins are harmful — so called nocebo effect — which could be responsible for more than 50% of all symptoms, rather than the drug itself. Use of Statin-Associated Muscle Symptom Clinical Index (SAMS-CI) to assess the likelihood that a patient's muscle symptoms are caused or worsened by statin use can be useful to identify correctly cases with statin intolerance.

Be Cautious…. Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Cefoperazone	Bleeding and hypoprothrombinemia
2.	COVID-19 vaccine NRVV Ad (ChAdOx1 nCoV-19)	Guillain-Barre syndrome (GBS)
3.	Vemurafenib	Hyperglycemia
4.	Escitalopram	Postpartum Haemorrhage
5.	Amiodarone	Gastrointestinal Haemorrhage

Clinical drug development is a lengthy and difficult process that takes 6–15 years to complete. From research and development to marketing approval, the cost of generating a new medicine is around USD 2.6 billion. Approximately 85% of medicines fail during the early stages of clinical development, and only half of those that make it to phase 3 are authorised. Patient recruitment is the single most common cause of clinical trial delays, with enrolling difficulties accounting for 30% of phase 3 research terminations.

Virtual clinical trials (VCTs) are a relatively new and underutilised technique of conducting clinical research that makes use of technology (apps, electronic monitoring devices, and so on) and online social interaction platforms. VCTs are not a new or distinct type of clinical trial; rather, they are a modification of clinical trials that make them more cost-effective, time-saving, and user-friendly. VCT is able to recruit more quickly, enhance retention, and expand participant diversity and representation by utilising digital health technology.

Recruitment, Informed Consent and Pre-screening of Virtual Clinical Trial

1. Web-based platforms (e.g., Google search engine) and social media are used to recruit patients in VCT. The availability of patients is not limited by geography, and possible eligible patients can be found all around the world.

2. If the ethical review board allows it, informed consent can be given remotely. Participants' understanding of informed consent can be tested via an online questionnaire. Before granting consent, participants have the option to ask questions and discuss pertinent topics with the investigator through phone or online call-in addition to the online material.

3. Patients can participate in VCT pre-screening by signing up, providing extra information, and answering on his/her demographic, disease history, and geographic location on the questionnaires provided in the specified website of the investigator.

4. The inclusion requirements can be met by validating the diagnosis on the same online recruitment platforms by uploading images of body portions affected by the disease.

Trial Site of Virtual Clinical Trial

VCT involves a small number of research sites. In global trials, there is generally only one site, or one site in each country, overseen by a main investigator whose team reviews all of the data as it is provided in real time to monitor the participants' health and safety. A remote study coordination centre oversees all research efforts and manages them centrally.

Advantages of Virtual Clinical Trial

1. Participants who might be normally excluded from or hesitant to participate in a standard clinical trial can benefit from VCT. The aged, disabled, and those with mobility concerns can take part in VCT. It is open to patients who live in rural areas or who live a long distance from the trial sites. Trial-related activities such as education and information are carried out through videoconferences, telemedicine, and other technology.

2. VCT is also useful for studying rare diseases or unusual exposures, where it's vital to enrol as many people as possible. A more diversified patient population may also be more representative of the real-world than traditional clinical trials as a result of this broad recruitment strategy.

3. Photos, remote visits, or in-house nurse visits can all be used to conduct a physical examination of the patient. Microsampling, a home-based kit, a mobile phlebotomist, or a clinic close to the patient can provide laboratory tests and medical imaging in VCT. The medications are delivered to the patients' homes.

4. VCT data can be collected from a variety of sources and reporters, including mobile devices such as phones, applications, watches, electronic patient-reported outcomes, and e-diaries.

5. The electronic clinical outcome assessment, consumer-generated physiological and behavioural data acquired through connected digital technologies, such as digital biomarkers, can be used to assess the VCT's outcomes.

6. Savings related to money and time with VCT may be realised from an economic standpoint as well as shorter enrolment periods which leads to faster data collection and reduce the time spent in conducting the study.

Limitations of Virtual Clinical Trial

Despite its many advantages, VCT has several drawbacks that must be addressed.

1. Recruitment challenges, which could be explained by the fact that the older generation is unfamiliar with modern technologies and social media, which could affect elderly involvement in the VCT.

2. The lack of human involvement throughout the recruitment process can be a deterrent, particularly for elderly patients who want a personal bond.

3. The self-enrolment idea can lead to the recruitment of a convenience sample of the population that may differ from the broader population in terms of specific demographic or disease-related features, reducing the generalizability of the results.

