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FROM THE EDITORIAL DESK….

Dear Friends, Greetings from Department of Pharmacology and welcome to the 23rd issue of ESSENCE

Phase 4 clinical trials are of utmost importance in the progression of drug development because they ensure that the advantages reported in previous stages remain in real-world settings and for long periods of time. They act as a bridge between regulatory approval and standard clinical practice. Phase 4 trials are now an integral part of evidence-based medicine, leading to better patient care and public health.

Prescribing drugs in elderly populations is complex and fraught with difficulties. Older persons are frequently left out of premarketing medication trials, and approved dosages might not be suitable for them. Age-related variations in pharmacokinetics (i.e., drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (i.e., drug's physiological effects) mean that many drugs should be used extra cautiously. The current issue addresses these two crucial topics namely Phase 4 clinical trials and Drug prescribing in elderly population.

Sample size is one of the most important aspects to be considered when planning any research study and the current issue has a guest article on its various aspects including calculation of sample size for various types of study designs.

Further, as always, the current issue has new drug approvals, interesting news from the world of medicines, crossword puzzle on 'Drugs causing Bullous Pemphigoid' 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

Development of a new drug is a complex process. In most cases, it takes more than ten to fourteen years and involves a significant amount of research. This research may include preclinical studies, and various phases of clinical trials, beginning with phase zero (micro-dosing) and progressing all the way up to phase 4. In the phase zero trials, extremely small doses of a substance that are not pharmacologically active are administered in order to determine the pharmacokinetic profile of the drug in humans. Phase 1 clinical trials are done on healthy volunteers to test the drug's safety and tolerability. Phase 2 clinical trials are done on patients to test the drug's therapeutic efficacy and see if it can ultimately benefit the patient including dose ranging studies. This evaluation aids in the identification of an optimal dose and treatment regimen that can be further investigated in phase 3 trials. Potential drug's safety and efficacy are extensively evaluated in phase 3 trials before regulatory agencies consider granting market approval. Phase 4 trials are "post-marketing surveillance" studies after the approval.

Phase 4 trials, also known as "Therapeutic use studies." These are observational studies conducted on drugs that have received approval from the FDA. The objectives of these trials are two-fold; firstly, to identify rare but serious adverse drug reactions not apparent in earlier phases, and secondly, to confirm /assess the pharmacological effectiveness of drug in diseases, population, or doses that are either similar to or significantly different from the original study population. These studies additionally evaluate different dosage formulations, treatment durations, and other factors related to drug comparison. Therapeutic use studies extend beyond the previous validation of the drug's safety, effectiveness dosage determination and hold significant importance in optimizing the utilization of drug. The task at hand involves the continuous monitoring of safety within extensive populations, as well as the identification of other uses of drug. These studies include a sample size consisting of thousands of participants and it has no fixed duration. During the term of New Drug Status, manufacturers are required to submit Periodic Safety Update Reports (PSUR) to the Drug Controller Authority.

Phase 4 studies may be mandated by regulatory agencies or initiated by the sponsoring organization for competitive purposes, such as exploring new markets for the drug, or these studies may be conducted to assess potential drug interactions with other drugs or to evaluate the drug's effects on specific population groups, such as children, older people, pregnant women, etc.

During the Phase 1-3 clinical trials, there are usually a limited number of patients and a short amount of time to conduct the safety monitoring. The goal of the safety surveillance in Phase 4 trials, is to identify any unusual severe or long-term adverse effects over a significantly larger patient group. When severe adverse effects are detected during Phase 4 studies, the drug’s usage is restricted to specific therapeutic applications or discontinued from the market.

The following are the rationale for carrying out Phase 4 clinical trials:

1. Prior to phase 3, patients in clinical trials are selected, and the total number of participants is restricted.
2. The duration of trials is limited.
3. The conditions of use in clinical trials exhibit variations when compared from those observed in the context of routine clinical practice.
4. Rare but serious adverse drug reactions, chronic toxicity, appropriate dosing for vulnerable populations such as children, the elderly or pregnant women, and drug interactions are frequently unknown.

