ESSENCE

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, MANGALAGIRI

PHARMACOLOGY BULLETIN

SEPTEMBER-OCTOBER 2020, ISSUE 6

FROM THE EDITORIAL DESK….

Dear Seniors and Friends, Welcome to the Sixth issue of ESSENCE from AIIMS Mangalagiri.

Patient safety in recent years has emerged as a distinct health care discipline that aims to prevent & reduce risks, errors and harm that occur to patients during provision of health care. The World Health Organization (WHO) celebrates the 'World Patient Safety Day' on 17 September every year. Medication errors can occur in any patient but patients who move across transitions of care are most vulnerable. The current issue of ESSENCE discusses the importance of Medication Reconciliation in ensuring accurate and consistent communication of patient's medication information through transitions of care so as to minimize medication errors and safeguarding patient safety.

Drug repurposing, also termed drug repositioning, re-profiling or re-tasking, is a strategy for identifying new indications for already approved drugs. Because the safety of these drugs has already been tested in clinical trials for other applications, re-purposing known drugs can bring medications to patients much faster and with less cost than that of developing new drugs.

The current issue also discusses the recent drug approvals and also safety alerts of various drugs. Finally, the readers can test their knowledge with the cross word puzzle on 'Drugs Causing Pulmonary Infiltrates/fibrosis as an adverse effect'.

Happy Reading.

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

Consider the following Case scenarios:

An elderly woman is admitted to a hospital with community-acquired pneumonia. Appropriate antibiotics and management were ordered and commenced. Four days later the patient suffered an MI and it was found that a medication she was taking for CHD had been unintentionally omitted on admission.

A young patient's anti-epileptic medicine was temporarily discontinued during the patient's hospitalization due to a potential drug interaction. However, the drug was not renewed upon discharge and the patient later experienced recurrence of his grand mal seizures.

"Show me your Medicines" is a common instruction by medical staff when patients report to the OPD/Ward/hospital and the patient empties the medicines he/she has got in the polythene gag. But how effective is this "Poly Bag" review process? Does it reliably give a complete picture of the pills patients are taking or can it lead to errors? It is estimated that between 10% and 67% of medication histories have at least one error, and up to 33% of these errors have the potential to cause patient harm.

Medication errors can occur in any patient but patients who moves across transitions of care are most vulnerable. Out of the total medication errors that occur, more than 50% of medication errors occur at transitions of care. Transition points of care are particularly prone to unintended changes in medication regimes and other medication discrepancies. Many of these events occur as a result of poor communication between health care professionals (HCP) and between HCP and patients or care givers when care is transferred, such as when patients are admitted to hospital, move between wards, inter-hospital transfer or when they are discharged to home. The majority of these errors can be prevented through a formal medication reconciliation process designed to improve the accuracy of medication histories recorded and their use when prescribing.

Medication Reconciliation:

It is a system of effectively communicating changes to medication regimens to patients and healthcare providers within the patient's circle of care as he/she transitions through the healthcare system. The process of medication reconciliation is intended to ensure accurate and consistent communication of patient's medication information through transitions of care.

Medication reconciliation is the process of creating the most accurate list possible of all medications a patient is taking — including drug name, dosage, frequency, and route — and comparing that list against the physician's admission, transfer, and/or discharge orders, with the goal of rectifying any discrepancies and providing correct medications to the patient at all transition points within the hospital.

Steps involved in Medication Reconciliation

Step 1: Obtaining a Best Possible Medication History (BPMH) :

The safe use of medications while treating patients requires knowledge and consideration of all the medications that the patient is currently taking or receiving in order to avoid omissions, duplications, dosing errors, and potential adverse interactions with new drugs being prescribed.

BPMH is a medication history obtained by a HCP which includes a thorough history of all regular medication use (prescribed and non-prescribed), using a number of different sources of information. Types of medication to be noted on the BPMH include ALL prescribed and non-prescribed medications (self-medications/herbal) and very frequently would involve talking to the patient's family and caregivers.

Step 2: Confirming the accuracy of the Medication history:

We know that patients are poor historians and the medication information should always be verified with more than one source as appropriate. These may include: a) inspection of medication containers b) patient medication lists c) previous patient health records d) pharmacists, physicians and/or home care providers.

Step 3: Medication Reconciliation at admission: Reconcile BPMH with medication orders and identify discrepancies:

Medication reconciliation at admission generally fits into two models: the proactive process or the retroactive process, or a combination of the two. The *proactive model* occurs when the BPMH is created prior to writing admission medication orders. In the *retroactive model***,** admission orders are written before the BPMH is created.

In the Proactive model, the BPMH is created and documented upon patient arrival or when the decision is made to admit the patient. It is used by the prescriber to write the admission medication orders (AMO). This process depends on the BPMH being created before admission medication orders (AMOs) are written.

