ESSENCE

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, MANGALAGIRI

PHARMACOLOGY BULLETIN

SEPTEMBER-OCTOBER 2021, ISSUE 12

FROM THE EDITORIAL DESK....

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

The use of placebo to make a patient comfortable has been used since a long time. Research has shown that a placebo treatment can have a positive therapeutic effect even though the pill or treatment is not active. Placebo is also used widely in clinical trials. These "double-blind" and "placebo-controlled" are considered the gold standard for experimental drug research. However, the use of placebo in medical practice and clinical trials is controversial and fraught with ethical issues and the current issue of ESSENCE examines this aspect.

With Anti-Microbial Resistance increasing worldwide at a rapid pace and very few new antibiotics being developed, existing antibiotics are becoming a limited resource. Anti-Microbial Stewardship (AMS) is one of the most important pillars in this regard and can help to preserve antibiotics for our future generations. Classifying the antibiotics to encourage appropriate usage of these antibiotics is crucial under AMS. The present issue of ESSENCE highlights the WHO-EML antibiotic classification under the AMS programme.

Further, as always, the current issue of ESSENCE also covers the new drug approvals and drug safety alerts. Finally, the readers can test their knowledge with the cross-word puzzle on 'Drug induced Lupus Erythematosus'.

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

Placebo comes from the Latin word meaning 'I shall please'. A Placebo is an inert or inactive substance, typically a tablet, capsule or other dose form that does not contain an active drug ingredient. Typically, placebo pills or liquids may contain starch, sugar, or saline. Physical placebos, or "sham" treatments have also been used, such as inactive acupuncture devices or even sham surgeries.

Placebo in Medical Practice:

The use of placebo to make a patient comfortable has been used since a long time. Research has shown that a placebo treatment can have a positive therapeutic effect even though the pill or treatment is not active. This is known as the "placebo effect". Placebo effects have been reported to occur in 21% to 40% of patients depending upon the condition being treated. In pain studies utilizing brain imaging, administration of a placebo to patients led to activation of the endogenous opioid system. It has also been shown that the placebo response in patients with post-surgical pain could be blocked by the opiate antagonist Naloxone. Furthermore, analgesic effects of placebo are inhibited by the peptide cholecystokinin (CCK) and they are potentiated when a CCK antagonist is administered. Considered together, these studies demonstrate that some mechanisms of placebo operate by altering the activity of both CCK and endogenous opioids.

In clinical practice, physicians may prescribe placebo treatments with or without the patients' knowledge that they are receiving an inactive therapy. Placebos have been used in treatment of sleep, anxiety, gastrointestinal disorders, chronic pain and other disorders. Psychologically, the patient may believe that they are receiving a treatment for their ailment that they believe will have beneficial effect, and in turn the placebo may actually provide some relief. In one survey, around 40% of U.S. physicians reported that they had used vitamins as placebos for their patients. 68% of physicians described the placebo to their patients as a potentially beneficial medicine, and roughly two-thirds of the doctors felt the practice was ethical. In another study, physicians used reduced doses of active drugs in combination with a placebo to successfully treat diseases that involve the mental state and immune system, including, asthma, multiple sclerosis and chronic pain.

The therapeutic use of placebo in medicine is very controversial. Whenever a physician uses a placebo for treatment, the only concern must be the well-being of the patient and the placebo must be given in the spirit of alleviating the patients suffering and distress without any other vested interest.

Placebo in Clinical trials:

The interest in placebo effects arose with the widespread adoption of the randomized controlled trial (RCT) after World War II. Since then, several trials using placebo as a control group have been carried out. These "double-blind" and "placebo-controlled" are considered the gold standard for experimental drug research. However, many clinical trials, such as those in cancer research, do not include placebo groups because it would not be unethical to leave the patient's cancer untreated. In such trials, the experimental drug may be compared to a treatment that is already FDA-approved instead of a placebo.