FDA programs allow drug manufacturers, physicians, and consumers to report problems pertaining to approved drugs. MedWatch serves as a platform via which individuals may report issues related to drugs, medical devices, as well as get updated safety information. Individuals have the option to enroll in periodic MedWatch safety notifications. In India, the Pharmaco-vigilance programme of India (PvPI) looks after the Adverse Drug Reaction (ADR) reporting and monitoring of drugs and generate country specific data which is also shared with the WHO centre at Uppsala.

Conclusion:

Phase 4 clinical trials are of utmost importance in the progression of drug development because they ensure that the advantages reported in previous stages remain in real-world settings and for long periods of time. These studies not only assist continual safety surveillance, but also shed light on the efficacy and cost of drug therapies. Phase 4 trials provide a dynamic platform for improving treatment guidelines, making the most use of healthcare resources, and deepening our understanding of the long-term effects of drug therapies. They act as a bridge between regulatory approval and standard clinical practice. Phase 4 trials are now an integral part of evidence-based medicine, leading to better patient care and public health.

References:

1. Umscheid CA, Margolis DJ, Grossman CE. Key concepts of clinical trials: a narrative review. Postgrad Med. 2011;123(5):194-204.
2. U.S. Food and Drug Administration (FDA). The Drug Development Process. Step 5: FDA Post-Market Drug Safety Monitoring; https://www.fda.gov/patients/drug-development-process/step-5-fda-post-market-drug-safety-monitoring.

Recent new/Update from the world of medicines ….

A new dawn in the fight against Tuberculosis

Medical researchers are striving to fast-track the development of innovative Tuberculosis (TB) treatments. They have announced the start of a phase 2B/C clinical trial program (UNITE4TB). UNITE4TB's innovative phase 2B/C trials will test 14 combinations of nine existing drugs, as well as two newly developed candidates (GSK656 and BTZ-043). The ultimate aim is to create regimens that can further improve multidrug-resistant (MDR) treatment, and also be effective for drug-sensitive TB. UNITE4TB's explorative regimens have been constructed by combining the novel compounds GSK656 and BTZ-043 with the most recently licensed drug classes: diarylquinoline (bedaquiline) and nitroimidazoles (delamanid or pretonamid). The trial will also explore the efficacy of a totally new combination of GSK656 and BTZ-043 together with bedaquiline and delamanid. The announcement is a major milestone for the project and the TB community as a whole.

Long-Term Use of ADHD medicines increase CVD Risk

Longer cumulative use of medication to treat attention-deficit/hyperactivity disorder (ADHD) is associated with a small, but statistically significant, increased risk for cardiovascular disease (CVD), results of a large Swedish nested case-control study suggest. The increased risk was evident for Hypertension and Arterial disease, was dose-dependent, and was higher for stimulant than nonstimulant ADHD medications. Across the 14-year follow-up period, each additional year of ADHD medication use was associated with an average 4% increased CVD risk, with a larger 8% increased risk in the first 3 years of cumulative use, followed by stable risk over the remaining follow-up. When focusing on specific ADHD medications, methylphenidate and Lisdexamphetamine was associated with an increased risk for CVD. In contrast, use of the nonstimulant Atomoxetine was associated with elevated CVD risk only for the first year of use.

