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FROM THE EDITORIAL DESK….

Dear Friends,

Greetings from Department of Pharmacology and Welcome to the 22nd issue of ESSENCE

Drug discovery and development is a long and expensive process involving multiple phases including Target selection and lead development, preclinical development, and then clinical trials. Among these phases, phase 3 clinical trials stand as the crucial stage, where a potential drug's safety and efficacy are extensively evaluated before regulatory agencies consider granting market approval. The current issue highlights the important elements of Phase 3 clinical trials.

Hepatic disease can alter the pharmacokinetics of a drug including the absorption and disposition and the pharmacodynamics including efficacy and safety. Drugs are often metabolized by one or more enzymes located in cellular membranes in different parts of the liver and may also be excreted by biliary secretion. Hepatic disease may lead to drug accumulation, failure to form an active or inactive metabolite, increased bioavailability after oral administration, and other effects including possible alteration in drug–protein binding. The current issue discusses the drug dosages in Hepatic impairment.

Acquisition, retention, arrangement, and analysis of Data is one of the important aspects in medicine. The current issue also has a guest article on Medical Data, its understanding, preparation and data management.

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

We hope you enjoy reading it.

Jai Hind.

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Introduction:

Development of a new drug is a complex process, usually lasting more than 10 to 14 years and involving extensive research, including in vitro studies, preclinical studies, and multiple phases of clinical trials from phase zero (micro- dosing) to phase 3. 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 and one of the primary objectives of phase 2 studies is to assess the impact of drugs administered at various dosages or dose ranging studies. Phase 2 studies aid in the identification of an optimal dose and treatment regimen that can be further investigated in phase 3 trials. Among these phases, phase 3 clinical trials stand as the crucial stage, where a potential drug's safety and efficacy are extensively evaluated in patients before regulatory agencies consider granting market approval. Phase 3 studies are time-consuming, expensive and difficult to design and perform owing to the large sample size and long duration, particularly when testing treatments for chronic medical diseases.

Phase 3 clinical trials play a pivotal role in drug development. These trials provide robust evidence required to ascertain a drug's effectiveness in treating a specific medical condition, often comparing it to existing treatments or placebos (efficacy confirmation). Phase 3 trials continue to assess a drug's safety profile, scrutinizing for adverse effects (safety evaluation) that may not have been apparent in phase 2 clinical trials. By involving a larger and more diverse patient population, these trials help uncover rare or long-term adverse effects and also useful in finding most effective dosage and dosing schedule of the drug (Dose optimization). This is an important step in ensuring that the drug provides maximum therapeutic benefit with minimal side effects.

The successful completion of phase 3 trials is typically a prerequisite for seeking regulatory approval from agencies like the FDA (Food and Drug Administration) in the United States or the EMA (European Medicines Agency) in Europe or Drug Controller General of India (DCGI). Regulatory approval is the gateway to making a new drug available to the broader population. In certain cases, Phase 3 clinical trials are sometimes divided into phase 3a and 3b. Phase 3a clinical trials occur before regulatory submission, while phase 3b occur after regulatory submission and prior to approval and launch. Approximately 20 to 30 percent of drugs successfully progress from phase 3 clinical trials to the New Drug Application (NDA) stage.

Important characteristics of phase 3 clinical trials:

These trials are designed with features like randomization, blinding, placebo controls, multi centric in larger population to ensure accurate data collection.

Randomization

Patients participating in phase 3 trials are assigned to treatment groups randomly and randomization helps eliminate bias and ensures that each group is comparable in terms of patient characteristics and disease severity.

Blinding

These trials are often double-blind, wherein both the subjects and the researchers remain unaware of the allocation of the experimental drug and the control group. This blinding helps prevent subjective influences on the results.

Large Sample Size

These trials are often conducted across multiple centres or sites to enhance the generalizability of the results. This approach ensures that the findings are applicable to a broader population. Phase 3 trials involve thousands of participants usually 300 to 3000 patients. The larger sample size improves the statistical power of the trial, making it more likely to detect meaningful differences between treatment groups.