The use of a placebo in clinical research continues to be a topic of debate in the medical community. Critics of placebo-controlled trial cite Article 11.3 of the Declaration of Helsinki: "In any medical study, every patient including those of control group, if any should be assured of the best proven diagnostic and therapeutic methods and no patient should suffer from unnecessary pain." They further argue use of placebo compromises the right of the patient to receive the best care possible and violates the ethical principle of therapeutic beneficence. Furthermore, these clinicians have argued that when proven therapy exists, the use of a placebo-

controlled trial lacks both scientific and clinical merit. The use of placebo is also questioned in vulnerable groups like children, psychiatric patients, and patients suffering from cancer.

The Office for Human Research Protection (OHRP) published guidelines for the use of placebo in clinical trials which state that, "Placebos may be used in clinical trials where there is no known or available alternative therapy that can be tolerated by subjects." The use of placebos in controlled clinical trials must be justified by a positive risk-benefit analysis, and the subjects must be fully informed of the risks involved in the assignment to the placebo group. The duration of time that a subject will be on a placebo, degree of discomfort, and potential effects of not receiving medication must all be explained. A statement in the risk section of the consent that the condition of the subject may worsen while on placebo should be included. A discussion in the benefits section that subjects who receive placebo will not receive the same benefit as those who receive active treatment if that treatment is effective should also be included. Continued assignment of subjects to placebo is unethical, once there is good evidence to support the efficacy of the trial therapy.

Increased monitoring for deterioration of subjects and the use of rescue medications may be included in the protocol when placebo is used. 'Early escape' mechanisms and explicit withdrawal criteria may be built in so that subjects will not undergo prolonged placebo treatment if they are not doing well. The size of the population placed on placebo may be kept smaller than the number in the active treatment arms. Placebo and active treatment may be compared in an add-on' method, keeping the subjects on identical maintenance treatments and then adding on the active treatment to one arm and the placebo to the other. This design is especially applicable when the available treatment is known to decrease mortality or morbidity. Shortened treatment periods reduce the risks associated with delayed treatment. In situations in which long-term placebo treatment would not be acceptable, the use of a placebo group for a short period at the beginning of a trial could establish short-term effects. The trial could then continue without the placebo group. Unblinded data review by a data safety monitoring board with interim analysis of study results and safety issues is desirable. This is especially important for multicenter site studies.

Some drug trials involve a period during which all participants receive only a placebo prior to the initiation of the study. This period is called a 'placebo washout'. The purposes of a washout period include: i) Terminating the effects of any drug the subject may have been taking before entering the clinical trial, so that the effects of the trial drug-and only the trial drug-may be observed. ii) Understanding whether the subjects co-operate with instructions to take drugs. iii) Understanding which subjects are 'placebo responders', in that they experience a high degree of placebo effect. Iv) In some protocols, the investigators plan to exclude those subjects they find either poorly compliant or highly responsive to the placebo.

Conclusion: There is a definite place for the use of Placebo in medical practice and in clinical trials. Whenever a physician uses a placebo for treatment, the only concern must be the well-being of the patient and the placebo must be given in the spirit of alleviating the patients suffering and distress. Further, Placebo-controlled trials are justifiable when they are supported by sound methodologic consideration and when their use does not expose research participants to excessive risk of harm. Consideration should be given to the 'best-available therapy' control groups in the evaluation of a new therapy or intervention over an existing therapy.

References:

1. Gupta U, Verma M. Placebo in clinical trials. Perspect Clin Res 2013;4:49-52.
2. Colloca L. The Placebo Effect in Pain Therapies. Annu Rev PharmacolToxicol. 2019 Jan 6;59:191-211.

Recent new/Update from the world of medicines ….

Atogepant: First oral CGRP Receptor Antagonist for the Preventive Treatment of Migraine

U.S. Food and Drug Administration (FDA) approved Qulipta (atogepant) for the preventive treatment of episodic migraine in adults. Qulipta is the first and only oral calcitonin gene-related peptide (CGRP) receptor antagonist (gepant) specifically developed for the preventive treatment of migraine. Qulipta can help by reducing monthly migraine days with a once-daily, oral dose that works quickly and continuously. CGRP and its receptors are expressed in regions of the nervous system associated with migraine pathophysiology, and studies have shown that CGRP levels are elevated during migraine attacks. Qulipta blocks CGRP through a once-daily dose and is available in three strengths – 10 mg, 30 mg and 60 mg.

