ESSENCE

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PHARMACOLOGY BULLETIN

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FROM THE EDITORIAL DESK....

Welcome to the Second issue of 'ESSENCE' from AIIMS Mangalagiri...

We write prescriptions everyday but when was the last time we De-Prescribed? The health care system is geared toward starting medications, not reducing or stopping them, and guidelines typically include recommendations for initiating medications, but not discontinuing them. This leads to the clinical problem of Polypharmacy with many of these medications being potentially inappropriate. This issue talks about how the health care professionals can approach such patients and ensure that these medications are de-Prescribed.

Recent updates from the world of medicines including the controversial use of Paracetamol for cooking meat in certain African countries and the guidelines recommending use of SGLP inhibitors and GLP-1 analogues in Type 2 DM and atherosclerotic heart disease are also discussed. The most expensive drug ever to be marketed (you won't believe the cost!!!) also finds a place in this issue of ESSENCE.

Further, despite the rapid advancements in the field of Monoclonal Antibodies (mAbs), the nomenclature of these mAbs is poorly understood and may seem daunting to many health care professionals. The next section discusses how to navigate the seemingly challenging nomenclature of the monoclonal antibodies.

Finally, a cross word puzzle on the drugs which cause peripheral neuropathy as an adverse effect has been incorporated to test the knowledge of the readers.

Wishing all the readers a very Happy New Year 2020.

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

DE-PRESCRIBING: AN ESSENTIAL COMPONENT OF GOOD PRESCRBING

Polypharmacy is a clinical challenge because the health care system is geared toward starting medications, not reducing or stopping them, and guidelines typically include recommendations for initiating medications, but not stopping them. Although medications may offer potential benefit, they also give rise to potential harm. When combined, the risk of interactions with other medications or conditions or cumulative harms can outweigh the benefits. This is especially important in elderly populations who are more likely to be on potentially inappropriate medications (PIMs) especially in the setting of polypharmacy

The mindset of 'There is a pill for every ill" of many patients may lead them to demand/expect drug therapy for every ailment they may be having, real or imagined. Patients often complain of insomnia, constipation, and such other symptoms, which are more often due to underlying depression, sedentary lifestyle, or when they are on CNS depressants like sedative-hypnotics, and such factors. One often tends or is pressurized, to prescribe a hypnotic, laxative, which adds to the cost, hidden ADR such as falls.

It has been found that 44% of patients at hospital discharge are prescribed at least one unnecessary drug. Every third patient receiving five or more drugs suffer an ADR every year, with more than 25% deemed preventable. Apart from the greater potential for ADR, the rate of compliance is inversely proportional to the number drugs prescribed, and this has been found to be as high as 85%.

<u>De-Prescribing as an essential component of Good Prescribing:</u>

An essential component of good prescribing is de-prescribing, which is defined as the process of tapering, stopping, discontinuing, or withdrawing drugs, with the goal of managing polypharmacy and improving outcomes.

Some authors have used the term "Prescription metabolism" to refer the de-prescribing process as the process is analogous to drug metabolism. Like drug metabolism, prescription metabolism is a way of elimination of unwanted/troublesome/cost-ineffective medications.

<u>Approach to De-prescribing:</u>

Scott et. al., have suggested the S and S approach that can be utilized to de-prescribe and wean off potentially inappropriate medications:

- **Seek and Screen** – Obtain the current prescription(s) along with the drugs currently the patient is on. Screen and segregate them into essential and nonessential ones, taking into account the current clinical condition, benefit-harm proportion, patient preference and cost.
- **Save and Severe** – Save (retain) those that are considered as absolutely essential and severe (delete) those drugs that are harmfully interacting, unnecessary, duplicated including self-administered over-the-counter products like vitamins, nutritional products etc.

- **Sensitize and Supervise** – Sensitize the patient on the benefits of deletions of drugs and the benefits they may realize and emphasize on nonpharmacological, quality enhancing lifestyle approaches wherever possible. Finally supervise (monitor) for adherence and implore for further pruning as and when needed.