Be Cautious…. Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Hydrochlorothiazide	Acute Respiratory Distress Syndrome (ARDS)
2.	Itraconazole	Hypokalaemia
3.	Methotrexate	Progressive Multifocal Leukoencephalopathy (PML)
4.	Olanzapine	Hyponatraemia
5.	Terlipressin	Respiratory Failure, Sepsis
6.	Systemic Corticosteroids	Pheochromocytoma Crisis (PC)

An important aspect of providing care for an elderly person is optimising medication therapy. A complex series of steps go into writing a prescription, including determining whether a drug is indicated, selecting the best medication, figuring out a dose and schedule that suit the patient's physiologic status, monitoring the drug's effectiveness and toxicity, informing the patient about potential side effects, and indicating when to seek a consultation. There are particular difficulties when prescribing for elderly individuals. Older persons are frequently left out of premarketing medication trials, and approved dosages might not be suitable for them. Age-related variations in pharmacokinetics (i.e., drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (i.e., drug's physiological effects) mean that many drugs should be used extra cautiously. When administering medication to elderly persons, special consideration must be given to the dosage. As people age, their proportionate increase in body fat in comparison to skeletal muscle may lead to an increased volume of distribution. Even in the absence of renal illness, decreased medication clearance may arise from the age-related natural loss in renal function. Elderly people have higher plasma drug concentrations due to longer drug half-lives and reduced clearance, which result in larger drug storage reservoirs.

Prescription drug appropriateness and overall quality are influenced by a number of factors. Keeping an eye out for side effects and drug levels, avoiding drug-drug interactions, avoiding improper pharmaceutical use, involving the patient and integrating patient values are a few of these.

Polypharmacy

Polypharmacy is defined simply as the use of multiple medications by a patient. The exact minimum quantity of drugs required to characterise "polypharmacy" varies, but typically falls between five and ten. When it comes to older people, the problem of polypharmacy is especially concerning because they typically have more medical conditions than younger people, for which prescriptions are written. Increased risk of hospital admission and increased risk of an adverse drug event (ADE) have been found to be independently correlated with the use of more pharmacological regimens, regardless of age. Even when the disease load is taken into account, polypharmacy has also been linked to a decline in both physical and cognitive functioning. Drug-drug interactions and the administration of possibly inappropriate prescriptions are made more likely by polypharmacy. Having many prescription drugs makes "prescribing cascades" more likely to occur. To help in the customization of drug schedules to meet the needs of each patient, a more methodical approach is needed. A crucial tenet is to tailor the drug schedule to the patient's condition and treatment objectives. This involves giving serious thought to which prescriptions need to be switched out or terminated.

Inappropriate Medications

Expert panels in the US and Canada have created a number of criteria to evaluate the standard of prescription practises and medication use among older adults. The Beers criteria are the most commonly applied standards for improper medication usage. Another method involves developing a Drug Burden Index that includes the total number of prescriptions, daily dosage, and pharmaceuticals that have sedative or anticholinergic effects. In high-functioning community-based elderly people, a higher drug burden for sedative and anticholinergic drugs was linked to worse performance on mobility and cognitive tests. A high Drug Burden Index has been linked to a higher chance of falls in long-term care facility residents as well as a higher risk of functional decline in community residents.

The Beers criteria are the most often used standards for evaluating inappropriate medication prescribing. They were first created by an expert consensus group in 1991. A list of drugs that are deemed perhaps inappropriate for use in elderly patients, largely because of a high risk of adverse outcomes, makes up the criterion. Medication is divided into five categories: drugs to use cautiously because of the possibility of harmful adverse effects, drugs that should normally be avoided in older adults with specific conditions, drug-drug interactions, and drug dose adjustment based on kidney function.

Underutilization of Appropriate Medication

While overprescribing for older persons has received a lot of attention, under prescribing necessary medications is also a cause for worry. In an attempt to improve treatment quality, prescribing techniques that merely aim to reduce the total quantity of medications supplied to older persons may be gravely flawed. It should be acknowledged that the majority of elderly patients have several illnesses, and that the criteria used to determine "under-prescribing" are based on recommendations that target specific disease entities. Affordability, dose availability, and physicians' failure to recognise the benefits of medications for the elderly population are among the factors that cause unintentional underutilization.

