DEPARTMENT OF PHARMACOLOGY
ARMED FORCES MEDICAL COLLEGE, PUNE-40

The Pill Box

Issue: Third, Jul– Sep 2021

Dear Readers,
The purpose of this bulletin is to disseminate some important information related to drugs and medical devices likely to be of interest to everyone, involved directly or indirectly in patient care. The current issue highlights about the various medication safety programmes running in our country, drug withdrawals, recent drug approvals and few potential pre-clinical research studies. Feedback and suggestions, if any, may be sent at email Id: thepillboxafmc@gmail.com .

Pharmacovigilance
An important tool for medication safety

"Pharmacovigilance"

Pharmacon (Greek)-Drug + Vigilare (Latin)-to keep watch

WHO Definition: The science and activities relating to the detection, evaluation, understanding and prevention of adverse drug reactions or any other drug-related problems.

National Pharmacovigilance Week: 17-23 Sept 21
Theme: Pharmacovigilance: A step towards Patient Safety

Why Pharmacovigilance?

-Insufficient evidence of drug safety from clinical trials due to limited size and age/sex/disease specific study population, shorter study period duration and controlled study environment
-Adverse Drug Reactions among top ten causes of mortality.
-Percentage of hospital admissions due to drug related events in some countries is about or more than 10%

Goals of Pharmacovigilance

-Early detection of unknown safety problems
-Detection of increase in frequency
-Identification of risk factors
-Quantifying risks
-Preventing patients from being affected unnecessarily

Rational and Safe use of Medicines

Programmes in India for ADR monitoring

-Pharmacovigilance programme of India (PvPI)
-Haemovigilance programme of India (HvPI)
-Materiovigilance programme of India (MvPI)
-Adverse Event Following Immunization (AEFI)

New Drugs Corner

Difelikefalin
MOA: Kappa opioid receptor agonist
Indication: Treatment of moderate-to-severe pruritus associated with chronic kidney disease (CKD-aP) in adults undergoing hemodialysis (HD).

Finerenone
MOA: Non-steroidal mineralocorticoid receptor antagonist
Indication: To reduce the risk of kidney and heart complications in chronic kidney disease associated with type 2 diabetes

Belumosudil
MOA: Kinase inhibitor
Indication: To treat chronic graft-versus-host disease after failure of at least two prior lines of systemic therapy

Odevixibat
MOA: Ileal bile acid transporter (IBAT) inhibitor
Indication: Treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC)

Anifrolumab-fnia
MOA: Type I interferon (IFN) receptor antagonist
Indication: To treat moderate-to severe systemic lupus erythematousus along with standard therapy.

Reference: USFDA

The Pill Box Quiz: 03

Instructions:
Scan the QR code to attempt the questions and find correct answers.

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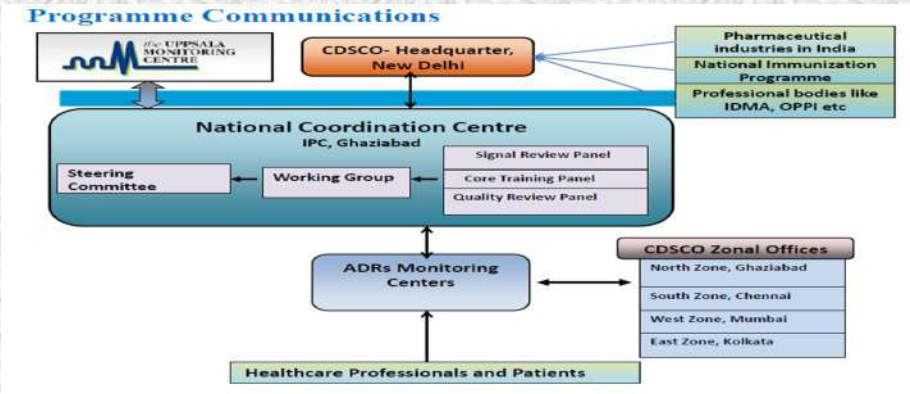
Pharmacovigilance Programme of India (PvPI)