Longer duration

Phase 3 trials are distinguished by their prolonged duration (1 to 4 years), which allows for the collection of long-term data and the identification of rare or delayed side effects.

Conclusion

It can be stated that phase 3 clinical trials are regarded as the epitome of evidence-based medicine and serve as a crucial component in the process of drug development. They serve the critical role of confirming a new drug's safety and efficacy, validating its therapeutic benefits, and determining its optimal use in clinical practice. These trials exhibit distinct features such as a meticulous design, substantial sample sizes, and prolonged duration. All of these factors contribute to the improvement of the reliability of their findings. Introducing novel therapeutic alternatives, improving the advancement of medical knowledge, and ultimately enhancing the well-being of innumerable individuals who are suffering from various diseases is the goal of this phase of clinical trials.

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). Step 3: Clinical Research. The Drug Development Process; https://www.fda.gov/patients/drug-development-process/step-3-clinical-research.

Recent new/Update from the world of medicines ….

World's First: England introduces 7-min cancer treatment injection

A novel anti-cancer subcutaneous injection of atezolizumab that can significantly shorten the length of cancer therapy has been introduced by the National Health Service (NHS) England. Atezolizumab is an immunotherapy drug that Inhibits PD-L1 and thereby engender an anti-tumour response. It is currently administered to cancer patients via intravenous transfusion, a procedure that takes 30 to 60 minutes but this ground-breaking injection could cut the length of some patients' treatments significantly. The first injection of its kind will be given to hundreds of cancer patients on the NHS each year and just takes 7 minutes to administer. The UK's Medicines and Healthcare Products Regulatory Agency (MHRA) is tasked with ensuring the efficacy and security of pharmaceuticals and medical devices.

First Oral Treatment for Postpartum Depression

The first oral drug suggested to treat postpartum depression (PPD) in adults. Zuranolone has received approval from the US Food and Drug Administration. It is a neuroactive steroid with antidepressant activity. Two randomised, double-blind, placebo-controlled, multicenter studies showed that zuranolone is effective in treating PPD in adults. Women with PPD who matched the DSM-IV criteria for a major depressive episode and whose symptoms started in the third trimester or within four weeks of delivery made up the trial's subjects. Zuranolone has a 50mg suggested dose per day. For 14 days, it should be taken once daily in the evening with a fatty meal.

Be Cautious…. Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Amoxicillin	Drug-Induced Enterocolitis Syndrome (DIES)
2.	Cabergoline	Hypertension, Myocardial Infarction, Seizures, Stroke or Psychiatric disorders
3.	Bupropion	Cardiac arrest or Sudden death through unmasking of Brugada syndrome
4.	Codeine with Ibuprofen	Serious Renal and Gastrointestinal harms
5.	Haloperidol	Cogwheel Rigidity
6.	Imatinib	Thrombotic Microangiopathy

Hepatic disease can alter the pharmacokinetics of a drug including the absorption and disposition and the pharmacodynamics including efficacy and safety. Drugs are often metabolized by one or more enzymes located in cellular membranes in different parts of the liver. Drugs and metabolites may also be excreted by biliary secretion. Hepatic disease may lead to drug accumulation, failure to form an active or inactive metabolite, increased bioavailability after oral administration, and other effects including possible alteration in drug–protein binding. The major difficulty in estimating hepatic clearance in patients with hepatic disease is the complexity and stratification of the liver enzyme systems. In contrast, creatinine clearance has been used successfully to measure kidney function and renal clearance of drugs. Clinical laboratory tests measure only a limited number of liver functions. Some clinical laboratory tests, such as the aspartate aminotransferase (AST) and alanine aminotransferases (ALT), are common serum enzyme tests that detect liver cell damage rather than liver function. Other laboratory tests, such as serum bilirubin, are used to measure biliary obstruction or interference with bile flow. Presently, no single test accurately assesses the total liver function.