Adverse Drug Events

Adverse drug events (ADEs) are any harm that results from taking a medication, such as unpleasant reactions, errors made during administering the medication, and other situations that cause harm. Older persons are more likely to acquire ADEs due to a variety of variables, such as frailty, underlying medical conditions, memory impairments, and the use of various prescription and over-the-counter medications. Due to the fact that they frequently have several chronic medical illnesses needing various pharmacological regimens, older persons are especially susceptible to drug-drug interactions. When taking many medications, the likelihood of an adverse event resulting from drug-drug interactions increases significantly.

• Older people: Compared to younger persons, hospitalisations due to ADEs occur four times more frequently in older adults. Preventable adverse drug events (ADEs) can be caused by prescription cascades, medication-drug interactions, and incorrect drug dosages.

• Patients in long-term care settings: Warfarin and atypical antipsychotic medicines are the most often implicated substances in antidrug encounters (ADEs) among nursing home residents.

A Stepwise Approach to Prescribing

A stepwise approach to prescribing for older adults should include: periodic review of current drug therapy; discontinuing unnecessary medications; considering nonpharmacologic alternative strategies; considering safer alternative medications; using the lowest possible effective dose; including all necessary beneficial medications.

Changes in intrinsic or receptor qualities (pharmacodynamic variables) are typically not of main relevance, but polypharmacy and changed pharmacokinetics are contributing reasons to the comparatively high prevalence of adverse drug responses in the elderly. Currently, there is no justification for the use of geriatric medications, or substances that are supposed to slow down the ageing process.

References:

1. Alldred DP, Kennedy MC, Hughes C, et al. Interventions to optimise prescribing for older people in care homes. Cochrane Database Syst Rev 2016; 2:CD009095.

New Drug Approvals…

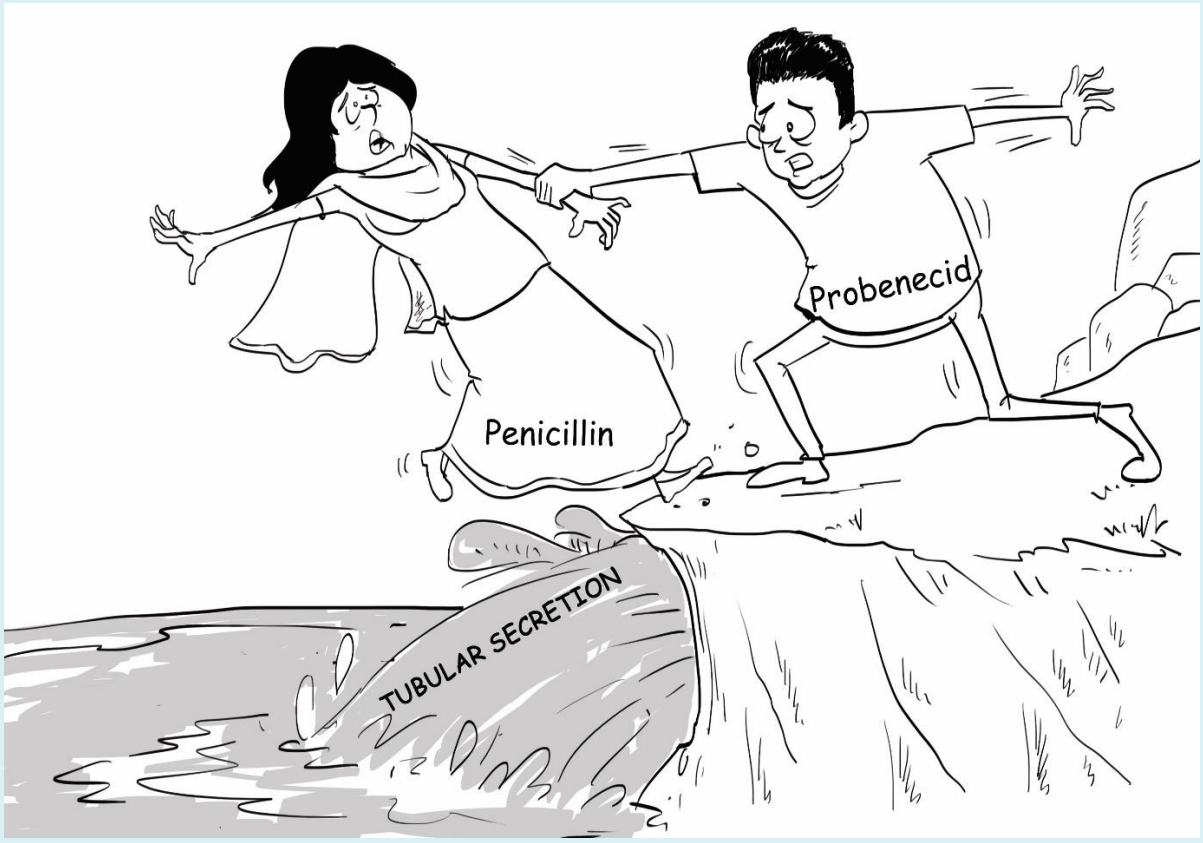
Etrasimod is a sphingosine 1-phosphate receptor modulator approved for the treatment of moderately to severely active ulcerative colitis in adults. The recommended dose 2 mg orally once daily.