4. There are concerns about sending significant amounts of sensitive health data via the internet. The recruited participants' privacy is also a problem.

5. For implementation and operational efficiency, the study coordination centre requires a sophisticated information technology platform.

6. Furthermore, the regulatory framework for approving VCT for pharmaceutical research is still in its infancy, making guidance in this area ambiguous.

7. A full VCT may not be recommended for acute life-threatening disorders (e.g., strokes).

To summarise, research has shown that VCT is not only operationally possible, but also successful. VCT has a higher rate of recruitment, better compliance, reduced drop-out rates, and faster. VCT has shown promising effects in phase 2–4 clinical trials.

Reference

1. Ali Z, Zibert JR, Thomsen SF. Virtual Clinical Trials: Perspectives in Dermatology. Dermatology. 2020;236(4):375-382.

New Drug Approvals…

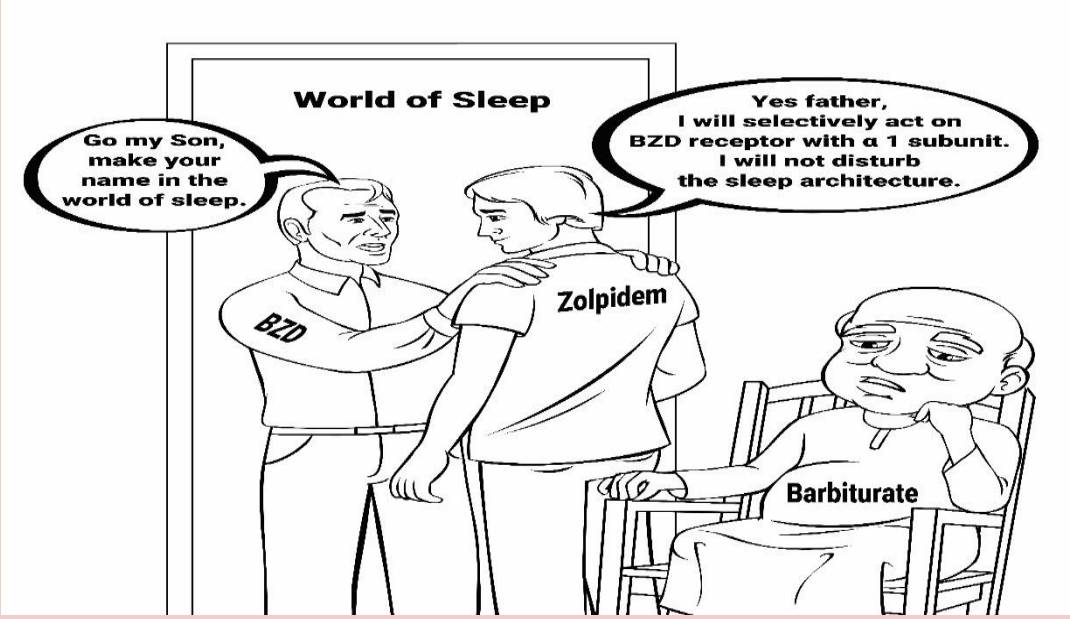
Daridorexant is a dual orexin receptor antagonist approved for the treatment of insomnia. The recommended dose is 25 -50 mg orally once per night.

Inclisiran is a small interfering RNA (siRNA) directed to PCSK9 (proprotein convertase subtilisin kexin type 9) mRNA approved for the treatment of heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease as an add-on therapy. The recommended dose is 284 mg subcutaneous injection at the start, at 3 months and later every 6 months.

Tebentafusp is a bispecific gp100 peptide-HLA-directed CD3 T cell engager approved for the treatment of unresectable or metastatic uveal melanoma. The recommended dose is 20 mcg intravenously on Day 1, 30 mcg intravenously on Day 8, 68 mcg intravenously on Day 15, and 68 mcg intravenously once every week thereafter.

Sutimlimab is a classical complement inhibitor approved to decrease the need for red blood cell (RBC) transfusion due to hemolysis in adults with cold agglutinin disease (CAD). The recommended dose is 6,500 mg by intravenous infusion weekly for two weeks then every two weeks.

Cartoon Corner…



"Drug Autobiographies in Pharmacology" by Dr. Sushil Sharma

The following scheme of treatment is predominantly based on 2022 guidelines of the American Diabetes Association.[1]

Initiating treatment:

Treatment is generally started as monotherapy with metformin in the absence of contraindications such as chronic kidney disease (CKD) with a glomerular filtration rate < 30 ml/min/1.73 m^2. Dose of the sustained release preparation varies from 500 mg to 2000 mg per day.

