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 Tenth issue of ESSENCE.

The 'International day against drug abuse' is observed every year on 26 June to spread awareness about the serious issues caused by drug abuse which is a major challenge affecting every corner of the world across all socio-economic strata. There are only a few modestly effective FDA approved drugs for the management of drug addiction. In this scenario, therapeutic vaccines against drug abuse and drug addiction can play a role in preventing relapse and breaking the cycle of addiction. On the occasion of the international day against drug abuse, this issue of ESSENCE deliberates on the role of vaccines for drug addiction.

The current issue also highlights the role of Pharmacometrics as an important field in quantitative clinical pharmacology that affects decision-making throughout the drug development and regulatory review process. The applications of Pharmacometrics in terms of interpreting and describing pharmacology in a quantitative fashion are also discussed.

The tenth issue of ESSENCE also has sections on new drug approvals and other important news in the field of therapeutics. Finally, the readers can test their knowledge with the cross word on 'Drugs causing Neutropenia'.

Happy Reading and Stay safe.

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

Drug Abuse and Addiction: Can Vaccines be the answer?

Drug abuse is a major problem for the society affecting people from all countries and economical status. According to the World Health Organisation, drug abuse not only leads to billions of dollars in monetary loss in terms of adverse impact on human productivity and health-care cost but also on cost of crimes due to abuse of these drugs.

Even after decades of research, people with addiction still have very few medication options. While there are a handful of modestly effective FDA-approved drugs to treat alcohol, nicotine and opioid-use disorders, there are none at all for Cocaine, Methamphetamine, Cannabis and other narcotics. And the fact remains that most people with a substance use disorder will relapse – from 40 to 60%, according to the National Institute of Drug Abuse (NIDA).

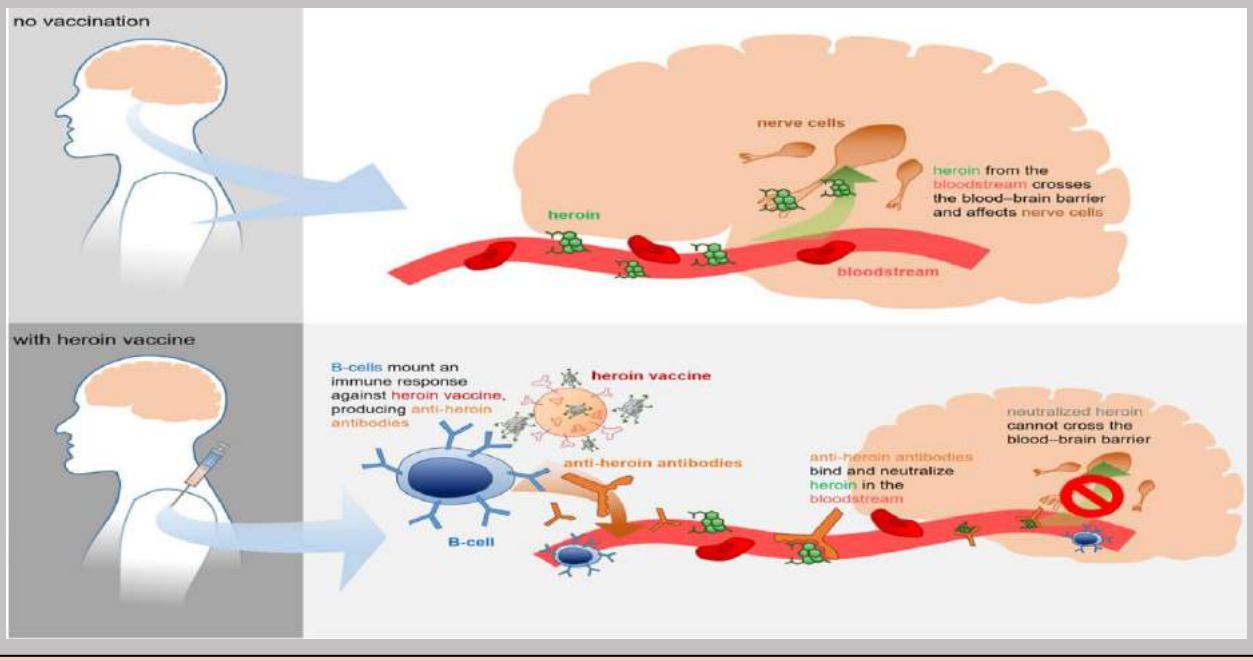
A major hurdle is that addiction is a complex condition involving the brain, body and psychology. If addiction has to be treated we have to do three things; take away withdrawal symptoms, reduce craving and block the high.