Dosage Considerations in Hepatic Disease

Several physiologic and pharmacokinetic factors are relevant in considering dosage of a drug in patients with hepatic disease. Chronic disease or tissue injury may change the accessibility of some enzymes as a result of redirection or detour of hepatic blood circulation. Liver disease affects the quantitative and qualitative synthesis of albumin, globulins, and other circulating plasma proteins that subsequently affect plasma drug protein binding and distribution). As mentioned, most liver function tests indicate only that the liver has been damaged; they do not assess the function of the cytochrome P450 enzymes or intrinsic clearance by the liver. Because there is no readily available measure of hepatic function that can be applied to calculate appropriate doses, enzyme-dependent drugs are usually given to patients with hepatic failure in half-doses, or less. Response or plasma levels then must be monitored. Drugs with flow-dependent clearance are avoided, if possible, in patients with liver failure. When necessary, doses of these drugs may need to be reduced to as low as one-tenth of the conventional dose, for an orally administered agent. Starting therapy with low doses and monitoring response or plasma levels provides the best opportunity for safe, efficacious treatment.

Fraction of Drug Metabolized

Drug elimination in the body may be divided into: 1). fraction of drug excretion unchanged, fe, and 2). fraction of drug metabolized. The latter is usually estimated from 1 – fe; alternatively, the fraction of drug metabolized may be estimated from the ratio of Cl_h/Cl, where Cl_h is hepatic clearance and Cl is total body clearance. Knowing the fraction of drug eliminated by the liver allows estimation of total body clearance when hepatic clearance is reduced. Drugs with low fe values (or, conversely, drugs with a higher fraction of metabolized drug) are more affected by a change in liver function due to hepatic disease.

$Cl_h = Cl\ (1\text{-}fe)$, This equation assumes that all metabolism occurs in the liver, and all the unchanged drug is excreted in the urine.

Active Drug and the Metabolite

For many drugs, both the drug and the metabolite contribute to the overall therapeutic response of the patient to the drug. The concentration of both the drug and the metabolite in the body should be known.

When the pharmacokinetic parameters of the metabolite and the drug are similar, the overall activity of the drug can become more or less potent as a result of a change in liver function; that is, 1). when the drug is more potent than the metabolite, the overall pharmacologic activity will increase in the hepatic impaired patient because the parent drug concentration will be higher; 2). when the drug is less potent than the metabolite, the overall pharmacologic activity in the hepatic patient will decrease because less of the active metabolite is formed. Changes in pharmacologic activity due to hepatic disease may be much more complex when both the pharmacokinetic parameters and the pharmacodynamics of the drug change as a result of the disease process. In such cases, the overall pharmacodynamic response may be greatly modified, making it necessary to monitor the response change with the aid of a pharmacodynamic model.

Hepatic Blood Flow and Intrinsic Clearance

Blood flow changes can occur in patients with chronic liver disease (often due to viral hepatitis or chronic alcohol use). In some patients with severe liver cirrhosis, fibrosis of liver tissue may occur, resulting in intra or extrahepatic shunt. Hepatic arterial-venous shunts may lead to reduced drug fraction of drug extracted and an increase in the bioavailability of drug. In other patients, resistance to blood flow may be increased as a result of tissue damage and fibrosis, causing a reduction in intrinsic hepatic clearance.

While the hepatic blood flow model is useful for predicting changes in hepatic clearance resulting from alterations in hepatic blood flow, Q_a and Q_v, extrahepatic changes can also influence pharmacokinetics in hepatic impaired patients. Global changes in distribution may occur outside the liver. Extrahepatic metabolism and other hemodynamic changes may also occur and can be accounted for more completely by monitoring total body clearance of the drug using basic pharmacokinetics. For example, lack of local change in hepatic drug clearance should not be prematurely interpreted as “no change” in overall drug clearance. Reduced albumin and alpha acid glycoprotein (AAG), for example, may change the volume of distribution of the drug and therefore alter total body clearance on a global basis.