Likely candidates/scope of De-Prescription:

- Routine prescription of vitamin supplements is unlikely to be useful and should be de-prescribed.
- When a nondrug therapy is likely to have better benefit-risk ratio, such as physiotherapy/heat therapy, for neck, back pain compared to nonsteroidal anti-inflammatory drugs.
- Prescribing two or more drugs of the same class, where one should suffice – e.g., a cardioselective beta-adrenergic blocker like atenolol in a hypertensive ischemic heart disease patient would suffice than prescribing two different drugs (one for each condition). This also happens when a patient consults different specialists and is prescribed two brands of the same drug or class such as statin, antiplatelet agent etc.
- Polypharmacy also often results from "Prescribing Cascades", which occur when an adverse drug effect is misinterpreted as a new medical problem, leading to the prescribing of more medication to treat the initial drug-induced symptom. In such cases, a simple reduction in dosage or prescribing an alternate drug of the same class or of a different class could avoid the need for a second drug.
- "Legacy Prescribing," also must be identified and drugs de-prescribed in such cases. Legacy prescribing is when medications are initially prescribed for an intermediate duration, but continued indefinitely, for example PPIs, SSRIs, Benzodiazepines.
- Stopping a drug needing cumbersome administration (intravenous) and substituting suitably (with an oral formulation)
- Taking drug cost into consideration and substituting with low cost/generic but equally effective agent, which would also enhance the compliance.
- Following a wait and watch policy till strong evidence of favorable efficacy/ADR ratio emerges, regarding newer drugs.

Conclusion:

Primum non nocere, i.e., "first, do no harm" is the foremost duty of a doctor and deprescribing of potentially inappropriate is a step in fulfilling this important obligation. It is important that health care professionals overcome the "therapeutic inertia" and actively explore de-prescribing in their patients.

References:

Farrell B, Mangin D. Deprescribing is an essential part of good prescribing. *Am Fam Physician* 2019; 99(1):7-9.

Sivagnanam G. Deprescription: The Prescription Metabolism. *J Pharmacol Pharmacother* 2016; 7(3):133-7.

Scott IA, Gray LC, et. al. Minimising inappropriate medications in older populations: a 10 step conceptual framework. *Am J Med* 2012;125(6):529-37.

SGL2 Inhibitors and GLP-1 agonists in Type 2 DM and atherosclerotic cardiovascular disease:

American Diabetes Association (ADA) – Standards of Medical Care in Diabetes 2020 recommend that patients of Type 2 diabetes with established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 (SGL2) inhibitor or glucagon-like peptide 1 receptor (GLP-1) agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors.

Onasemnogeneabeparvovec-The Costliest drug ever to be marketed:

The US FDA has approved onasemnogene abeparvovec for the treatment of spinal muscular dystrophy (SMA). The drug developed by Novartis, has been approved to be used in children under 2 years of age, who are confirmed to be a case of SMA through genetic testing. Onasemnogeneabeparvovec is an adeno-associated virus vector based gene therapy that delivers a fully functional copy of human SMN gene into the target motor neuron cells. The drug is given as one time infusion over 1 hr and costs $2.125 million (approx. 14 crore rupees). This makes onasemnogene the costliest drug ever to be marketed.

Paracetamol being used to cook meat in African countries:

There are reports of food vendors in many African countries like Ghana and Nigeria using paracetamol to cook meat. This is to quickly tenderise meat and avoid long boiling times in order to meet the increasing demands of their customer. For many houses and restaurants, using paracetamol is the quickest way to prepare meat. It saves gas, kerosene and firewood and costs much less as one tablet of paracetamol can cause a pot full of meat to cook soft within few minutes. However, when paracetamol is used for cooking, it gets hydrolysed to 4-aminophenol which is highly acidic product and very toxic to the kidney. This has led to rise in the instances of renal failures and chronic kidney disease. The Nigerian FDA has warned against this practise and has called for a ban on the use of paracetamol for cooking meat.

Monoclonal antibodies: Understanding the Nomenclature:

In 1975, Georges Kohler and Cesar Milstein succeeded in the production of a hybridoma by making fusions of myeloma cell lines with B cells. This immortalized hybridoma could produce antibodies, specific to known antigens and were designated as Monoclonal antibodies (mAbs). Since these cells are produces from a single parent cell, these antibodies are all identical and are able to bind to the same antigenic determinant. This is therapeutically beneficial because it allows providers to target the drug therapy to a specific entity.

In the short time, these biological agents have been in the market, they have occupied an important place in the management of various conditions including autoimmune disorders, cancer therapy, cardiovascular disorders etc. Despite the rapid growth in this field, the nomenclature of these mAbs is poorly understood and may seem daunting to many health care professionals. The following is an attempt to explain how to navigate the seemingly challenging nomenclature of the monoclonal antibodies.