In the Retroactive model, a primary medication history is completed and orders written before the BPMH is created. In this case the BPMH is created and compared against the admission medication orders retroactively. Discrepancies are identified and resolved with the prescriber, if clinically appropriate. The medication should be reconciled within 24 hours.

In both models, reconciliation takes place between the BPMH and the admission orders with the aim to identify discrepancies. Discrepancies between the admission medication orders and the BPMH can be divided into two categories and resolved:

• Undocumented intentional – discrepancies in which the prescriber has made an intentional choice to add, change or stop a medication but this choice is not clearly documented.

• Unintentional– discrepancies in which the prescriber unintentionally changed, added or omitted a medication the patient was taking prior to admission

Step 4: Medication Reconciliation at Discharge/Transfer:
Patients with one or more medicines missing from their discharge information are 2.3 times more likely to be readmitted to hospital than those with correct information on discharge. Hence, it is important that the Best Possible Medication Discharge/Transfer Plan (BPMDTP) should be created based taking in to account the medication updates during the treatment. This should be communicated to the patient, primary care physician, or health care team that wills next be providing care to the patient. On receiving a BPMDTP, the various recipients should assure that their records are updated to accurately reflect the patient's current medications. Proper medication reconciliation at discharge can play a major role in preventing adverse drug event related readmissions.

Conclusion:
Preventing harm from medications, or adverse drug events (ADEs), remains a top patient safety priority not only in hospitals but also across the continuum of care for patients. Implementing medication reconciliation at all transitions in care — at admission, transfer, and discharge — is an effective strategy for preventing ADEs.

References:

1. WHO Global Patient Safety Challenge: Medication Without Harm: Available from. https://www.who.int/patientsafety/medication-safety/en/
2. High 5 S: Standard Operating procedures: Available from https://www.who.int/patientsafety/topics/high-5s/en/

Recent news/Updates from the world of medicines ……..

AstraZeneca resumes COVID-19 vaccine trial after a glitch

AstraZeneca, one of the frontrunners in this endeavour, received a setback when the trial of its COVID-19 vaccine candidate was paused. The trials have now been resumed and the world is waiting with baited breath to how the vaccines will be delivered to them. In India, Serum Institute of India (SII) also resume the trials in the country after the drug regulator, Drugs Controller General of India, gives it requisite permission.

New smart drug delivery system may help treatment for neurological disorders

A Rutgers-led team has created a smart drug delivery system that reduces inflammation in damaged nervous tissues and may help treat spinal cord injuries and other neurological disorders. The system, which uses extremely thin biomaterials implanted in the body, also protects nerve fibres (axons) that connect nerve cells in injured neural tissues, according to a study in the journal *Advanced Materials*. The system, which releases an anti-inflammatory molecule (methylprednisolone), can create a favourable micro-environment to promote tissue repair and recovery after neurological injury.

Be Cautious…..Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Fulvestrant	Injection site necrosis and ulcer
2.	Ketamine	Potential risk of liver and bile duct damage
3.	Memantine	Risk of bradyarrhythmia
4.	Ondansetron	Potential risk of oral cleft defects
5.	Levetiracetam	Risk of abnormal and aggressive behaviours
6.	Ticagrelor	Potential risk of bradyarrhythmia

Drug Repositioning/Drug Repurposing: Finding novel indications for existing drugs

The development of a drug is a long and complex process, with extremely high investment and small expectation of success. Currently, it takes an average of $1.4 billion and 10-17 years to develop a new drug and bring it into the market. Statistically, in a screening of one million potential drug candidates, only one has a profile to entry in clinical studies, and is still susceptible to a significant number of failures. Currently, the main developmental failure in the clinical stage occurs in phase II and phases III and is associated mainly with issues of safety and efficacy. Over the past 60 years, powerful tools have been developed that directly support the development of new drugs, such as molecular biology, biotechnology, DNA sequencing, databases of three-dimensional protein structures and combinatorial chemistry. However, there is a significant decline observed in the number of new drugs approved for clinical use in recent years, showing a discrepancy in the face of scientific advances and R&D investments.

As a result, Drug Discovery programs are pursuing strategies that optimize the R&D process. Among them, we highlight the drug repositioning (DR) - an approach that seeks new therapeutic applications for already approved drugs, different from its initial indication. This strategy is intended to reduce costs and research time considerably when compared to traditional R&D methods. DR (or repurposing) can be defined as a process of identification and discovery of new therapeutic uses, outside and beyond the scope of the original pharmacological indication, for already approved drugs.

