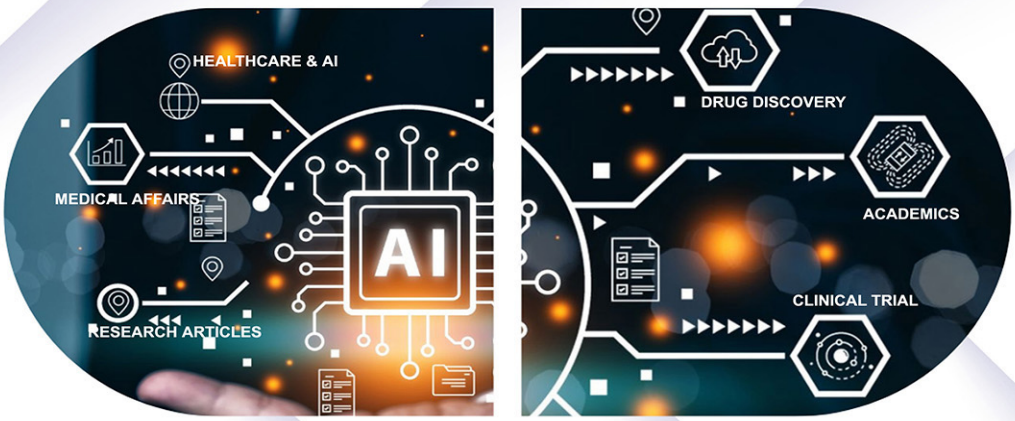
NEMPSule

THE E-BULLETIN OF NEMPS

North Eastern Medical Pharmacological Society



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NEMPS
(NORTH EASTERN MEDICAL PHARMACOLOGICAL SOCIETY)

Design by Ashish Debnath, Creative Design, Dibrugarh

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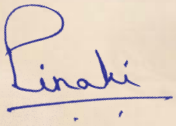
From the President's desk

North Eastern Medical Pharmacologist Society (NEMPS) is publishing its first e-bulletin by the name NEMPSULE. It is my pleasure and honor to have this opportunity to thank the editor Dr Gayatri Sarma and her team. Pharmacology in the present day context is important for everyone. Medical education is offering pharmacology as an elective choice in undergraduate study. The information in this bulletin should help the reader. Knowledge is required to be shared. Text books are essential in any curriculum to learn. Journal and bulletin may add more than what is available in the textbook. These days e-books are common and preferred by the students. Technologies have made access easy to e-learning. The conferences organised under NEMPS in Shillong and Dibrugarh were a huge success. Guwahati this year will be hosting the annual conference. We are looking forward eagerly with a change of guards. Being a founder member of this society I am thankful to all my friends who made the organisation grow. Many new doctors will join us and take the society to reach a new dimension. NEMPS is formed in COVID times when everything was performed online. The future of the society lies on the young generation and I am sanguine that it's going to be bright.

Long Live NEMPS.



Prof Pinaki Chakravarty
President
Head of the department of Pharmacology
Tezpur Medical College and Hospital, Tezpur

Message from the General Secretary, NEMPS

It gives me immense pleasure in writing this message for the 1st edition of the NEMPS bulletin "NEMPSule". It was a long standing dream of NEMPS to start an endeavour like this and I am really happy to see this happening now. I thank and congratulate our new Editor of NEMPS, Dr. Gayatri Sarma, for taking the pain of initiating this process and finally making this dream come true.

I being the founder General Secretary of NEMPS feel myself privileged to get the opportunity to write this message for the first edition of NEMPSule, which is being released on a very auspicious day of Saraswati Puja 2024 and pray to the "Goddess of Education" to shower her blessings and make this a very successful one.

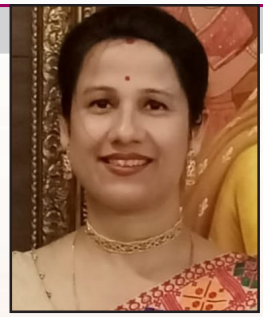
This e-bulletin will hopefully ignite the analytical minds of the Medical Pharmacologists of NEMPS and help improve their knowledge in the subject of Pharmacology and their scientific writing skills.

I wish all the best to the Editorial team and hope that this e-bulletin will be released regularly.

Long Live NEMPS.

Dr. Nishanta Thakuria
General Secretary
NEMPS

From The Desk of The Editor



"Coming together is a beginning, keeping together is progress, working together is success"

So said American author and historian Edward Everett Hale. And this dictum is a true reflection of the success story of North Eastern Medical Pharmacological Society (NEMPS), ever since its inception in the year 2021. In an attempt to add another feather to the cap, the Executive Committee of NEMPS has come up with a magnificient idea of publishing an e-bulletin "NEMPSule" biannually, that would serve as a platform for disseminating knowledge regarding pharmacological research and therapeutics , regulatory updates and recent guidelines , medical education, adverse drug reactions etc. among it's members as well as among all pharmacologists at large.

I feel extremely blessed and priviledged to have been entrusted with the responsibility of editing and publishing the 1st edition of this prestigious e- bulletin "NEMPSule". I am thankful for the same and have left no stone unturned to publish the e-bulletin in the best possible manner in an unbeliveably short span of time.

NEMPSule contains a myriad of topics ranging from Artificial Intelligence (including first AI drug in trials) to Pharmacovigilance, Materiovigilance and Cosmetovigilance. We have articles on Rational Polypharmacy, Antibiotic Resistance and Monoclonal Antibodies. An interesting article on Ferroptosis has also been included in the bulletin. The novel antibiotic Clovibactin has been discussed as also the anaesthetics, Articaine and Centbucridine. Articles on Micronized progesterone, Newer dyslipidemic drugs and role of pharmacogenomics in the drug therapy of dementia are some of the other inclusions. We also have an article on medical education entitled "Assessment in Pharmacology".

