ESSENCE

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, MANGALAGIRI

PHARMACOLOGY BULLETIN

NOVEMBER-DECEMBER 2020, ISSUE 7

FROM THE EDITORIAL DESK….

Dear Friends, Greetings from AIIMS Mangalagiri and Welcome to the seventh issue of ESSENCE.

It has been known for decades that patients with the same disease when given the same drugs do not respond in the same way. On an average only about 25-60% of patients respond positively to their medications with the rest not responding or worse, having adverse effects. Many of these inter-individual differences are due to the differences in the genetic make-up of these patients.The role of pharmacogenomics in paving the path to personalized medicine by identifying individuals who are likely to respond to a drug or who are prone to adverse effects to that same drug is increasingly being understood. The current issue of ESSENCE highlights the role of pharmacogenomics in medical practise.

The Covid-19 pandemic is one of the greatest challenges in the modern medicine with Doctors and Scientists scrambling to find treatments and drugs that can save the lives of the patients. There are hundreds of clinical trials of COVID-19 therapies taking place across the world.While some are accumulating evidence that they are effective, most are just junked at various phase of the trials due to lack of substantial evidence. A snapshot of the important trials and their findings is also given.

The current issue of ESSENCE also discusses the new drug approvals and adverse effects of many drugs. Finally, the readers can test their knowledge with the crossword puzzle on Microsomal enzyme inhibitors.

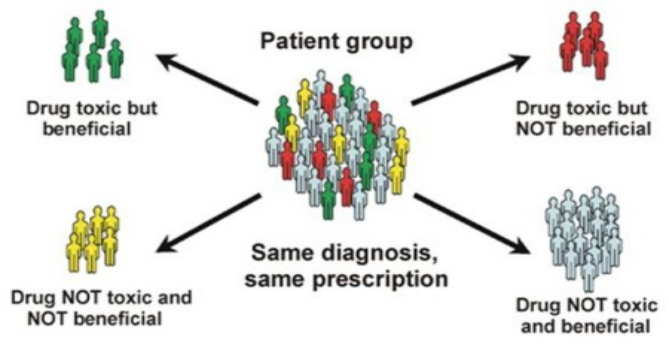
Happy Reading and Stay safe.

Jai Hind.

Chief Editor: Dr. Sushil Sharma
Editor: Dr. Arup Kumar Misra
Co-Editors: Dr. Madhavrao, Dr. Gaurav MRangari

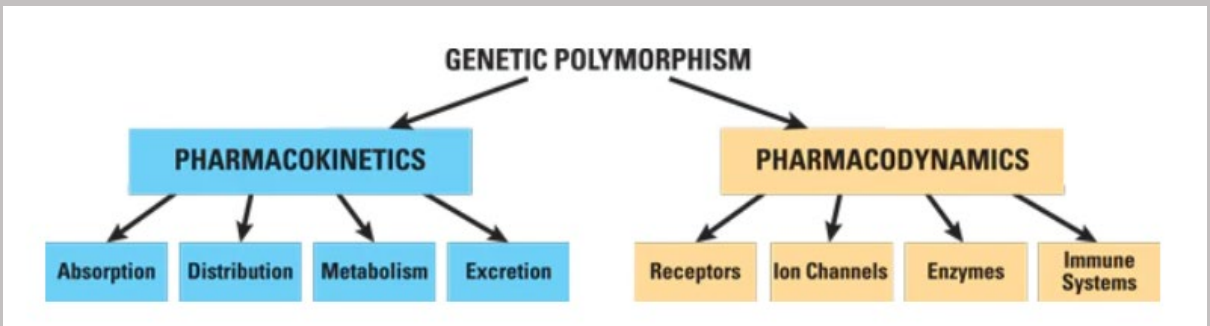
Feedback and Suggestions may be sent to Department of Pharmacology, All India Institute of Medical Sciences, Mangalagiri, Andhra Pradesh at email id: pharmacology@aiimsmangalagiri.edu.in

The image below describes the current approach to drug therapy. A group of patients who have the same diagnosis normally receive the same drugs/prescription. Many drugs that are currently available don't work the same way for everyone. It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience negative side effects.