When the glycated haemoglobin (HbA1c) is ab initio greater than 1.5% above the target level of 7% i.e., > 8.5%, metformin and vildagliptin (50 mg BD) combination is the preferred initial treatment as starting with this combination slowed the progressive worsening of glycaemic control in comparison to sequential therapy with metformin followed by metformin plus vildagliptin combination in the VERIFY trial.[2]

When the plasma glucose is more than 300 mg/dl or HbA1c is > 10% or patient has osmotic symptoms (thirst, polyuria) or weight loss, it is preferable to initiate treatment with either insulin or sulphonylurea- preferably insulin. See the section on injectable therapy for details on how to initiate and titrate insulin.

Intensifying treatment:

Treatment is usually started with the lowest dose of the selected drug and titrated upwards till the glycaemic targets are achieved or till the limit of tolerance is reached or maximum permissible dose is reached, whichever is least. The targets of treatment are: pre-prandial glucose -80-130mg/dl; peak postprandial glucose < 180 mg/dl and a HbA1c < 7%. HbA1c may be repeated every 3 months to achieve and maintain control.

As diabetes is a progressive disease, a second or a third drug each of a different class may need to be added consecutively. The preferred second drug to be added after metformin may be DPP IV inhibitors or SGLT2 inhibitors due to their low risk of hypoglycaemia and low likelihood of weight gain. Sulphonylureas may be prescribed if cost is a major consideration - however they are notorious for hypoglycaemia and weight gain. Thiazolidinediones, though low cost, are less often prescribed, usually as third or fourth agent in view of their numerous side effects such as weight gain, oedema, bone loss and precipitation of cardiac failure.

Specific agents for specific situations/co-morbidities/ complications:

1. CKD stage 3 or below (GFR < 60ml /min/1.73 m^2): Sodium Glucose Co-transporters (empagliflozin, canagliflozin and dapagliflozin) should be part of glucose lowering regime in patients with GFR > 25 ml/min/1.73 m^2 and albuminuria > 300 mg per 24 hours.

2. Patients with atherosclerotic cardiovascular disease (ASCVD), those at high risk of ASCVD or those in CKD stage 3 or below without albuminuria, following drugs may be preferred irrespective of metformin use for their cardiovascular disease benefits, alone or in combination:

a) SGLT2 inhibitors – empagliflozin or canagliflozin

b) Glucagon like Peptide -1 (GLP-1) analogues: dulaglutide, liraglutide and semaglutide. Of these semaglutide alone has an oral form, rest require subcutaneous injection.

3. Heart failure: Empagliflozin, canagliflozin or dapagliflozin are to be included if not contraindicated.

4. Predominantly post-prandial hyperglycaemia: When the pre-prandial is controlled (80-130 mg/dl) with existing medication and post-prandial remains high (> 180 mg/dl); thereby contributing to an HbA1c higher than target, alpha-glucosidase inhibitors (acarbose, voglibose and miglitol) are an excellent choice.

Injectable Therapy:

Once it has been judged that the higher efficacy of injectable therapy is required to control glycaemia, the ADA recommends the usage of GLP-1 analogues in the first instance as an add on to pre-existing oral therapy. This may not be practical in India due to the high cost.

The next best injectable approach would be to start with basal insulin 0.1-0.2 U /Kg/day (Glargine, Degludec, Detemir or NPH). Titrate upwards at 2U per day every 3 days to achieve fasting target (usually 80-130 mg/dl). All oral agents may be continued at this stage.

Intensified Insulin therapy:

If after achieving normal fasting, HbA1c remains above normal, prandial insulin (regular, lispro, aspart, glulisine) may be added at 4U or 10% of basal dose; one, two and then three times before the meals, stepwise. starting with the largest meal or the one with maximum post-prandial excursion. Prandial insulin is titrated by 1-2 U weekly to achieve post-prandial glucose below 180 mg/dl.

An alternate approach would be to split the total daily dose of basal insulin into twice daily premixed insulin given two thirds in the morning and one third in the evening and titrated to achieve specific glycaemic targets.

At this stage of intensified insulin therapy metformin, thiazolidinediones and SGLT-2 inhibitors can be continued or even newly added, while sulphonylureas and DPP IV inhibitors can be stopped.