At the start of a repositioning/repurposing project, a range of toxicological, pharmacological and clinical safety information is already available, as candidates have now gone through various stages of development such as structural optimization, preclinical and/or clinical trials, in addition to the possibility of the candidate being an approved drug, having its clinical safety already been attested by the time of use. In this way, there is a reduction of the risks associated with failures in the early stages of development, which are high in traditional approaches, as well as a significant cost reduction and a possible increase in clinical safety. When comparing traditional drug discovery programs with others using DR, a significant reduction of the time spent in R&D can be observed. In traditional approaches, it is estimated that 10 to 17 years are spent for the development of a new drug, while in DR the estimated time is between 3 to 12 years. Although this strategy is far from new, it has gained considerable momentum in the last decade: about one-third of the approvals in recent years correspond to drug repurposing, and repurposed drugs currently generate around 25% of the annual revenue for the pharmaceutical industry

The DR has two profiles: on target and off target. In the first one, the known pharmacological mechanism of a drug or drug candidate is applied to new therapeutic indications, i.e., they are molecules that act on the same biological target in the treatment of different diseases. For example Finasteride is a 5 alpha reductase inhibitor approved for BPH and was subsequently repositioned to be used in Hair loss acting through the same target. In the off-target profile, the pharmacological mechanism is unknown and many of the successful and best-known drug repurposing stories (e.g. Minoxidil, Valproic acid) has emerged from serendipitous observations, from unorganized ('field') discovery processes, often relying on an off-target adverse effect to solve a clinical problem from another domain. Drugs and drugs candidates act on new targets, out of the original scope, for new therapeutic indications. Therefore, both the targets and the indications are new. These repositioning, in the main, are discovered through the serendipity and several computational strategies using different databases, algorithms, molecular coupling, among others.

Two basic strategies can be adopted for drug repositioning namely:

1. Activity-based screening strategies

a). Existing Drug's Data Bank

b). Phenotypic, Screening and Target Oriented Approach

2. Computational Based Approach

a). Transcriptional-based or Signature-based Drug Repositioning

b). Genome-Wide Association Studies

Table: Repurposing Drugs with original and new therapeutic indication

Drug	**Original Indication**	**Re-purposed New Indication**
Sildenafil	Angina	Male Erectile Dysfunction
Naltrexone	Opioid addiction	Alcohol dependence syndrome
Thalidomide	RA	Multiple Myeloma
Remdesevir	Ebola, MERS	SARS-CoV-2
Minoxidil	Hypertension	Hair Loss
Leflunomide	RA	Prostate Cancer
Gabapentin	Epilepsy	Neuropathic pain
Finasteride	BPH	Hair Loss
Duloxetine	Depression	Urinary Incontinence
Amphotericin	Fungal Infections	Leishmaniasis
Bromocriptine	Parkinson's disease	Diabetes Mellitus
Propranolol	Hypertension	Migraine prophylaxis
Penicillamine	Copper chelating therapy	RA

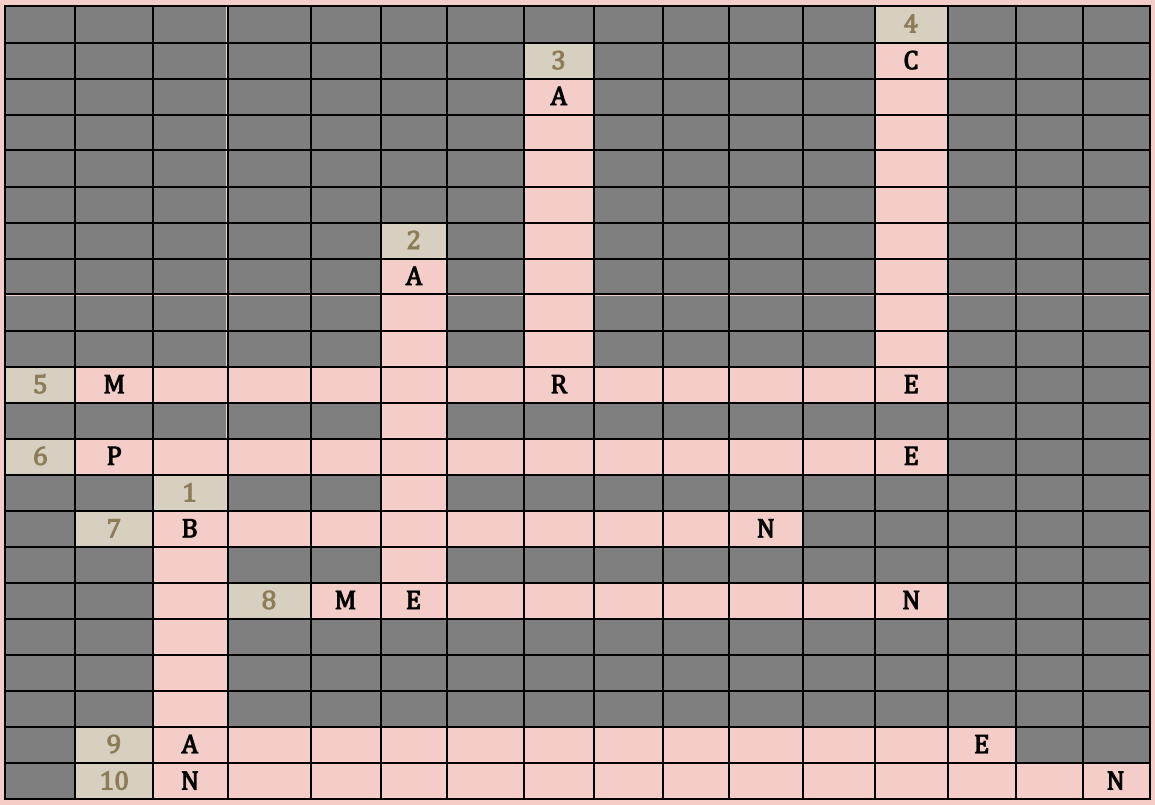
Drug Repositioning in COVID 19: In the recent scenario of Covid-19 pandemic, more than 80 clinical trials have been launched including 24 clinical trials that are investigating repositioning/repurposing of more than 20 medicines such as Hydroxychloroquine, Remdesivir, Favipiravir, Lopinavir, Ritonavir, Oseltamivir, Ivermectin, Methylprednisolone, Bevacizumab, and interferons. It is hoped that most of the studies found these repositioning trials may help to find solutions for COVID-19 treatment by this year.