Clinicians have known for decades that not all patients respond to the same drug in the same way. The proportion of patients who respond positively to their medications is, on average, only approximately 50% (ranging from 25 to 60%), implying that the rest of the patient population is not receiving the proper medication or is suffering from significant therapeutic delays by switching from one medication to another until appreciable clinical benefit is attained .

Many of these inter-individual differences are due to differences in the genetic make-up of these patients and genetic polymorphisms can profoundly alter the pharmacokinetics and pharmacodynamics. This is because the enzymes, transporters, proteins, receptors etc are all genetically determined and any polymorphism in any of these can alter the way the individual may react to the drug.



Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines 'pharmacology' and 'genomics' and how genetic information can be used to guide the choice of drug therapy and that is tailored to a person's genetic makeup.

With the knowledge gained from the Human Genome Project, researchers are learning how inherited differences in genes affect the body's response to medications. These genetic differences can be used to predict whether a medication will be effective for a particular person and to help prevent adverse drug reactions. The implementation of genetic data for a better prediction of response to medications and adverse drug reactions is becoming a reality in some clinical fields.

Pharmacogenomics for Cancer Therapeutics:

Trastuzumab, a monoclonal antibody (MAb) blocking HER2 receptors, is indicated for breast cancer. Pharmacogenetic testing has become an integral part of the treatment of breast cancer with trastuzumab. In this case, variable expression of the *HER2* receptor gene determines whether or not a patient will respond to trastuzumab. HER2 testing predetermines patients who overexpress HER2 and who will respond to trastuzumab.

Irinotecan has been approved for the treatment of advanced colorectal cancer both as first line and salvage treatment. The drug has limiting toxicities, comprising diarrhea and severe neutropenia. The *UGT1A1*28* polymorphism in some individuals is associated with reduced *UGT1A1* gene expression and decreased glucuronidation of the active metabolite. This results in increased toxicity owing to increased blood levels of the active metabolite. In July 2005, the FDA recommended an addition to the irinotecan package insert to include *UGT1A1*28* genotype as a risk factor for severe neutropenia.

The anti- cancer agents 6-mercaptopurine and azathioprine, are metabolized by the thiopurine methyltransferase (TPMT) enzyme. Patients with inherited TPMT deficiency suffer severe, potentially fatal hematopoietic toxicity when exposed to standard doses of these drugs. A *TPMT* pharmacogenomic test enables physicians to predetermine patients' TPMT activity levels based on whether or not they have inherited the alleles associated with TPMT deficiency. The test classifies patients according to normal, intermediate and deficient levels of TPMT activity. Lower doses are tailored to avoid toxicity in deficient and intermediate patients, who represent approximately 10% of each of these populations and who are liable to suffer exaggerated, potentially life-threatening toxic responses to normal doses of these drugs.

Pharmacogenomics for Cardiovascular Disease:

Despite its indisputable effectiveness, Warfarin has a narrow therapeutic window and is associated with high risk of major bleeding and there is substantial variation in individual response necessitating frequent monitoring and dosage adjustment. This is primarily influenced by genetic polymorphism in two enzymes, namely *CYP2C9*, the enzyme that metabolizes warfarin and vitamin K epoxide reductase (VKORC1), the pharmacologic target enzyme of these drugs. The FDA has relabelled warfarin with genomic information and several pharmacogenetic-based dosing algorithms incorporating CYP2C9 and VKORC1 genotype are available to personalise warfarin to individual patients. A Mayo Clinic study involving 3,600 subjects showed that hospitalization of heart patients was reduced by 30 percent when doctors were made aware of the pharmacogenetic data prior to treatment with warfarin.