Zilucoplan is a complement inhibitor approved for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti acetylcholine receptor (AChR) antibody positive. The recommended dose is 32.4 mg subcutaneous once daily for weight 77 kg and above, 23 mg for weight 56 kg to 77 kg and 16.6 mg for weight less than 56 kg.

Nedosiran is a LDHA-directed small interfering RNA approved for the treatment of primary hyperoxaluria type 1 (PH1). The recommended dose is 160 mg subcutaneous once monthly in adults and adolescents 12 years and older having weight more than 50 kg.

Repotrectinib is a kinase inhibitor approved for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer. The recommended dose is 160 mg orally once daily for 14 days, then increase to 160 mg twice daily.

Cartoon Corner…



Excerpt from “Drug Autobiographies in Pharmacology” by Dr. Sushil Sharma

A larger sample than required although better representative of the population and therefore provides more accurate results but beyond a certain point, the increase in accuracy is small and hence not worth if the feasibility, time and financial aspects are considered for recruiting more patients. Furthermore, an excessively larger sample would cause inconvenience to more patients than that is needed for the study objectives; and hence this becomes unethical. On the other hand, a sample that is smaller than required does not have adequate statistical power to answer the primary research question. Hence, nonsignificant statistical result could be due to inadequate sample size i.e., Type 2 or false negative error. This is also ethically not correct. Hence the optimal sample size needs to be calculated.

Type I and Type II errors. These have to be specified while calculating the sample size.

Probability of making Type I error is α.

α is also known as P value, "P < 0.05" refers to the α value.

Probability of making Type II error is β.

Power of a study = 1- β.

The following table explains the Type I and Type II errors

Possible Conclusions by Researchers	**Reality (Hypothesis testing)**	
	Treatments are NOT different. Null Hypothesis is True.	Treatments are Different. Null Hypothesis is False.
Researchers • *Conclude* - treatments are NOT different. • *Accept that Null Hypothesis is True.*	Correct decision ✓ (1- α)	Type II error (probability= β) *False negative*
Researchers • *Conclude* that treatments are different. • *Reject Null Hypothesis*	Type I error (probability= α) *False positive*	Correct decision ✓ Power (1- β)

Sample size: This depends on the study design and purpose of the study.

A). Sample sizes for descriptive studies:

In the case of descriptive studies, often the objective is to obtain an estimate of a population parameter.

- What is the measure of interest? For example, to estimate the prevalence of a certain disease in the population by taking a sample from the population.
- What is the sampling distribution of the measure? In calculating sample sizes, it is often assumed that the sampling involves simple random sampling however the formula is complicated for multistage cluster sampling techniques.
- How accurate does the researcher wants the results to be?