Hormonal Influence

Hormones can also affect the rate of metabolism. In hyperthyroid patients, the rate of metabolism of many drugs is increased, as are, for example, the rates for theophylline, digoxin, and propranolol. In hypothyroid disease, the rate of metabolism of these drugs may be decreased. In children with human growth hormone (HGH) deficiency, administration of HGH decreases the half-life of theophylline.

Hepatic Impairment and Dose Adjustment

Hepatic impairment may not sufficiently alter the pharmacokinetics of some drugs to require dosage adjustment. Drugs that have the following properties are less likely to need dosage adjustment in patients with hepatic impairment: 1). The drug is excreted entirely via renal routes of elimination with no involvement of the liver, 2). The drug is metabolized in the liver to a small extent (<20%), and the therapeutic range of the drug is wide, so that modest impairment of hepatic clearance will not lead to toxicity of the drug directly or by increasing its interaction with other drugs, and 3). The drug is gaseous or volatile, and the drug and its active metabolites are primarily eliminated via the lungs.

For each drug case, the physician needs to assess the degree of hepatic impairment and consider the known pharmacokinetics and pharmacodynamics of the drug.

Reference:

1. Delcò F, Tchambaz L, Schlienger R, Drewe J, Krähenbühl S. Dose adjustment in patients with liver disease. Drug Saf. 2005;28(6):529-45.

New Drug Approvals…

Ritlecitinib is a kinase inhibitor approved for the treatment of severe alopecia areata in adults and adolescents 12 years and older. The recommended dose is 50 mg orally once daily.

Avacincaptad pegol is a complement C5 protein inhibitor approved for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration. The recommended dose is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly.

Quizartinib is an oral FLT3-ITD (FMS-like tyrosine kinase-3-internal tandem duplication) inhibitor approved for the treatment of FLT3-ITD positive acute myeloid leukemia. The recommended dose is 17.7 mg orally once daily.

Palovarotene is a retinoid approved for the treatment of fibrodysplasia ossificans progressiva to decrease the volume of new heterotopic ossification in adults and children. The recommended dose is 5 mg orally once daily.

Cartoon Corner…

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

Medical data management refers to the systematic procedures involved in the acquisition, retention, arrangement, safeguarding, and examination of medical data. The data may encompass several types of information, such as patient records, clinical trial data, and research data. The primary objective of medical data management is to guarantee the accuracy, security, and availability of data to those with proper authorization. The management and use of medical data serves as the fundamental basis for the practice of data mining. The utilization of data mining techniques enables the identification of patterns and trends within datasets, hence facilitating enhancements in medical care, advancements in research, and improvements in public health. A wide range of medical data and factors are found inside EHRs in use. Several prevalent categories of medical data include: Patient demographics, medical history, laboratory findings, imaging data and clinical notes.

Data understanding

Several often-encountered variables in the medical feature space (as variable are addressed in the field of data mining) include:

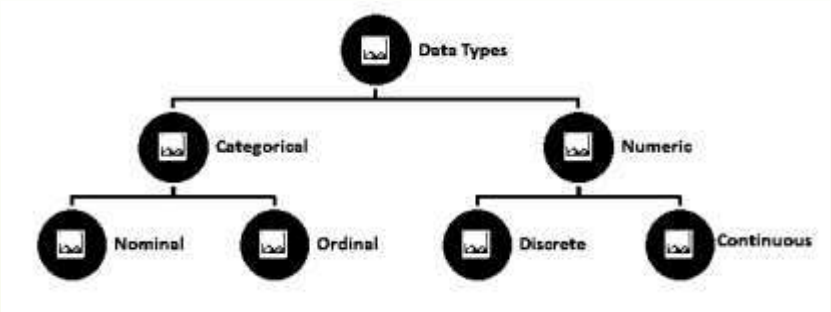
- Continuous variables refer to variables that have the ability to assume any value within a specified range. Height, weight, blood pressure, and blood sugar levels are among the prominent instances of continuous variables observed in medical data.
- Discrete variables refer to variables that possess a finite or countable set of possible values. Discrete variables commonly observed in medical data encompass the count of prescriptions prescribed to a patient, the frequency of doctor visits within a given year, and the blood type of the patient.
- Categorical variables refer to variables that can be classified into distinct categories. Categorical variables commonly observed in medical data encompass the patient's gender, race, and diagnosis.