No current medication can do all three things. That's why the idea of vaccines for addiction has long been embraced by researchers. A vaccine could prevent a person from getting high in the first place, which would theoretically address the issue of cravings and withdrawal symptoms; other potential advantages of vaccines are the long duration of action, the certainty of administration and a potential reduction of toxicity to important organs.

How addiction vaccines work:

All drugs of abuse have to first cross the blood brain barrier (BBB) and act on the brain to show their effects. If somehow a drug is prevented from passing through the BBB, it would prevent it from showing its addictive and psychoactive effects.

This would help motivated addicts, who frequently first quit a drug and after brief period of abstinence, start abusing it again. If at this point of abstinence, a drug can be prevented from showing its psychological effects, it would prevent relapse. From here came the theory of stopping the drugs into the circulation before it can enter the blood–brain barrier by antibody binding.



Normally, the immune system ignores small-molecule drugs in the bloodstream. The molecules are tiny enough that they sneak past the immune cells circulating in the body. The major challenge in making an anti-drug vaccine is that the B lymphocytes, normally do not detect or respond to drugs. To alert these cells to the presence of drug molecules, scientists must attach these drugs to larger conjugates that can provoke the immune system. If a drug is conjugated with a large particle and vaccinated, it is capable of producing immunological response and producing IgG antibodies against the drug. At this point, when the vaccinated individual takes the drug the IgG antibodies will bind to the drug and the compound drug-antibody molecules are now too big to go through the blood brain barrier. Hence the drug cannot enter the brain and cannot produce psychoactive or addictive effects. Hence the addict will obtain no reward or relief of craving from taking the target drug, and so will have reduced motivation to continue taking the drug.

Therapeutic Vaccine against Alcohol Abuse: These vaccines act by causing genetic mutation of aldehyde dehydrogenase enzyme, which is the second most important enzyme involved in alcohol metabolism. This leads to accumulation of acetaldehyde which is not metabolized due to lack of the enzyme involved. This leads to feeling of uneasiness, nausea, and increased heart rate which leads to aversion for alcohol in the addict. One injection will have its effect for 6 months. Animal studies have shown promising results and clinical trials are currently being planned.

Examples of Vaccines being developed for Drug addiction:

DRUG	DEVELOPER	STATUS	REFERENCE
Cocaine	Weill Cornell Medicine/Scripps Research Institute	Phase I	*CNS Neurol. Disord.: Drug Targets* 2011 DOI:10.2174/187152711799219334
Nicotine	Selecta Biosciences	Phase I	
Fentanyl	Scripps Research Institute	Preclinical	*Angew. Chem. Int. Ed.* 2016, DOI: 10.1002/anie.201511654
Heroin	Scripps Research Institute	Preclinical	*J. Am. Chem. Soc.* 2017, DOI: 10.1021/jacs.7b03334
Heroin	Walter Reed Army Institute of Research	Preclinical	*J. Med. Chem.* 2017, DOI: 10.1021/acs.jmedchem.7b01427
Oxycodone	Minneapolis Medical Research Foundation	Preclinical	*PLOS One* 2014, DOI: 10.1371/journal.pone.0096547

Conclusion:

Therapeutic vaccines are a promising approach to tackle the problem of drug abuse and addiction. The main goal of the vaccines is to help people break the cycle of addiction. The vaccines may also offer advantages over existing medications in terms of cost and length of effect. So far, scientists have repeatedly demonstrated that the vaccine concept works in animals. These vaccines establish high antibody levels for months in animals, and in multiple studies, the vaccines have stopped animals from self-administering drugs.