International Nonproprietary Name for MAb consists of four parts: Prefix- SubstemA - SubstemB- Suffix. The prefix is a random word selected in order to provide a distinctive and euphonious name and is different for all mAbs. Further, except for Muromonab, which was the first monoclonal antibody (nomenclature for monoclonal antibodies was not yet developed by then), all the other monoclonal antibodies end with MAb, which is placed as a suffix. The substem A denotes the target on which the mAb is acting while the substem B denotes the source from which the antibody is obtained. The following table gives an overview of the four parts of the nomenclature of the mAbs as per their therapeutic target and their origin.

Prefix (Variable)	**Substem A (Target)**		**Substem B (Origin)**		**Suffix**
Random	**-b(a)-**	bacterial	**a**	Rat	-mab
	-c(i)-	cardiovascular	**e**	hamster	
	-f(u)-	fungal	**i**	primate	
	-k(i)-	interleukin	**o**	mouse	
	-l(i)-	immunomodulating	**u**	human	
	-o(s)-	bone	**xi**	chimeric (x indicates cross)	
	-tox(a)-	toxin	**zu**	humanized	
	-t(u)-	tumour	**axo**	rat/mouse hybrid (x indicates cross)	
	-v(i)-	viral	**xizu**	chimeric/humanized	

A few examples of the monoclonal antibodies with nomenclature are shown in the table given below:

Prefix	Target	Origin	Suffix		Monoclonal Antibody	Indication
ab	ci (cardio-vascular)	xi (chimeric)	mab	ab-ci-xi-mab	Abxicimab	Anti-platelet
beva	ci (cardio-vascular)	zu (humanised)	mab	beva-ci-zu-mab	Bevacizumab	Metastatic cancer and Retinopathy of prematurity
ri	tu (tumour)	xi (chimeric)	mab	ri-tu-xi-mab	Rituximab	Cancer and Immune disorders
tras	tu (tumour)	zu (humanised)	mab	tras-tu-zu-mab	Trastuzumab	Breast Cancer
Olara	t(tumour)	u (human)	mab	olara-t-u-mab	Olaratumab	Cancer
nata	li (immune-modulating)	zu (humanised)	mab	nata-li-zu-mzb	Natalizumab	Multiple sclerosis and Crohn's disease
ada	li (m) (immune-modulating)	u (human)	mab	ada-lim-u-mab	Adalimumab	Immune Disorders
den	os (bone)	u (human)	mab	den-os-u-mab	Denosumab	Osteoporosis
afe	li (m) (immune-modulating)	o (mouse)	mab	afe-lim-o-mab	Afelimomab	Sepsis

The advent and use of MAbs have revolutionized the treatment of cancers, organ transplants, autoimmune diseases, cardiovascular, respiratory and various neurological diseases as well as infections. Efficacy and safety have improved with the use of fully human MAbs. The immunogenicity reactions, cytokine storm and failure of treatment have reduced with the use of fully human MAbs. The cost has been a limiting factor in its use, particularly in developing countries. But as the biosimilars are being granted market approval, the cost of the MAbs will decrease leading to increase affordability and its use with time. There is still vast potential for MAbs in many conditions which are still not manageable with standard therapy.