These concepts are very important when we are trying to use the tools for data management in health sciences. Several widely used software applications for data analysis include right from Microsoft Excel (a spreadsheet), SPSS, R, Python, Tableau, MySQL, SAS, and Jupyter Notebook etc.

Data preparation

MS-Excel or Google Sheets will capture data any which way you want it because they are spreadsheets for accounting being used as surrogate databases. A spreadsheet is a structured arrangement of data, consisting of rows and columns that create a grid-like framework. Every individual unit inside the grid possesses the capability to contain and retain data, which is commonly organised and stored in a structured tabular fashion. True databases such as MS-Access have a different architecture and have an organised methodology, commonly comprising tables that possess predetermined structures encompassing fields (columns) and records (rows). The predetermined structure of the system ensures and maintains the integrity of the data. SPSS for example would be called a database rather than a spreadsheet. The databases have a design page or a tab for capturing meta-data (the codebook in a way) which is the data about the data being captured. NFHS data of our country has the following data structure in SPSS. Spreadsheets have a wide range of capabilities in facilitating basic data administration, analysis, and reporting tasks. However, their effectiveness diminishes when confronted with intricate data linkages and extensive datasets. Databases are purposefully constructed to facilitate the storing of structured data, accommodate scalability requirements, and uphold data integrity.

Consequently, they are well-suited for effectively handling extensive volumes of data, supporting intricate applications, and guaranteeing the consistency and security of data. Computers (or software such as Excel) treat variables in two distinct categories as shown above. Strings and numeric variables are nothing but continuous and categorical variables. The latter can be later sub-grouped as nominal (name-based/unordered categories) and ordinal (ordered/scale) variables in the measure column. Further in data mining we can define roles (attributes) for the variables e.g., Target or Label for dependent variables or features. The independent variables will be predictors for the dependent (outcome) variable.



Explore data

This task addresses the inquiries related to data mining, which can be resolved through the use of querying, visualization, and reporting techniques. These encompass various aspects such as the distribution of important characteristics, such as the target attribute in a predictive task, the relationships between pairs or a small number of attributes, the outcomes of basic aggregations, the characteristics of relevant sub-populations, and simple statistical studies. The aforementioned studies have the potential to directly address the objectives of data mining. Additionally, they can make valuable contributions to the enhancement and refinement of data description and quality reports.

Data integrity analysis aims to evaluate the integrity of the data by considering factors such as its completeness. If there are errors, how prevalent are they? Are there any instances of missing values within the dataset? In what manner, are they depicted, where do they manifest, and what is their prevalence? The process of data cleaning encompasses the identification and resolution of a range of issues present within a dataset, including but not limited to missing values, outliers, duplicates, and formatting errors.

Upon being satisfied regarding accuracy and structure of the data, we may opt for soft locking of the data. Soft locking allows for more concurrent access, which can improve system performance when conflicts are infrequent. Once the conflicts are all resolved the data can be hard locked. Hard locking ensures data consistency and prevents conflicts by allowing only one user or process to access data at a time. It is preferred in situations where data consistency is critical and conflicts are likely to occur frequently.