Clinical trials are underway, however not all participants receiving the vaccine react similarly. Some people's immune systems produced high levels of antibodies against the drug, and others do not. An anti-drug vaccine will be clinically useful if the antibody response it induces is sufficiently strong to intercept all or almost all of the target drug molecules before they reach the blood-brain barrier. Further, the antibody titre should remain high for sufficient period of time. These are the challenges that must be overcome before therapeutic vaccines against drug addiction can become a reality.

Zolgensma: The world's most expensive drug

Zolgensma has been reported to be the costliest drug in the world with price of £1.79 million (₹18 crore) per dose. Zolgensma was approved on May 24, 2019 by the US Food and Drug Administration, was approved by the United Kingdom's National Health Services (NHS) on March 9, 2020. It is an adeno-associated virus vector-based gene therapy indicated for the treatment of paediatric patient less than 2 years of age with spinal muscular atrophy (SMA). It can enable mobility in babies and young children suffering from a rare genetic condition. The drug contains a replica of the missing gene. The active ingredient onasemnogene abeparvovec passes into the nerves and restores the gene, which then produces proteins necessary for nerve function and controlling muscle movement. This drug is a one-time intravenous infusion which is administered on a patient for over an hour. The dose is determined based on the weight of the patient.

REGEN-COV2: The promising antibody cocktail against Covid-19

REGEN-COV2 is a combination of monoclonal antibodies Casirivimab and Imdevimab, had received the Central Drugs Standard Control Organisation's restricted emergency use permission in May. It is indicated for use in those with mild to moderate Covid-19 who do not require oxygen and who are at a high risk of progressing to severe disease. REGEN-COV2 at a maximum retail price of approximately Rs 1.20 lakh per pack. It targets the SARS-CoV-2 spike protein. The monoclonal antibodies bind to specific parts of the spike protein, blocking its ability to infect healthy cells. In RECOVERY trial, it is found to reduces the risk of death by a fifth compared to those who had received standard care. The therapy reduced the hospital stay of patients lacking their own natural antibody response by four days. It also reduced their risk of requiring a ventilator.

FDA Approves First New Alzheimer's Drug in Nearly 2 Decades

Aducanumab was approved under the accelerated approval pathway and is a first-of-its-kind amyloid beta-directed antibody treatment for Alzheimer disease. Individuals receiving the treatment had significant dose- and time-dependent reduction of amyloid beta plaque. It comes in 2 dosages of 170mg/1.7ml and 300mg/3ml solution. The recommended dosage for this drug is 10mg/kg as an intravenous infusion for over 60 minutes every 4 weeks. This is the first FDA-approved drug that delays decline due to Alzheimer's disease. This means individuals may have more time to actively participate in daily life, have sustained independence and hold on to

Pharmacometrics: The Science of Quantitative Pharmacology

Pharmacometrics is branch of science concerned with mathematical models of biology, pharmacology, disease, and physiology used to describe and quantify interactions between xenobiotic and patients, including beneficial effects and side effects resultant from such interfaces. Pharmacometrics is quantitative clinical pharmacology that affects decision-making throughout the drug development and regulatory review process. It is the science of interpreting and describing pharmacology in a quantitative fashion. It is bridging discipline that facilitates translation of complex biologic processes and communicates them in a quantitative manner. Pharmacometrics uses mathematical and statistical models based on pharmacology, physiology and disease for quantitative analysis of interactions between drugs and patients.

One of the most visible applications of pharmacometrics is the integration of population-based pharmacokinetics/pharmacodynamics (PK/PD) models with a clinical trial simulation model from which trial design and execution can be explored relative to performance and outcomes. This approach has the added benefit of exploring doses, regimens, and compliance patterns outside of historical patient experience as well as clinical assumptions regarding the exposure-response-efficacy relationship.

Another area of great impact of Pharmacometrics is the use of modelling and simulation to facilitate drug candidate selection. Pharmacometrics in this regard has been applied both preclinically using *in silico* approaches and in animals and clinically inpatients. Through the process of evaluating and comparing drug candidate characteristics, valuable information regarding an agent's therapeutic window can be identified as well as the probability that such information can be generalized across class or across agents with similar homology. Another area of applied pharmacometrics research is in the area of disease progression; where models for HIV, osteoporosis, multiple sclerosis, and rheumatoid arthritis offer great potential to provide new targeted therapies.