Mosquirix: World's First Malaria Vaccine

RTS,S/ASO1 (RTS.S), trade name Mosquirix, which was endorsed by the World Health Organisation (WHO) on Wednesday (October 6), is the first and, to date only, vaccine shown to have the capability of significantly reducing malaria, and life-threatening severe malaria, in tests on young African children. The vaccine acts against P. falciparum, the deadliest malaria parasite globally, and the most prevalent in Africa. Among children who received 4 doses in largescale clinical trials, the vaccine was able to prevent approximately 4 in 10 cases of malaria over a 4-year period. RTS,S is developed by PATH Malaria Vaccine Initiative (MVI) and GlaxoSmithKline (GSK) with support from the Bill and Melinda Gates Foundation.

Be Cautious…. Drug Safety Alerts

S. No.	Drug	Safety Alerts
1.	Baclofen	Encephalopathy
2.	Remdesivir	Pancreatic toxicity
3.	Donepezil	QT prolongation
4.	Lamotrigine	Arrhythmia
5.	Theophylline	Encephalopathy
6.	Levetiracetam	Hypokalaemia

Stewardship is defined as "the careful and responsible management of something entrusted to one's care". It was originally applied in the health-care setting as a tool for optimizing antimicrobial use, termed as "Anti-Microbial Stewardship" (AMS). Antimicrobial stewardship programmes optimize the use of antimicrobials, improve patient outcomes, reduce antimicrobial resistance (AMR)and health-care-associated infections, and save health-care costs amongst others. According to the Organisation for Economic Co-operation and Development (OECD), implementing AMS programmes together with other policies can reduce overuse of antibiotics and promote hospital hygiene could save up to 1.6 million lives by 2050 and US$ 4.8 billion per year in the 33 OECD countries.

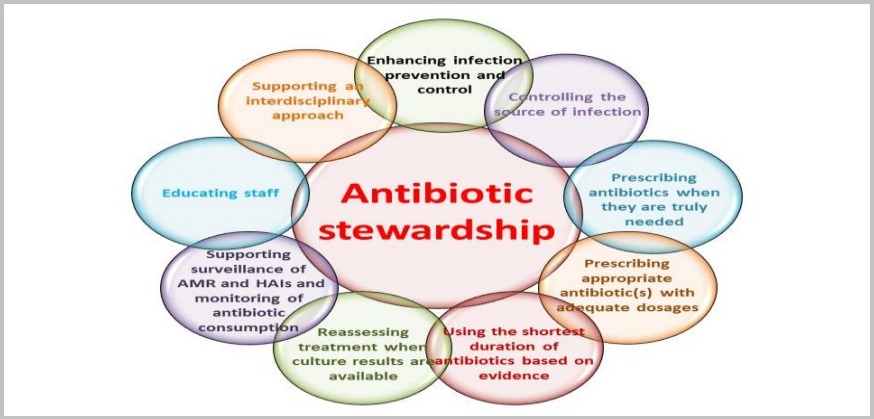


Figure: Objectives of Antibiotic Stewardship

The EML and AWaRe classification: Use of antibiotics in health-care facilities

Today, AMS is one of most important pillars of an integrated approach to health systems strengthening. With rates of AMR increasing worldwide, and very few new antibiotics being developed, existing antibiotics are becoming a limited resource. To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, the Access, Watch, Reserve (AWaRe) classification of antibiotics was developed – where antibiotics are classified into different groups to emphasize the importance of their appropriate USE. It is therefore essential that antibiotics only be prescribed - and that last-resort antibiotics (AWaRe RESERVE group) be reserved - for patients who truly need them.

The WHO EML AWaRe classification of commonly used antibiotics into three groups - ACCESS, WATCH and RESERVE- provides a tool to support antibiotic monitoring and AMS activities, with recommendations on when to use the antibiotics in each category. The AWaRe database, along with further guidance can be applied for developing and updating national EMLs, developing and updating treatment guidelines, and for monitoring antimicrobial consumption and use (including more intense surveillance of the RESERVE antibiotics).