India joined WHO programme for International Drug Monitoring in 1998 but was not very successful. Later, the National Programme of Pharmacovigilance was launched in 2005, and was renamed as the Pharmacovigilance Programme of India (PvPI) in 2010. The present headquarter of PvPI is at Indian Pharmacopoeia Commission (IPC), Ghaziabad. Presently there are about 395 Adverse Drug Monitoring Centres (AMCs) at medical colleges and hospitals throughout the nation. Adverse Drug reactions are captured through a well-structured format and reported to the AMCs or directly to PvPI-NCC by health providers and even general people. The ADRs are analysed by PvPI-NCC and report submitted to CDSCO and WHO-UMC. On the basis of this report CDSCO takes necessary action on the use of the drug. There are three more parallel programmes like Haemovigilance, Materiovigilance and AEFI which are integrated to the PvPI.



Materiovigilance Programme of India (MvPI)

After several horrific cases associated with malfunctioning of medical devices like infants burnt to death due to short circuits in incubators, or hip implants causing blood poisoning, the Ministry of Health and Family Welfare (MoHFW), Government of India have launched Materiovigilance Programme in July 2015. The main aim is to address potential adverse events related to medical devices, thereby improving medical device quality, in addition to creating database on medical device adverse event. It is meant to analyse, scrutinize and prevent the recurrence of harmful effects due to use of medical devices. The Indian Pharmacopoeia Commission (IPC) functions as National Coordination Centre (NCC). Sree Chitra Tirunal Institute for Medical Sciences & Technology (SCTIMST), Thiruvananthapuram act as National Collaboration Centre. MvPI is a good initiative to ensure safety of medical devices use . Based on the risk involved, the medical devices have been classified as class A (low risk) to class D (high risk).

Haemovigilance Programme of India (HvPI)

The Haemovigilance Programme of India (HvPI) was launched on 10th December, 2012 . It is a set of surveillance procedures covering the whole transfusion chain from the collection of blood and its components to the follow-up of its recipients intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products and to prevent their occurrence and recurrence. It is an important tool for improving safe blood transfusion practices in a country.

Adverse Event Following Immunization (AEFI)

AEFI surveillance is a vaccine safety initiative. An adverse event following immunization (AEFI) is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

"To undergo treatment you have to be very healthy, because apart from your sickness you have to withstand the medicine" - *Molière*

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Drug ban/withdrawn/black box warning: A glimpse

Due to the constant ADR monitoring activities, there are certain drugs which have been banned/ withdrawn or black box warning/ drug label changes occurred due to action by regulatory authorities. Some of these drugs along with their reason for withdrawal are shown below:-

Drugs withdrawn/black box warning placed

Drug Name	Drug Class	Date of release	Date of Indian ban// warning	Reason for ban/ withdrawal
Astemizole	2nd gen anti-histamine	1997	2003	Rare but fatal QT interval prolongation and related arrhythmia
Cisapride	5-HT_4 agonist	1980	2011	Rare but fatal QT interval prolongation and related arrhythmia
Diclofenac	NSAIDS	1973	2008	Liver toxicity in vultures and hence banned for **animal use** in India in 2008
Phenformin	Biguanides	1957	2003	Lactic Acidosis in the late 1970s which was fatal in 50% of cases
Terfinadine	2nd gen anti-histamine	1985	2003	Liver damages and severe cardiovascular complications
Gatifloxacin	Fluoroquinolone	1999	2011	Diabetes risk reported in a Canadian study published in NEJM 2006 led to a FDA black box warning in 2006 and withdrawn from Indian market in 2011
Rosiglitazone	Thiazolidinedione	2006	2010	Increased risk of heart attacks by 43% and subsequent deaths led to a US FDA alert
Tegaserod	5-HT4 agonist	2002	2011	Banned globally due to 10 fold increase in risk of heart attacks and strokes in 2007 and withdrawn from Indian market after a report DTAB in 2011
Rofecoxib	Selective COX -2 inhibitor	1999	2004	Increased risk of heart attack and stroke on long term use in high doses led voluntary withdrawal by Merck from the US market and in India.
Fluoroquinolone	Quinolones antibiotic	-	2008	Black box warning: increased risk of tendinitis and/or tendon rupture
Rimonabant	Selective cannabinoid CB-1 receptor antagonist	2006	2009	Serious suicidal tendencies led the European drug regulator and the National Health Regulator to recall in 2009 and in 2009 in India.
Letrozole	Nonsteroidal aromatase inhibitor	2007	2011	Severe genetic abnormalities in babies born to infertile women led the Indian Union health ministry to withdraw the drug in 2011.
Medroxy-progesterone	Progesterone	-	2013	Black box warning: decreased bone density with long term use