Conclusion: Drug repositioning means finding novel indications for currently marketed drugs. Repositioning is an approach that has been used for a long time, but the ability to carry it out in a systematic and rational way is an innovation that can meet social and market needs. This approach offers lower R&D costs, greater chances of success, shorter research time and lower investment risk. These advantages are of benefit to patients and pharmaceutical companies, enabling the application of DR in rare and neglected diseases that have several limitations in traditional approaches. Thus DR can be a tool in the development of treatments for diseases that suffer historically from limited resources and a huge need for effective therapies.

S. No.	Drug	Pharmacological Class	Indication	Dosage
1.	Oliceridine	Opioid agonist	Moderate to severe acute pain in adults.	1.5 mg/dose IV
2.	Risdiplam	SMN2 splicing modifier	Spinal muscular atrophy	5 mg Orally OD
3.	Belantamab mafodotin	Anti-BCMA(B cell maturation antigen) immunoconjugate	Multiple Myeloma	2.5 mg/kg IV for 30 min every 3 weeks
4.	Viltolarsen	Antisense oliogonucleotide	Duchenne muscular dystrophy with DMD gene mutation	80 mg/kg IV/Week
5.	Satralizumab	Interleukin-6 (IL-6) receptor antagonist	Neuromyelitis Optica Spectrum Disorder	120 mg SC at Weeks 0, 2, and 4
6.	Ofatumumab	CD20-directed cytolytic antibody	Multiple Sclerosis	300 mg IV
7.	Somapacitan	Human growth hormone analog	Adult Human Growth Hormone Deficiency	1.5 mg SC /Week
8.	Azacitidine	Nucleoside metabolic inhibitor	Acute myeloid leukemia	75 – 100 mg/m2 IV/day
9.	Pralsetinib	Selective RET kinase inhibitor	Non-Small Cell Lung Cancer	100- 400 mg/day-Orally
10.	Tafasitamab	CD19-directed cytolytic antibody	Diffuse Large B-Cell Lymphoma	12 mg/kg IV

Crossword Puzzle…

Hint: ***Drugs Causing Pulmonary Infiltrates/fibrosis as an adverse effect***



Downward	**Across**
1. Second line drug for chronic phase of Myelocytic leukaemia (8)	**5.** Folic acid analogue which inhibits dihydrofolate reductase and used as DMARD in RA (12)
2. Anti-arrhythmic agent with K^+, Na^+, Ca^{2+} and β blocking actions (10)	**6.** Alkylating agent with weak MAO inhibitor property and associated with disulfiram like reactions *(12)*
3. Antiviral drug active against herpes group of viruses and has highest sensitivity towards HSV -1 (9)	**7.** Glycopeptide antibiotic with potent anti-tumour and chelating properties *(9)*
4. Cell-cycle phase non-specific alkylating antineoplastic agent used in the treatment of brain tumors (10)	**8.** Effective against multiple myeloma and advanced ovarian cancer *(9)*
	9. Potent immunosuppressant used in autoimmune disorders as well as in organ transplantation *(12)*
	10. Bacteriostatic drug but is Cidal at higher concentrations – Used in UTI *(14)*

Answers:

Downward
1. Busulfan
2. Amiodarone
3. Acyclovir
4. Carmustine

Across
5. Methotrexate
6. Procarbazine
7. Bleomycin
8. Melphalan
9. Azathioprine
10. Nitrofurantoin