If the probability sampling technique is done, for estimating the population proportion, for qualitative variable:

$$\text{Sample size} = \frac{(Z_{1-\alpha/2})^2\, p\,(1-p)}{d^2}$$

$Z_{1-\alpha/2}$ = Is standard normal variate at 5% type 1 error (P<0.05) it is 1.96.

p = Expected proportion in population based on previous studies or pilot studies.

d = Absolute or Relative precision (also called error) – Has to be decided by the researcher.

For quantitative variable, the formula is

$$\text{Sample size} = \frac{(Z_{1-\alpha/2})^2\, SD^2}{d^2}$$

$Z_{1-\alpha/2}$ = Is standard normal variate as mentioned above.

SD = Standard deviation of variable.

d = Absolute or Relative precision.

For example, to calculate average systolic blood pressure in geriatric age group of a village, the above formula can be used.

B). **Sample size calculation for independent case control studies (not Matched case-control studies) using statistical software**. Example, sample size for case-control study to determine association between cigarette smoking and lung cancer, taking power of study at 80% and expected proportions in case group and control group are 39% and 24% respectively, and considering equal number cases and control with 95% confidence level (1- α);

By Epi-Info: (Link: https://www.cdc.gov/epiinfo/index.html)

Open Epi-Info software→ select STATCALC→select 'unmatched case-control study'

StatCalc - Sample Size and Power

Unmatched Case-Control Study (Comparison of ILL and NOT ILL)

Two-sided confidence level:	95%
Power:	80 %
Ratio of controls to cases:	1
Percent of controls exposed:	24 %
Odds ratio:	2.02459
Percent of cases with exposure:	39 %

	Kelsey	Fleiss	Fleiss w/ CC
Cases	151	150	163
Controls	151	150	163
Total	302	300	326

The sample size needed will be 150 cases and 150 controls, total 300.

C). **Sample size calculation of cohort studies:** Using Epi-Info (Link: https://www.cdc.gov/epiinfo/index.html)

Open software→ select STATCALC→select "cohort or cross-sectional'' →enter data and calculate sample size.

Example, % outcome in the unexposed group 35%, enter the % outcome in the exposed group 55%. With 80% statistical power and 5% alpha error (95% confidence level), assuming two equal group, calculate sample size as follows:

StatCalc - Sample Size and Power

Unmatched Cohort and Cross-Sectional Studies (Exposed and Nonexposed)

Two-sided confidence level:	95%
Power:	80 %
Ratio (Unexposed : Exposed):	1
% outcome in unexposed group:	35 %
Risk ratio:	1.57143
Odds ratio:	2.26985
% outcome in exposed group:	55 %

	Kelsey	Fleiss	Fleiss w/ CC
Exposed	98	96	106
Unexposed	98	96	106
Total	196	192	212

The total sample size required is 192 (96 exposed and 96 unexposed).

D). Sample size calculation for Randomized Clinical Trials (RCT)

A placebo controlled RCT to assess the effectiveness of Drug XYZ in treating certain disease. Based on previous study, it was found that proportion of cases cured by Drug XYZ was 77%. The clinically important difference of 19% is acceptable as compared to placebo, i.e., proportion of cases cured by placebo was 58%. With level of significance = 5%, Power = 90%, the total sample size comes out to be 254, (127 in intervention group) and (127 in control group).

Access open epi by clicking http://www.OpenEpi.com/ , select Cohort/RCT under Sample Size on left-hand column.