Be Cautious…..Drug Safety Alerts

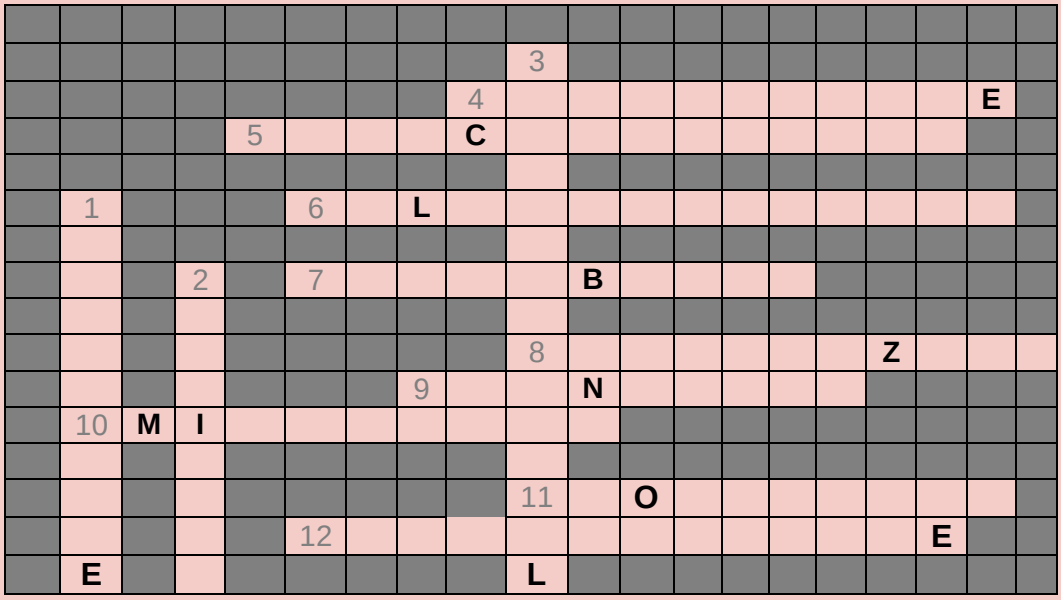
S. No.	Drug	Safety Alerts
1.	Tramadol	Hiccups
2.	Tranexamic acid	Seizure/Convulsion
3.	Glibenclamide	Palpitations
4.	Ofloxacin	Stevens Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)
5.	Phenobarbital	DRESS syndrome
6.	Quetiapine	Urinary Incontinence

New Drugs in the market…..

S. No.	Drug	Pharmacological Class	Indication	Dosage
1.	Ubrogepant	Calcitonin gene-related peptide receptor antagonists	Acute Migraine	100 mg/day
2.	Lemborexant	Orexin OX1 and OX2 antagonist	Treatment of Insomnia in adult patients	10 mg/day
3.	Lumateperone	5HT2A receptor antagonist/dopamine phosphoprotein modulator (DPPM)	Schizophrenia	42 mg/day
4.	Golodirsen	Antisense oligonucleotides	Duchenne Muscular Dystrophy	30 mg/kg IV per Week
5.	Voxelotor	Hemoglobin oxygen-affinity modulator	Sickle cell disease	1500 mg/day
6.	Crizanlizumab-tmca	P-selectin inhibitor	Prevention of vaso-occlusive crisis (VOCs) in patients with sickle cell disease (SCD).	5 mg/kg IV infusion over 30 minutes at Weeks 0 and 2, then every 4 weeks
7.	Cenobamate	Voltage-gated sodium channel (VGSC) blocker	Partial-onset seizures in adults	12.5 mg- 400 mg/daily
8.	Givosiran	Aminolevulinate synthase 1-directed small interfering RNA i	Adults with acute hepatic porphyria (AHP).	2.5mg/kg monthly by subcutaneous injection
9.	Pitolisant	Histamine H3 Antagonist/Inverse Agonist	Treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy	9 – 36 mg/day
10.	Cefiderocol	SiderophoreCephalosporin	Complicated urinary tract infections, treatment of multi-drug-resistant Gram-negative bacteria including Pseudomonas aeruginosa	2 gram IV every 8 hr for 7-14 days

Crossword Puzzle…

Hint: *Drugs Causing Peripheral Neuropathy*



Downward

1. Second line anti-tubercular agent with intense gastric irritation and neurological toxicity (11)
2. Pharmacogenetics modifies the half life as 1 hour for slow acetylators and 3 hour for fast acetylators (9)
3. Associated with super-infections, bone marrow suppression and Gray baby syndrome (15)

Across

4. An anti-malaria used in extraintestinal amoebiasis, lepra reactions, rheumatoid arthritis (11)
5. Tetracycline antibiotic used in SIADH (14)
6. First generation Sulfonylureas (14)
7. Anti-tubercular agent, causes problem in red-green colour discrimination (10)
8. K^+ channel opener, indicated in hypertensive emergencies (11)
9. An anti-epileptic drug, causes gingival hyperplasia, hirsutism and megaloblastic anemia (9)
10. A broad spectrum anti-arrhythmic causing pulmonary fibrosis (10)
11. A lipid lowering agent acting through Peroxisome Proliferator-Activated Receptor (PPAR) α agonist (10)
12. An anti-amoebic associated with metallic taste as common side effect (13)

Answers

Downward
1. Ethionamide
2. Isoniazid
3. Chloramphenicol
4. Chloroquine
5. Demeclocycline
6. Chlorpropamide

Across
7. Ethambutol
8. Hydralazine
9. Phenytoin
10. Amiodarone
11. Clofibrate
12. Metronidazole