Finally, no treatment for diabetes mellitus is complete without appropriate blood pressure and anti-lipidemic therapy titrated to specified targets. Appropriate diet, smoking cessation, stress relief, exercise and an active lifestyle remain the cornerstone of treatment, without which pharmacological control of glycaemia alone is not sufficient.

References:

1.Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2022 Diabetes Care 2022;45(Suppl. 1): S125–S143.

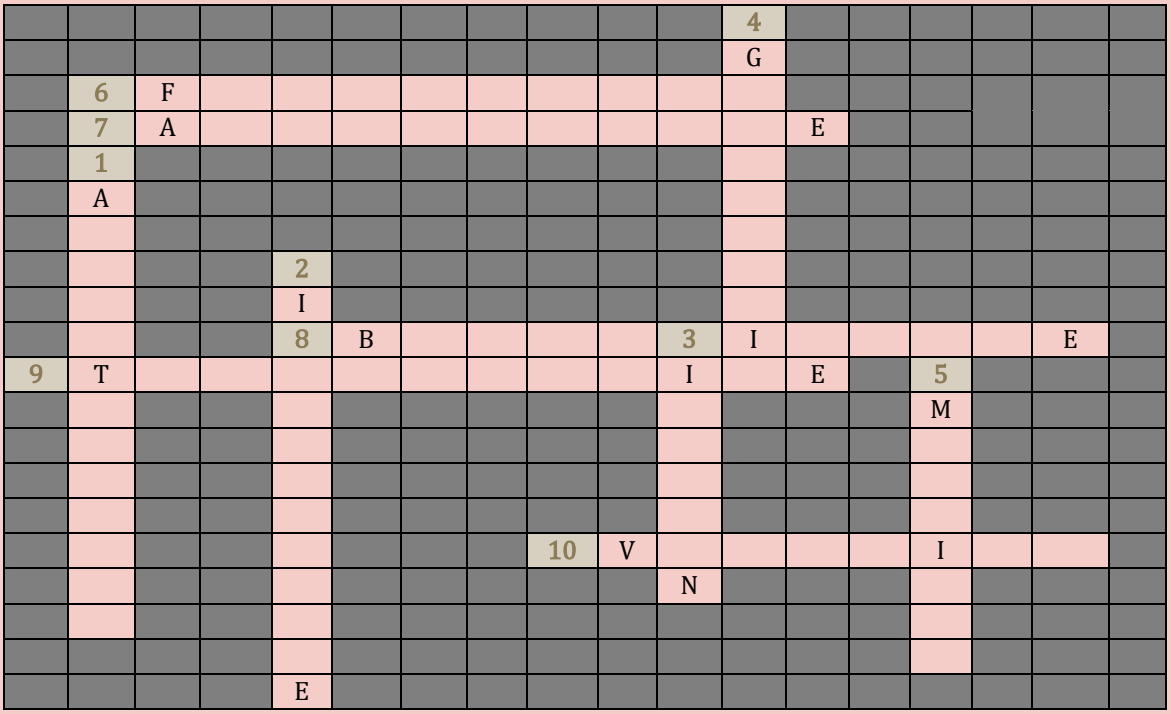
2. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S; VERIFY study group. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. Lancet. 2019; 394:1519-1529.

Authored by:

Dr. Suresh Vaikkakara
Professor and Head
Department of Endocrinology
AIIMS, Mangalagiri

Crossword Puzzle…

Hint: *Drugs Causing Hypokalaemia*



Downward	**Across**
1. Antibiotic obtained from fungus and used against other fungi (13) 2. Sympathomimetic drug which acts on all β receptors with devoid of alpha action (12) 3. Endocrine hormone which is a polypeptide made of 51 amino acids (7) 4. Antimicrobial agent acts selectively on Gram –ve aerobic organisms (10) 5. Osmotic diuretic (8)	6. High ceiling diuretic which acts at thick ascending limb of loop of Henle (10) 7. Mineralocorticoid which conserves the maximum Na^+ in the body (11) 8. Drug acts at distal convoluted tubule of nephron by blocking Na^+ -Cl^- co-transporter (12) 9. Phosphodiesterase non-specific inhibitor used in bronchial asthma (12) 10. Water soluble vitamin (8)

Answers:

Downward

1. Amphotericine
2. Isoprenaline
3. Insulin
4. Gentamicin
5. Mannitol

Across

6. Furosemide
7. Aldosterone
8. Benzthiazide
9. Theophylline
10. Vitamin B_{12}