Clopidogrel is the standard of care for acute coronary syndromes and is the second best-selling drug in the world. It is indicated in patients undergoing percutaneous coronary interventions with or without stenting, and is also used for the reduction of athero-thrombotic events in patients with recent myocardial infarction, recent stroke or diagnosed peripheral arterial disease. Non-responsiveness to clopidogrel is widely recognized and is related to recurrent ischemic events; approximately 25% of patients receiving clopidogrel experience a sub-therapeutic antiplatelet response associated with increased risk of recurrent ischemic events. There is growing evidence that the response to Clopidogrel may be determined by the *CYP2C19* genotype. Specifically, it was shown that the *CYP2C19*2*allele, which leads to impaired CYP2C19 function, is associated with a marked decrease in platelet responsiveness to Clopidogrel. Consequently, in May 2009, the FDA relabelled the drug information for Clopidogrel to highlight the impact of *CYP2C19* genotype on the drug's pharmacokinetics, pharmacodynamics and clinical response.

Over the last decade, FDA has been aggressive in providing genetic labelling on new drugs and also updating product labels for a number of existing therapies. At present some 140 drugs have pharmacogenetics information in their FDA product label. Some examples are where genetic testing is recommended are given in the table below.

#	Drug	Gene	#	Drug	Gene	#	Drug	Gene
1	abacavir	HLA-B	13	doxepin	2C19, 2D6	25	phenytoin	2C9, HLA-B
2	allopurinol	HLA-B	14	escitalopram	2C19	26	rasburicase	G6PD
3	amitriptyline	2C19, 2D6	15	fluorouracil	2D6	27	ribavirin	IFNL3
4	atazanavir	UGT1A1	16	fluvoxamine	2D6	28	sertraline	2C19
5	azathioprine	TPMT	17	imipramine	2C19, 2D6	29	simvastatin	SLCO1B1
6	capecitabine	DPYD	18	ivacaftor	CFTR	30	tacrolimus	CYP3A5
7	carbamazepine	HLA-B	19	mercaptopu-rine	TPMT	31	tegafur	DPYD
8	citalopram	2C19	20	nortriptyline	2D6	32	thioguanine	TPMT
9	clomipramine	2C19, 2D6	21	ondansetron	2D6	33	trimipramine	2C19, 2D6
10	clopidogrel	2C19	22	paroxetine	2D6	34	tropisetron	2C19
11	codeine	2D6	23	peginterferon alfa-2a	IFNL3	35	voriconazole	2C19
12	desipramine	2D6	24	peginterferon alfa-2b	IFNL3	36	warfarin	CYP2C9, CYP4F2, VKORC1

Conclusion:

Pharmacogenomics paves the path to personalized medicine with the application of genetic information in order to identify of those individuals who are likely to respond to a drug or likely to respond adversely to that same drug. The following image represents the role pharmacogenomics may play in therapeutics in the near future.

Recent new/Update from the world of medicines ……..

Lower Back Pain: NSAID + Muscle Relaxant No Better Than NSAID + Placebo

Patients with lower back pain prescribed skeletal muscle relaxants in addition to NSAIDs report the same outcomes as placebo plus NSAIDs in a new study. In the study, nearly 889 patients were enrolled with lower back pain for a randomized, placebo-controlled trial. All patients completed the Roland-Morris Disability Questionnaire before leaving the hospital and again after 1 week follow-up.The results showed that the muscle relaxants used to lower low back pain have limited role as showed by the evidences of the analysis. They don't add much benefit to the recommended analgesic regimen.

Global COVID-19 Drug Trials – In a nutshell

The Covid-19 pandemic is one of the greatest challenges in the modern medicine. Doctors and scientists are scrambling to find treatments and drugs that can save the lives of infected people and perhaps even prevent them from getting sick in the first place.There are thousands of clinical trials of COVID-19 therapies taking place across the world.While some are accumulating evidence that they are effective, most are just junked at the various phase of the trials due to lack of substantial evidence. The following is a snapshot of the important trials happening in India and in other parts of the world.

