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 eighth issue of ESSENCE.

Consider the following; there are around 18 beta-blockers, more than 10 ACE inhibitors and numerous statins and TCAs. The field of therapeutics is replete with examples of 'Me-Too' drugs. These have been variously defined as "multiple drugs within the same therapeutic class" or "drugs that are chemically related to the prototype which have an identical mechanism of action" as a drug that is already marketed. Goodman (of Goodman and Gilman's) dismissed them as "drugs without any advantage of any sort' while in 1964 Lasagna, described them as being "hard to justify putting into man". Do 'me-Too' drugs add value or are they simply money-making tools for pharmaceutical companies? The present issue deliberates some of these questions.

Artificial Intelligence (AI) is impacting health sector in more ways than ever. AI-driven interventions have supplemented clinical decision and have helped to identify disease outbreaks earlier than traditional approaches, thereby supporting timelier programme planning and policy making. This issue of ESSENCE also throws light on the scope and relevance of AI in clinical pharmacology and therapeutics.

Further, as always, we also cover some drug safety alerts and also new drugs developed recently. Finally, the readers can test their knowledge with the cross-word on 'Drugs which can cause hair loss or excessive hair growth.

Happy Reading and Stay safe.

Jai Hind.

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ME TOO DRUGS: DO THEY ADD VALUE OR ARE THEY SIMPLY COPY CATS TO MAKE MONEY FOR THE PHARMACEUTICAL COMPANIES?

Consider the following; there are around 18 beta-blockers viz Propranolol, Metoprolol, Atenolol, Bisoprolol etc, a total of seven Statins like Lovastatin, Simvastatin, Atorvastatin, Pravastatin, Rosuvastatin etc, TCA's like mipramine, Trimipramine, Desipramine, Amitryptyline or Captoril, Enalapril, Lisinopril, Perindopril etc. These are drugs that belong to the same pharmacological class and sometimes referred to as 'Me-Too' drugs.

The field of therapeutics is replete with examples of 'Me-Too' drugs. These have been variously defined as "multiple drugs within the same therapeutic class" or "drugs that are chemically related to the prototype which have an identical mechanism of action" as a drug that is already marketed. In fact, Goodman's in 1956 dismissed them as "drugs without any advantage of any sort" while in 1964 Lasagna, described them as being "hard to justify putting into man".

Reasons for developing and marketing Me-Too drugs?

Reason	Examples
To gain a market share	Probably the most common reason
To improve specificity at the target, and reduce the risks of off-target adverse reactions.	Atypical antipsychotic drugs, which are more selective for dopamine D2 receptors than their typical predecessors
To reduce the risks of adverse reactions and drug– drug interactions,	Ranitidine vs Cimetidine; Statins and their different interactions with grapefruit juice
To increase the chance of benefit, perhaps in a subset of patients	Ampicillin (broader spectrum) or Statins with varying efficacy in lowering cholesterol levels
To develop drugs with similar structures but new targets	Some diuretics and some oral hypoglycaemic drugs derived from the first-in-class sulphonamide antibiotic sulfamidochrysoïdine (Prontosil); acecainide, a metabolite of procainamide
To improve drug delivery and pharmacokinetics	Ampicillin (oral) vs benzylpenicillin (i.v.); amoxicillin vs ampicillin; congeners of insulin (e.g., insulin aspart)
To offer cheaper alternatives	Many examples, but me-too drugs are not always cheaper
Incremental innovation	Beta-blockers with more selectivity, hydrophilicity and vasodilator action
To use as replacements when there are drug shortages	A wide range of 'me-too' drugs may allow patients to use replacements if a certain drug from the class is not available.

Me-too drugs have been hugely successful. Over the last 50-year period, the time it takes for a second entry into a therapeutic area has declined steeply from 9 years down to 1.7 years. This is attributed in part to the tendency of the pharmaceutical industry to concentrate on "me too" drug development rather than on riskier, novel drugs; a case of putting money over science.

Some of the criticism of me-too drugs has been the assumption that their development occurs after the demonstration of clinical and commercial success by the first-in-class drug. However, that may not be always true and It's now seen that for every new drug class that's been introduced, at least one of the eventual 'me-too' drugs has already been synthesized before the first one's been approved by the FDA. In fact, it's been the case 90% of the time that a second drug has already filed to go into clinical trials before the first one has been approved, and 64% of the time another compound has, in fact, already started Phase III testing. Patent filings also show that for new drug classes approved since the 1970s, 90% have had at least one of the eventual follow-on/me-too drugs filing the patent before the first-in-class compound was approved.

To understand the marketing of me-too drugs by other companies, we must first look at the discovery process. Research scientists from competing companies meet at the same scientific conferences and talk to the same academics. It is therefore rare for a company to have an approach to a therapeutic problem that is not being considered by competitors. Near parallel discovery and development of a new chemical entity is therefore common and, by the time patents have been obtained, serious money has been expended.