Modeling Software in Pharmacometrics

PK-Sim, Simcyp, and GastroPlus are specialized PBPK modeling software packages, provide less flexibility in model development, but they also require less mathematical and modeling experience. Such software tools provide the user with either a click-and-drag assembly of the model structure or an already built model, and can either simulate particular PK-relevant processes (e.g., intestinal absorption or metabolism) or constitute a generic whole body PBPK model. Many offer additional features; for example, Simcyp and PK-Sim allow simulation of complex absorption, distribution, metabolism, and excretion outcomes involving multiple drug interactions and parent drug and metabolite profiles. They also allow the simulation of virtual patient populations such as obese/morbidly obese individuals and patients with renal impairment or liver cirrhosis, and include a clearance prediction model that incorporates knowledge about growth, development, and maturation of various organs and tissues involved in drug metabolism and elimination across paediatric age groups to predict clearance in children using adult values. Many software programs have been widely used in PopPK and PopPD such as NONMEM, ADAPT, and MONOLIX.

Application of Pharmacometrics

1. Drug Development.

2. Treatment Individualization.

3. Chemical/Drugs Risk Assessment.

4. Pregnancy Medication.

5. Paediatric Medication.

6. Drug Approval and Labelling Decisions.

Limitations of Pharmacometrics

PBPK modeling requires comprehensive data about the physiological, biochemical, and physicochemical processes that occur in biological systems in different age groups or under certain physiological and pathological conditions. These data are not available from only one source, which may lead to some confusion and to a problem in establishing a reliable source of accurate and consistent information. PBPK models reflect current scientific knowledge, and while some processes are known to be well characterized, others are partly or poorly characterized, as information gaps may exist. Moreover, as simulations are associated with prediction errors and uncertainty, they require accurate judgment and interpretation of their inferences to frame them in the right context. In addition, simulation results should be supported by experimental data, and should not be used to replace data from well conducted studies as primary degree of evidence. Care should be given to the fact that poor quality modeling and simulations practices could lead to a biased model or overestimation of the predictive power of the model. The researcher/user of this modelling technique should understand the physiological and pharmacological rationale behind the model and should be aware that PBPK modelling.

Conclusion

Pharmacometrics has the potential to influence decision making through the construction of mathematical models. In addition, it is a tool to assess the effects of covariates on the parameters of PK/PD/disease model. Despite its potential benefits and various implementations, does not provide the ultimate solution in and that there remains a shortage of prospective.