RECOVERY TRIAL: It was an 'Open Label' multi-arm adaptive clinical trial by Nuffield Departments of Population Health and of Medicine at the University of Oxford.The primary objective of the trial was to "provide reliable estimates of the effect of study treatments on all-cause mortality at 28 days after first randomisation. It included treatment with either Corticosteroid, Azithromycin, Convalescent plasma, Synthetic neutralizing antibodies (REGN-COV2), Tocilizumab or Aspirin for preventing death in patients with COVID-19. On 05 June 2020, the trial determined that there was no clinical benefit from use of hydroxychloroquine in people hospitalized with COVID-19.Patients treated with hydroxychloroquine saw a 25.7% 28-day mortality compared to 23.5% 28-day mortality in those treated with standard care.On 22 June 2020, preliminary results were published which showed that low-dose Dexamethasone treatment reduced the death rate by one third in hospitalized people needing ventilators due to severe COVID-19 infection, and by one fifth in people treated with oxygen therapy. On 29 June 2020, chief investigators of the trial reported there was no clinical benefit from use of Lopinavir-Ritonavir in 1,596 people hospitalized with severe COVID-19 infection over 28 days of treatment.

PLACID TRIAL: Convalescent plasma (CP) is a passive source of neutralizing antibodies and acts as immunomodulators for the management of viraldiseases. It was an open-label, parallel-arm, phase II, multicentre, randomized controlled trial in 464 adults with confirmed moderate covid-19 in 39 public and private hospitals across India. 235 were assigned to receive CP (intervention arm) along with best standard of care (BSC) and 229 to only BSC arm. Two doses of 200 mL CP was transfused 24 hours apart in theintervention arm.Composite of progression to severe disease ($PaO_2/FiO_2<100$) or all-causemortality at 28 days post-enrolment.Composite primary outcome was achieved in 44(18.7%) participants in the intervention arm and 41 (17.9%) in the control arm. Mortality was documented in 34 (14.5%) and 31 (13.5%) participants inintervention and control arm, respectively. The results showed that CP was not associated with reduction in mortality or progression to severeCOVID-19.

ACTT 1: It was a double-blind, randomized, placebo-controlled trial of intravenous Remdesivir in adults who were hospitalized with Covid-19 and had evidence oflower respiratory tract infection. Patients were randomly assigned to receive either Remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to9 additional days) or placebo for up to 10 days. The primary outcome was the timeto recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only. A total of 1062 patients underwent randomization (with 541 assigned to Remdesivir and 521 to placebo). Those who received Remdesivir had a median recovery time of 10 days as compared with 15 days among those who received placebo. The patients who received Remdesevir were found to have clinical improvement at day 15 than those who received placebo. The mortality was 6.7% with Remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29.The trial showed that Remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection.

WHO SOLIDARITY trial: The study drugs used in this trial were Remdesivir, Hydroxychloroquine, Lopinavir (fixed-dose combination with Ritonavir) and Interferon-β1a. COVID-19 in patients were randomized equally between whichever study drugs were locally available and open control (up to 5options: 4 active and localstandard-of-care). The intent-to-treat primary analyses were of in-hospital mortality in the 4 pairwise comparisons of each study drug vs. its controls. In 405 hospitals in 30 countries 11,266 adults were randomized, with Remdesivir (2750), Hydroxychloroquine (954), Lopinavir (1411), Interferon plus Lopinavir (651) , Interferon (1412) , and no study drug (4088) . 1253 deaths were reported were reported in the study with Kaplan-Meier 28-day mortality being 12%. Death rate ratios were as follows: Remdesivir RR=0.95, Hydroxychloroquine RR=1.19, Lopinavir RR=1.00 and Interferon RR=1.16. No study drug definitely reduced mortality, initiation of ventilation or hospitalisation duration.These Remdesivir, Hydroxychloroquine, Lopinavir and Interferon regimens appeared to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay.