Overall, this indicates that new drug development is better characterized as a race to market among drugs in a new therapeutic class, rather than a lower risk imitation of a proven breakthrough; a race in which several firms pursue investigational drugs with similar chemical structures or with the same mechanism of action before any drug in the class obtains regulatory marketing approval.

Many times, originator companies may market a 'me-too' drug when their first-in-class drug is reaching the end of its patent period. This may also happen because while researching a specific therapeutic area and screening structurally related groups of compounds. More than one candidate drug may look promising, and while one is selected for further development, another is chosen as a back-up in case the first fails. This is beneficial to the company its staff are already trained in both preclinical and clinical development and the clinical trials structure is in place. By the time the first candidate drug has shown itself to be marketable the follow-on compound is so far on in development that it is worth finalizing and marketing. It may then demonstrate some therapeutic advantage.

Another common scenario is that the "me-too" company A may have another compound in the same class lying somewhere in the pipeline and then when company A sees that company B has invested (risked) $100M in a phase III clinical trial that proved to be a success, then company A can be confident in taking that compound off the shelf and bringing it to market.

Is there a case for NOT approving Me-Too drugs?

If the first product in a class was the only product in a class, how many patients would never be adequately treated. Take for instance the statins, Would Lovastatin which was the first statin drug to be approved alone have been enough to adequately treat high risk patients who need substantial LDL reduction? If no other statin was developed after Lovastatin and development of other products ceased. How many lives would that have cost?

Take another example, of the class of 'Glitazones'. Troglitazone, first in class was withdrawn for liver toxicity. Liver toxicity was not seen with Rosiglitazone, but was withdrawn due to CVS issues. Pioglitazone, last me-too is still standing with a vastly different CV profile and still on the treatment algorithm for type 2 diabetes. Further, even if two me-too's have the same 'population' efficacy and toxicity profiles, there could be substantial differences in response among individuals, e.g., pharmacogenetics may be highly relevant. In the case of SSRIs for example, some people respond well to Fluoxetine but not Sertraline and vice versa.

Conclusion:

Many me-too and follow-on products are marketed in order to gain a fraction of a lucrative market. However, they have advantages apart from financial gain which include improved target specificity, reduced risks of off-target adverse reactions and drug–drug interactions, increased chance of benefit in some patients, and improved drug delivery and pharmacokinetics. Some me-too drugs feature major innovations, such as β-blockers and Penicillin. An example is Amitriptyline, the second tricyclic to have entered the market, which was found to be the most effective drug for severe depression, even when measured against more recent non-tricyclic compounds. However, me-too drugs that appear to have no advantages over their predecessors also continue to be prescribed. Me-too drugs may be useful when equivalent drugs can replace each other in the event of shortage.

Cone snail venom shows potential for treating severe malaria

Severe forms of malaria such as *Plasmodium falciparum* may be deadly even after treatment with current parasite-killing drugs. This is due to persistent cyto-adhesion of infected erythrocytes even though existing parasites within the red blood cells are dead. As vaccines for malaria have proved less than moderately effective, and to treat these severe cases of *P. falciparum* malaria, new avenues are urgently needed. Latest estimates indicate that more than 500 million cases of malaria and more than 400,000 deaths are reported worldwide each year. Anti-adhesion drugs may hold the key to significantly improving survival rates. Using venom from a cone snail, a new study suggests these conotoxins may potentially treat malaria. The study provides important leads toward the development of new and cost-effective anti-adhesion or blockade-therapy drugs aimed at counteracting the pathology of severe malaria.

'Gamechanger' drug for treating obesity cuts body weight by 20 percent

The findings from the large-scale international trial, published in the New England Journal for Medicine, are being hailed as a "gamechanger" for improving the health of people with obesity. The drug is semaglutide which works by hijacking the body's own appetite regulating system in the brain leading to reduced hunger and calorie intake. One third (35%) of people who took the drug for treating obesity lost more than one-fifth (greater than or equal to 20%) of their total body weight, according to a major global study involving UCL researchers. With evidence from this trial, semaglutide has been submitted for regulatory approval as a treatment for obesity to the National Institute of Clinical Excellence (NICE), the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).

Cell-selective nanotherapy can help treat atherosclerotic plaques

A microRNA-based therapy worked better than drug-eluting stents in a rat model of angioplasty. That work used an adenovirus vector to carry the cell-selective therapy to injured arteries. This anti-proliferative therapy specifically targets the cardiovascular smooth muscles cells and the infiltrating inflammatory cells but spares the endothelial cells thus achieving the therapeutic effects of drug-eluting stents without the downside of thrombosis and neoatherosclerosis. In this study, the viral vector was replaced with a nanoparticle alternative - a change needed to avoid safety concerns and advance the therapy toward use in patients. In addition, the nanoparticles efficiently delivered its mRNA cargo, without degradation, solely to regions of the artery where endothelial cells were damaged.