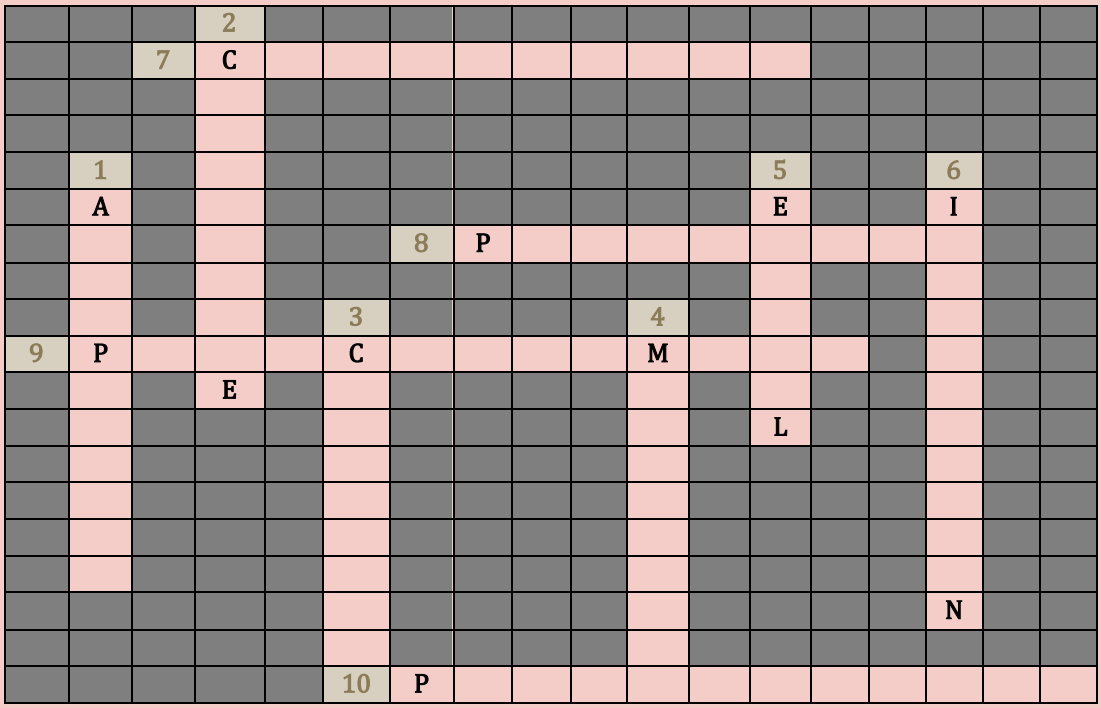
Be Cautious….Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Acetazolamide	Eye Disorders (choroidal effusion (CE) and acute myopia (AM))
2.	Ifosfamide	Encephalopathy
3.	Pomalidomide	Progressive Multifocal Leukoencephalopathy (PML)
4.	Pregabalin	Severe Respiratory Depression
5.	Sofosbuvir	Severe Cutaneous Adverse Reactions (SCAR)
6.	Ulipristal Acetate	Serious Liver Injury

S. No.	Drug	Pharmacological Class	Indication	Dosage
1.	Aducanumab	Amyloid beta-directed antibody	Alzheimer's disease	10 mg/Kg as an IV infusion
2.	Ibrexafungerp	Triterpenoid antifungal	Vulvovaginal candidiasis	300 mg twice daily
3.	Infigratinib	Kinase inhibitor	Cholangiocarcinoma	125 mg orally once daily for 21 consecutive days followed by 7 days off therapy, in 28-day cycles
4.	Sotorasib	RAS GTPase inhibitor	Non-small cell lung cancer	960 mg orally once daily
5.	Pegcetacoplan	Complement inhibitor	Paroxysmal Nocturnal Hemoglobinuria (PNH)	1080 mg by subcutaneous infusion, twice weekly
6.	Dostarlimab	Programmed death receptor-1 (PD-1)–blocking antibody	Endometrial carcinoma	500 mg/3 weeks
7.	Viloxazine	Selective Norepinephrine Reuptake Inhibitor	Attention Deficit Hyperactivity Disorder (ADHD)	100 -400 mg/day
8.	Ponesimod	Sphingosine 1-phosphate receptor modulator	Multiple sclerosis	20 mg once daily
9.	Rilpivirine	Human Immunodeficiency Virus type 1 (HIV-1) specific,	HIV	25 mg once daily
10.	Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)	Antihyperglycemic Agent	Severe Hypoglycaemia	0.6 mg single-dose by subcutaneous route

Crossword Puzzle…

Hint: ***Drugs Causing Neutropenia***



Downward	**Across**
1. Xanthine oxidase inhibitor (11) 2. H2 Antihistaminic which inhibits the cytochrome P-450 (10) 3. Angiotensin Converting Enzyme (ACE) inhibitor with highest bioavailability (9) 4. Central sympatholytic used as an antihypertensive drug (10) 5. Used as an antidote for methanol poisoning (7) 6. NSAID which is well known to cause frontal headache as an ADR (12)	7. Alkaloid with mitotic spindle poison properties (*10*) 8. Drug with very narrow therapeutic index and associated with gingival hyperplasia *(9)* 9. Used in copper & mercury heavy metal poisonings *(13)* 10. Na+ channel blocker with antiarrhythmic properties *(12)*

Answers:

Downward

1. Allopurinol 2. Cimetidine 3. Captopril
4. Methyldopa 5. Ethanol 6. Indomethacin

Across

7. Colchicine 8. Phenytoin
9. Penicillamine 10. Procainamide