Bibliography

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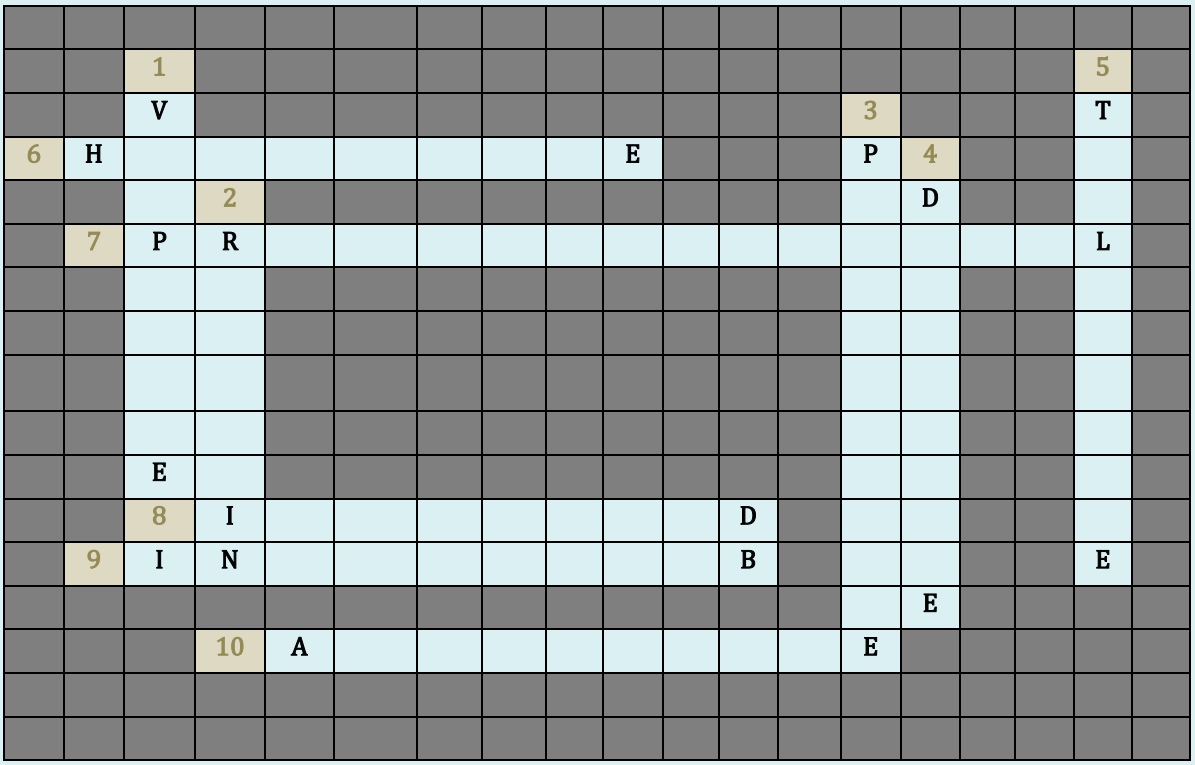

Downward	**Across**
1. Broad spectrum Antiseizure drug (9) 2. First line Antitubercular drug which is a semisynthetic derivative of Rifamycin B (8) 3. First line Antitubercular drug, which is chemically similar to INH (12) 4. Ryanodine receptor 1 antagonist used in malignant hyperthermia (10) 5. Antiplatelet drug acts by blocking P2Y12 Receptor (11)	6. General anesthetic agent which is delivered through inhalational route (*9*) 7. Antithyroid drug safe in pregnancy *(16)* 8. First line Antitubercular drug *(9)* 9. TNF-alpha blocker *(10)* 10. Broad spectrum antiarrhythmic drug *(10)*

Answer to the Crossword Puzzle (22nd Issue) is given below:

Downward

1. Valproate 2. Rifampin 3. Pyrazinamide 4. Dantrolene 5. Ticlopidine

Across

6. Halothane 7. Propylthiouracil 8. Isoniazid 9. Infliximab 10. Amiodarone