Artificial Intelligence (AI) is changing health services many high-income settings, particularly in specialty care. This development has been facilitated by the growing availability of large datasets and novel analytical methods that rely on such datasets. AI-driven interventions have supplemented clinical decision making towards reducing the workload of health workers. New developments in AI have also helped to identify disease outbreaks earlier than traditional approaches, thereby supporting timelier programme planning and policy making.

Treatment effectiveness and outcome prediction:

Treatment effectiveness and outcome prediction are also important areas with the potential clinical implication in disease management strategies and personalized care plans. A decade ago, only molecular and clinical information was exploited to predict disease outcomes. With the development of high-throughput technologies, including genomic, proteomic, and imaging technologies, new types of input parameters have been collected and used for prediction. Artificial Intelligence analytics can be used in chronic disease management characterized by multi-organ involvement, acute variable events, and long illness progression latencies. One of the goals of precision medicine is the accurate prediction of optimal drug therapies from the genomic data of individual patient. Precision medicine success depends on algorithm ability to translate large amount of data into clinically actionable predictions.

Drug discovery and repurposing:

Targeted drug discovery is preferred in pharmaceuticals due to the explicit mechanism, higher success rate, and lower cost when compared to traditional blind screening. Machine learning is now utilized in the drug discovery process due to the followings; 1) high costs of drug development; 2) increasing availability of three-dimensional structural information that can guide the characterization of drug targets, and 3) extremely low success rates in clinical trials. Machine learning can be used as a bridge to achieve cross-domain linkage. It can identify a newly approved drug by recognizing contextual clues like a discussion of its indication or side effects. Artificial intelligence has been successful when applied to available sources, including the use of drug information to extract insight about mechanism-of-action by applying techniques such as similarity metrics across all diseases to find shared pathways.

Adverse Drug Reactions:

Artificial intelligence has an important role in the use of drug information to extract insight about mechanism-of-action by applying techniques such as similarity metrics across all diseases to find shared pathways. It uses the natural language processing for identification of hidden or novel associations that might be important in the detection of potential drug adverse effects based on scientific publications.

Clinical trial and *in-silico* clinical trials:

Machine learning approach using *in-silico* dataset was introduced to describe the numerical methods used in drug development in oncology by modelling biological systems in the setting of clinical trial studies and hospital databases, paving the way to predictive, preventive, personalized and participatory medicine. This approach gives the researchers the ability to partially replacing animals or humans in a clinical trial and generates virtual patients with specific characteristics to enhance the outcome of such studies. These methods are especially helpful for paediatric or orphan disease trials and can be applied in pharmacokinetics and pharmacodynamics from the preclinical phase to post-marketing. The role of AI in *In-silico* clinical trials can have considerable potentials in design and discovery phases of biomedical product, biomarker identification, dosing optimization, or the duration of the proposed intervention.

AI's ultimate goal is to develop algorithms that are capable of self-improving with experience and continuously learning from new data and insights, to find answers to an array of questions. The compelling opportunities in precision medicine offered by complex algorithms are accompanied by computational challenges. The ethical challenges presented by data science have also been an area of debate. These challenges can be mapped within the conceptual space and described by three branches of research: the ethics of data and privacy, the ethics and morality of algorithms, and the ethics and values of practices.

Despite the field remaining nascent, AI-driven health interventions could lead to improved health outcomes in low- and middle-income countries. Although some challenges of developing and deploying these interventions might not be unique to these settings, the global health community will need to work quickly to establish guidelines for development, testing, and use, and develop a user-driven research agenda to facilitate equitable and ethical use.