Stratifying total antimicrobial consumption data by the AWaRe groups can be undertaken at facility and ward level. This allows benchmarking and overall monitoring of national and global progress towards WHO's goal of increasing the proportion of global consumption of antibiotics in the ACCESS group to ≥60%.

ACCESS GROUP	WATCH GROUP	RESERVE GROUP
This group includes antibiotics and antibiotic classes that have activity against a wide range of commonly encountered susceptible pathogens while showing lower resistance potential than antibiotics in Watch and Reserve groups. Access antibiotics should be widely available, affordable and quality-assured to improve access and promote appropriate use. Selected Access group antibiotics should be the first-choice or second-choice empirical treatment options for specific infectious syndromes. **Examples:** Amikacin, Amoxicillin, Cefazolin, Cefatrizine, Ceftezole, Chloramphenicol, Clindamycin, Doxycycline, Gentamicin, Metronidazole, Oxacillin, Nitrofurantoin, Sulfamethoxazole+ trimethoprim, Tetracycline, etc.	This group includes antibiotics and antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials (CIA) for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. Watch group antibiotics should be prioritized as key targets of national and local stewardship programmes and monitoring. **Examples:** Azithromycin, Cefixime, Cefotaxime, Cefepime, Ceftazidime, Ceftriaxone, Cefuroxime, Ciprofloxacin, Clarithromycin, Meropenem, Piperacillin +tazobactam, Vancomycin, etc.	This group includes antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi drug-resistant organisms, and treated as "last-resort" options. Their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. They could be protected and prioritized as key targets of national and international stewardship programmes, involving monitoring and utilization reporting, to preserve their effectiveness. **Examples:** Aztreonam, Ceftazidime + avibactam, Colistin, Dalbavancin, Faropenem, Fosfomycin (intravenous), Linezolid, Meropenem + vaborbactam, Minocycline (IV), Plazomicin, Polymyxin B, Tigecycline, etc.

The main purpose of collecting data on the use of antibiotics is to assess the extent and quality of antibiotic use, identify problematic prescribing practices, and compare appropriate use across health-care facilities and within a health-care facility, department or ward over time. Measuring the quantity and appropriateness of antibiotic prescribing and use will identify where there is room for improvement in targeting and monitoring AMS interventions.

Conclusion

Treatment is chosen according to which microbes are most likely to cause different infections. This strategy works well when resistance rates are low, or AMR surveillance can guide recommendations for empirical antibiotic treatment. There is a great need for affordable, sensitive, specific and rapid diagnostic tests that provide prescribers with quality-assured information about whether or not a patient has a bacterial infection, and which antibiotics the causative bacteria are sensitive to. Microbiology laboratories play a key role in informing the appropriate use of (ACCESS) antibiotics, ensuring first and second-line antibiotics are used whenever possible. The quality of the clinical diagnosis is still essential, as the tests need to be interpreted in light of it.

Avacopan is a C5a receptor inhibitor which blocks the C5a-mediated neutrophil activation and migration has been approved by FDA to treat severe active anti-neutrophil cytoplasmic autoantibody (ANCA) -associated vasculitis in combination with standard therapy, including glucocorticoids. The recommended dose is 30 mg BID.

Maralixibat is an ileal bile acid transporter (IBAT) inhibitor has been approved to treat cholestatic pruritus associated with Alagille syndrome. The recommended dose is 190- 380 mcg/kg/day.

Pegcetacoplan is a complement inhibitor that Binds to complement protein C3 and its activation fragment C3b, thereby regulating C3 cleavage and generation of downstream effectors of complement activation. It is indicated for Paroxysmal Nocturnal Hemoglobinuria. The recommended dose is 1080 mg SC infusion twice weekly.