IVERMECTIN TRIAL: Zagazig University in Egypt designed a multicenter, randomized, controlled clinical trial (RCCT) involving 600 subjects, including 400 COVID-19 diagnosed patients and 200 health care (e.g., health professionals & workers) and household contacts . They evaluated Ivermectin plus the standard of care for this region, which includes azithromycin, vitamin C, Zinc, Lactoferrin and Acetylcysteine and prophylactic or therapeutic anticoagulation if D-dimer was greater than 1000 for the treatment of mild to moderate and severely ill cases with COVID-19 infection. Additionally and importantly, the investigational team probed the prophylaxis benefit of health care and/or household contacts in comparison to Hydroxychloroquine plus standard treatment. The team concluded that Ivermectin is a very effective drug for the treatment of COVID-19 patients offering a significant reduction in the mortality rate compared to Hydroxychloroquine plus standard of treatment.

Apart from these major trials, there are many ongoing studies happening around the world with many repurposed drugs but till date none of the drugs have given substantial evidences as a therapeutic option against COVID-19. So, social distancing, wearing mask and washing hand is still the relevant option remain with the masses to fight against this deadly disease till vaccines are available for use.

Be Cautious…..Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Clozapine	Neural Tube Defects
2.	Cetirizine	Hiccups
3.	Cilostazole	Tinnitus
4.	Levamisole	Steven Johnson Syndrome
5.	Fluconazole	Mouth Ulceration
6.	Piperacillin and Tazobactam	Blurred Vision

S. No.	Drug	Pharmacological Class	Indication	Dosage
1.	Avapritinib	Kinase inhibitor	Unresectable or metastatic gastrointestinal stromal tumor (GIST)	300 mg/day
2.	Tazemetostat	Methyltransferase inhibitor	Epithelioid sarcoma	800 mg twice daily
3.	Eptinezumab	Calcitonin Gene-Related Peptide (CGRP) antagonist	Migraine prophylaxis	100 mg as an IV infusion over approximately 30 minutes every 3 months
4.	Sacituzumab	Trop-2-directed antibody & topoisomerase inhibitor	Metastatic triple-negative breast cancer	10 mg/kg once weekly on Days 1 & 8 of continuous 21-day treatment cycles
5.	Decitabine	Nucleoside metabolic inhibitor	Myelodysplastic syndromes	15 mg/m^2 by continuous IV infusion over 3 hours repeated every 8 hours for 3 days; Repeat cycle every 6 weeks
6.	Cedazuridine	Cytidine deaminase inhibitor	Myelodysplastic syndromes	100 mg/day
7.	Abametapir	Metalloproteinase inhibitor; Pediculicide	Head lice	Lotion (0.74%) for local application
8.	Nifurtimox	Antiprotozoal; Reactive oxygen species induced DNA damage & cell death	Chagas disease	8 -20 mg/kg body weight
9.	Clascoterone	Androgen Receptor (AR) antagonist	Acne	Cream (1%) for local application
10.	Copper Cu 64 dotatate	Binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSTR2)	Localization of somatostatin receptor positive neuroendocrine tumors (NETs)	148 MBq (4 mCi) administered as an IV bolus injection.

Crossword Puzzle…

Hint: Microsomal enzyme inhibitor drugs

[1]I		[2]O			[3]A			D										[4]M
R		R																O
					U										[5]C			
					N													
E		E						[6]V			P				T	E		Z
		[7]K						N				L						E
				[8]E				H			M				N			
															E			

Downward	Across
1. Tricyclic antidepressant having anticholinergic side effects (10) 2. Proton pump inhibitor used in peptic ulcer (10) 3. Xanthine oxidase inhibitor used in treatment of Gout (11) 4. Anti-amoebic drug which can cause disulfiram like reaction with alcohol (13) 5. H2 receptor blocker which can cause gynecomastia (10)	1. Anti TB drug having peripheral neuritis characteristic adverse effect (9) 6. Broad spectrum antiepileptic drug used in absence seizure (9) 7.Broad spectrum antifungal having anti-androgenic side effects (12) 8. Macrolide antibiotic which can cause diarrhea by combining with motilin receptors (12)

Answers:

Downward

1. Imipramine 2. Omeprazole 3. Allopurinol
4. Metronidazole 5. Cimetidine

Across

1. Isoniazid 6. Valproate
7. Ketoconazole 8. Erythromycin