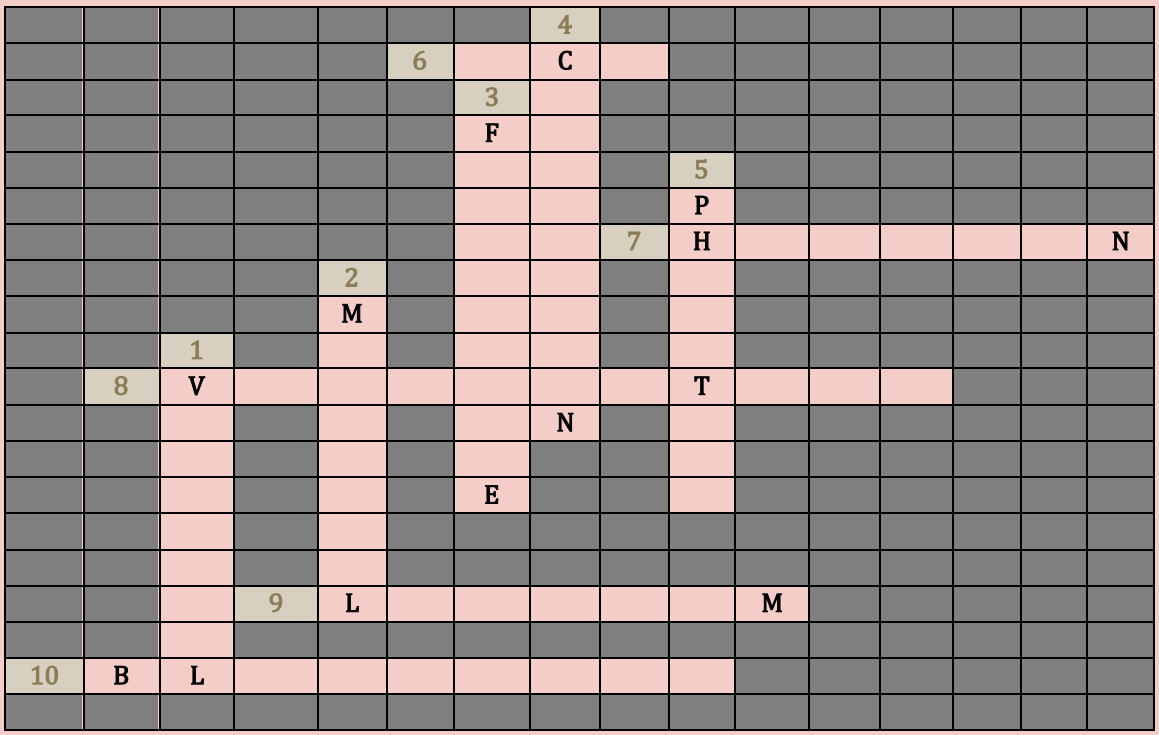
Be Cautious…..Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Carbimazole	Acute Pancreatitis
2.	Ketamine	Liver and Bile duct damage
3.	Levetiracetam	Abnormal and aggressive behaviours
4.	Ondansetron	Oral Cleft defects
5.	Ticagrelor	Bradyarrhythmia
6.	Levothyroxine	Myocardial Infarction

S. No.	Drug	Pharmacological Class	Indication	Dosage
1.	Relugolix	GnRH receptor Antagonist	Advanced prostate cancer	360 mg loading dose after then 120 mg daily
2.	Vibegron	B3 adrenergic agonist	Overactive Bladder Syndrome	75 mg Orally OD
3.	Tepotinib	Mesenchymal-epithelial transition (MET)	Non-Small Cell Lung Cancer	450 mg Orally OD
4.	Vericiguat	Soluble guanylate cyclase (sGC) stimulator	Heart Failure with Reduced Ejection Fraction (HFrEF)	2.5 mg Orally OD
5.	Cabotegravir	HIV-1-integrase strand transfer inhibitor (INSTI)	HIV infection	30 mg Orally OD
6.	Umbralisib	Dual inhibitor of phosphoinositide 3 kinase (PI3K) delta and casein kinase 1 (CK1)	Marginal Zone Lymphoma, Follicular Lymphoma	800 mg Orally OD
7.	Voclosporin	Calcineurin-inhibitor immunosuppressant	Lupus Nephritis	23.7 mg Orally BD
8.	Trilaciclib	Cyclin-dependent kinase 4/6 (CDK4/6) inhibitor	Small Cell Lung Cancer-Myelo-preservation Therapy	240 mg/m2 per dose IV infusion
9.	Evinacumab	Angiopoietin-like 3 (ANGPTL3) inhibitors	Homozygous Familial Hypercholesterolemia	15 mg/kg IV infusion once a month
10.	Casimersen	Antisense oligonucleotide	Duchenne Muscular Dystrophy	30 mg/kg IV infusion once weekly

Crossword Puzzle…

Hint: *Drugs Causing Hair Loss or Excessive Hair Growth*



Answers:

Downward	**Across**
1. Phenyl-alkylamine Calcium channel blocker with additional α adrenergic blocking action (9) 2. Prodrug which opens ATP sensitive K^+ channels (9) 3. Helps in reducing the static component of Benign Prostatic Hypertrophy (BPH) (11) 4. Calcineurin Inhibitor which is used as an immunosuppressant agent (11) 5. Anti-epileptic agent which follows zero order kinetics and has narrow therapeutic range (9)	6. Most commonly used drug(s) for birth spacing (3) 7. Anti-coagulant agent which is highly ionized drug and hence no oral absorption (7) 8. Spindle poison obtained from plant and used in AML and ALL (11) 9. Psychotropic agent with very narrow therapeutic index (7) 10. Cytotoxic agent with additional chelating properties (9)