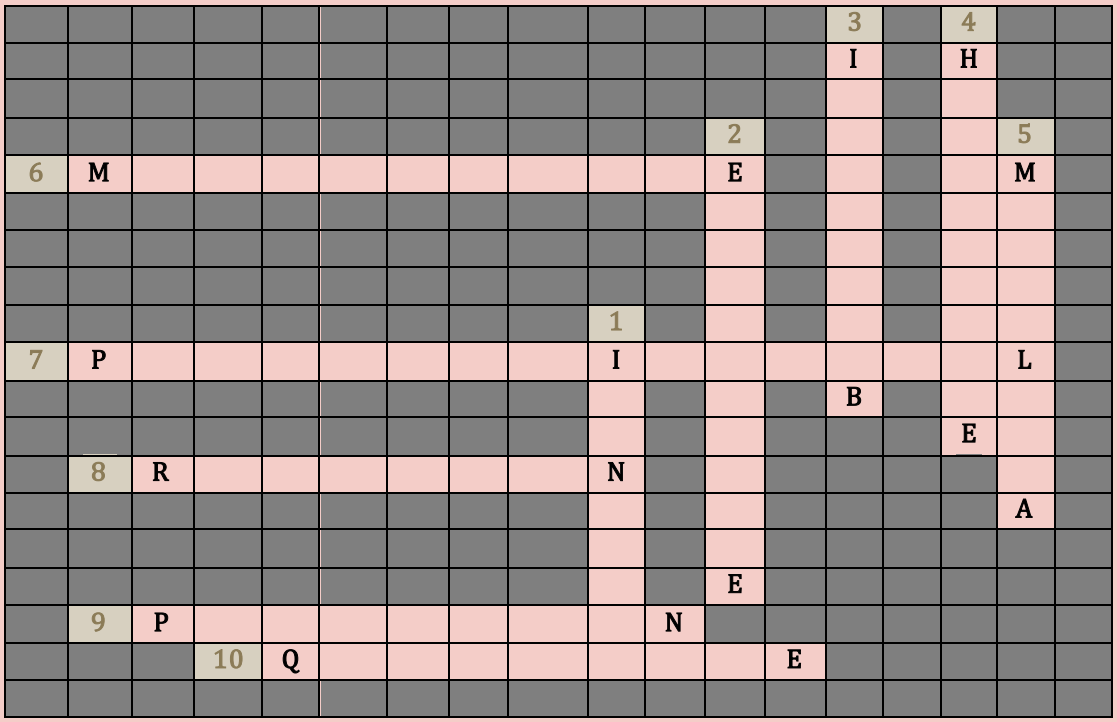
Tisotumab is a tissue factor-directed antibody and microtubule inhibitor has been approved for the treatment of patients with recurrent or metastatic cervical cancer. The recommended dose is 2 mg/kg IV every 3 weeks.

Mobocertinib is an EGFR Kinase inhibitor has been approved for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations. The recommended dose is 160 mg orally once daily.

Ruxolitinib is a Topical Janus kinase (JAK) inhibitor approved for the treatment of atopic dermatitis. It has been recommended for topical use.

Crossword Puzzle…

Hint: *Drugs Induced 'Lupus Erythematosus*



Downward	**Across**
1. First line anti-tubercular drug (*9*) 2. Anti-seizure drug acts by blocking 'T' type of calcium currents (*12*) 3. TNF –α Inhibitor (*10*) 4. Arteriolar dilator used in hypertension (*11*) 5. Anti-hypertensive drug with central sympatholytic action (*10*)	6. Tetracycline associated with vestibular toxicity as its adverse effects (*11*) 7. Anti-thyroid drug safe in pregnancy *(16)* 8. First line anti-tubercular drug associated with orange red colored urine one of its ADR *(8)* 9. Anti-seizure drug acts by blocking 'Na$^+$ channels *(9)* 10. Class I anti-arrhythmic drug acts by blocking Na$^+$ channels *(9)*

Answers:

Downwards

1. Isoniazid 2. Ethosuximide 3. Infliximab
4. Hydralazine 5. Methyldopa

Across

6. Minocycline 7. Propylthiouracil 8. Rifampin
9. Phenytoin 10. Quinidine