Pre-clinical research : Potential molecules

Blocking ABCB10 protein in liver cells protects against high blood sugar, fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is becoming increasingly common and found to be closely linked to obesity and other disorders related to insulin resistance. The mentioned study shows that increased bilirubin content inside the mitochondria driven by ABCB10 activity is contributing to fatty liver disease. In the study, the researchers removed the ABCB10 protein selectively from the livers of mice to test whether ABCB10 removal impacted the ability of obese mice to tolerate glucose and how well the mitochondria in their livers were working to convert nutrients into usable energy. In lean mice, the researchers found no difference in metabolism and health when ABCB10 was removed from their livers, while in obese mice they found that removing ABCB10 protected against insulin resistance and fatty liver disease. ABCB10 transports biliverdin out of the mitochondria and increases bilirubin production in liver cells. When they restored bilirubin content in the mitochondria, the benefits on the function of mitochondria resulting from the removal of ABCB10 were reversed.

Reference: Shum, M., et al. (2021) ABCB10 exports mitochondrial biliverdin, driving metabolic maladaptation in obesity. Science Translational Medicine. doi.org/10.1126/scitranslmed. abd1869

Promising bio-therapeutics for obesity and related medical complications

Obesity is a global pandemic associated with a significantly reduced life expectancy. It also increases the risk of type 2 diabetes, hypertension, coronary heart disease, stroke, chronic kidney disease and cancer. Adiponectin and adipokine regulates glucose levels, improve lipid metabolism and is a major player in the pathogenesis of obesity. Obese patients have low adiponectin levels, a condition known as hypoadiponectinemia, which contributes to increase risks of cardiovascular, metabolic diseases as well as aggressive development of malignancies with poor prognoses. Adiponectin supplementation is a long-sought-after strategy for the prevention and treatment of cancer and metabolic diseases, especially in obese patients. However, the adiponectin application in therapy has been hampered by the difficult production of human adiponectin. The researcher have developed an efficient synthetic approach to produce the adiponectin-derived glycopeptides that exhibit potent anti-tumor, insulin-sensitising and metabolic activities in various mouse models.

Reference: Wu, H., et al. (2021) Chemical Synthesis and Biological Evaluations of Adiponectin Collagenous Domain Glycoforms. Journal of American Chemical Society. doi.org/10.1021/jacs.1c02382.

New peptides allow cannabis-derived drugs to fight pain in mice without side effects

At present, there are two main types of analgesics prescribed based on the severity of the pain. Non-steroidal anti-inflammatory drugs are often used to treat mild pain, while opioids are used for severe pain. There is a lack of safe and effective drugs to treat moderate chronic or neuropathic pain (such as that caused by nerve damage for people with diabetes or herpes). Cannabis-derived drugs have an excellent opportunity to provide relief, but their therapeutic use is limited by their side effects, including problems with memory and other cognitive functions. THC produces analgesia by binding to cannabinoid type 1 (CB1) receptors. However, these receptors interact with the serotonin receptor 5HT2A, and this interaction causes memory loss when THC is present. Based on molecular dynamics simulations and current pharmaceutical chemistry strategies, the researchers have developed a smaller peptide with high stability, allowing oral administration while increasing its ability to cross the blood-brain barrier to access and act on brain cells. Mice treated with both THC and the optimized peptide obtained the benefits of THC in relieving pain and also showed better memory compared to those treated with THC alone.

Reference: Gallo, M., et al. (2021) orally Active Peptide Vector Allows Using Cannabis to Fight Pain While Avoiding Side Effects. Journal of Medicinal Chemistry. doi.org/10.1021/acs.jmedchem.1c00484.

"We have more to learn from animals than animals have to learn from us." A D Williams