Sample Size:X-Sectional, Cohort, & Randomized Clinical Trials

Two-sided significance level(1-alpha):	95
Power(1-beta, % chance of detecting):	90
Ratio of sample size, Unexposed/Exposed:	1
Percent of Unexposed with Outcome:	58
Percent of Exposed with Outcome:	77
Odds Ratio:	2.4
Risk/Prevalence Ratio:	1.3
Risk/Prevalence difference:	19

	Kelsey	Fleiss	Fleiss with CC
Sample Size - Exposed	129	127	137
Sample Size-Nonexposed	129	127	137
Total sample size:	258	254	274

Reference:

1. Andrade C. Sample Size and its Importance in Research. Indian J Psychol Med. 2020 Jan 6;42(1):102–3.

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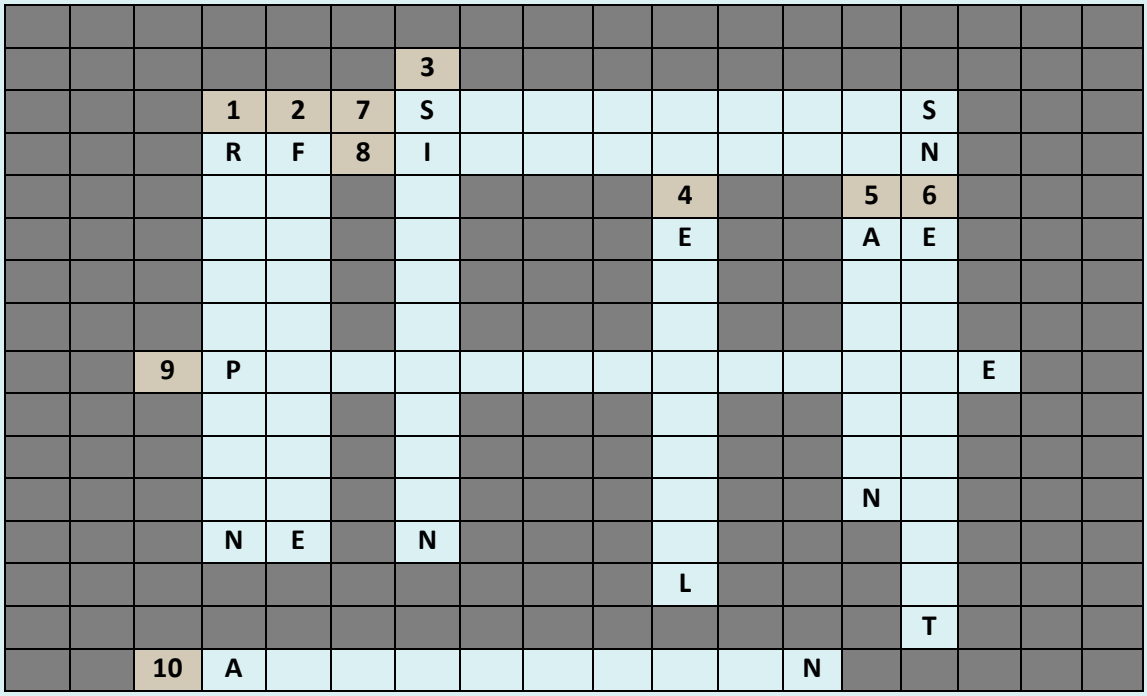

Downward	**Across**
1. First line anti-tubercular drug with bactericidal action (*10*) 2. High ceiling diuretic (*10*) 3. First DPP-4 inhibitor used in pharmacotherapy of DM (11) 4. ACE inhibitor associated with dry cough as ADR *(9*) 5. NSAID used as an Antiplatelet drug (7) 6. Tumour Necrosis Factor (TNF) inhibitor *(10)*	7. *m-TOR* inhibitor used as an Immunosuppressant Drug (*9*) 8. Nonselective COX inhibitor derivative of Propionic acid *(9)* 9. Chelating agent effective in copper, lead, and mercury poisonings *(13)* 10. *Dipeptidyl Peptidase*-4 (DPP-4) inhibitor with $t_{1/2}$ around 20 hours *(10)*

Answer to the Crossword Puzzle is given below:

Downward

1. Rifampicin 3. Sitagliptin 5. Aspirin 6. Etanercept 4. Enalapril 2. Furosemide

Across

7. Sirolimus 8. Ibuprofen 9. Penicillamine 10. Alogliptin