I am deeply indebted to all the contributors of this e-bulletin who took time off their busy schedule to pen down a few lines for the bulletin. Without their wholehearted support, NEMPSule would not have seen the light of the day.

I am also thankful to all my advisors Dr.(Mrs) Mangala Lahkar , Dr.(Mrs) Meghali Chaliha, Dr. Pinaki Chakraborty, Dr. Dhriti Brahma, Dr. Nishant Thakuria, Dr. Swapnanil Gohain , whose relentless advice and support made this herculean task much easier for me to handle. I also express deep gratitude to Dr. Bijoy Bakal for having taken the pains of designing the coverpage of NEMPSule inspite of a busy work schedule.

I wish my readers a happy academic voyage through the pages of the NEMPSule and look forward to future help and cooperation towards making NEMPSule successful.

With warm regards,

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The Rise of Smart Health care: The Revolutionary Role of Artificial Intelligence in Modern Health care

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What is Artificial Intelligence (AI)

Artificial Intelligence (AI) is the science and engineering of creating intelligent machines by means of algorithms or rules that the machine obeys in order to simulate cognitive processes like learning and problem solving that are common to humans. Artificial intelligence (AI) systems are capable of anticipating problems or addressing them as they arise, allowing them to function in a deliberate, intelligent, and adaptable way. The strength of artificial intelligence (AI) lies in its capacity to identify patterns and relationships from vast multidimensional and multimodal datasets. For instance, AI systems have the ability to convert a patient's whole medical record into a single number that indicates a probable diagnosis. AI systems are also dynamic and independent, learning and changing in response to new data.[1]

Artificial Intelligence (AI) has become a disruptive force in many industries, and it has had a revolutionary effect on the health care industry. Artificial intelligence (AI) has been used to improve patient care, speed up medical research, simplify administrative procedures, and improve diagnostic accuracy in recent years. This article examines the significant transformations AI has brought about in the field of modern health care.

Improved Diagnostics and Personalized Medicine

One of the significant contributions of AI in health care is its ability to revolutionize diagnostics. Advanced machine learning algorithms analyze vast amounts of medical data, including images, genomic information, and patient records, to detect patterns and provide more accurate diagnosis. This has led to early detection of diseases, allowing for timely intervention and improved patient outcomes.[2]

Furthermore, AI is essential to the advancement of customized treatment. AI systems are able to recognize particular biomarkers and forecast each patient's reaction to a given course of treatment by examining genetic and biological data. The ability to customize medical treatments to a patient's specific genetic composition offers enormous promise for more focused and successful treatment.

Enhanced Patient Care and Monitoring:

By enabling remote monitoring and condition management, AI-powered applications help to improve patient care. Wearables with AI algorithms built in can monitor vital signs continually, spot irregularities, and notify medical professionals of possible problems. This proactive strategy lessens the workload on health care institutions while simultaneously improving patient safety.

Facilitating the collection and exchange of information is one advantage that AI use offers to health systems. AI can make it easier for healthcare providers to manage patient data.

Diabetes is one such. The Centers for Disease Control and Prevention estimate that diabetes affects 10% of Americans. Patients can now utilize wearable technology and other monitoring tools to tell their medical team and themselves about their blood sugar levels. AI can assist providers with gathering, storing, and analyzing this data as well as producing data-driven insights from large populations.[3] By utilizing this data, medical practitioners can make more informed decisions about how to treat and manage illnesses.

Natural language processing algorithms power chat bots and virtual health assistants, which are used to give patients real-time information, respond to inquiries, and provide assistance in managing chronic diseases. These virtual assistants improve patient participation and offer an ongoing patient-provider feedback loop.

Streamlined Administrative Procedures:

AI is being used in health care in ways other than patient care, such as enhancing operational effectiveness and streamlining administrative duties. Routine and time-consuming tasks like billing, claims processing, and appointment scheduling are automated by AI-driven solutions. Health care workers' administrative workloads are lessened by this automation, which also lowers error rates and makes financial transactions more precise and transparent.

In addition, AI-powered tools for data analytics help health care organizations make informed decisions by analyzing large data sets. This facilitates resource optimization, better management of health care facilities, and improved overall efficiency in the delivery of health care services.[4]

Drug Discovery and Medical Research:

AI is revolutionizing the field of drug discovery and medical research by significantly accelerating the identification of potential treatments and therapies. Machine learning algorithms can analyze vast data sets to predict drug interactions, identify potential side effects, and streamline the drug development process. This not only reduces the time and cost associated with bringing new drugs to market but also opens up new avenues for innovation in health care.

Challenges and Ethical Considerations:

While the impact of AI in healthcare is undeniably transformative, it is not without challenges. Concerns regarding data privacy, algorithm bias, and the potential dehumanization of healthcare services need careful consideration. Striking a balance between technological innovations and maintaining the human touch in patient care remains a critical challenge for the industry.[5]

Conclusion:

The integration of AI in healthcare is a journey towards a future where medical practices are more precise, accessible, and patient-centric. While challenges persist, the potential benefits far outweigh the risks. Striving for responsible AI implementation, fostering collaboration between technologists and healthcare professionals, and addressing ethical concerns will be crucial in maximizing the positive impact of AI on the healthcare landscape. As we navigate this era of change, the fusion of human expertise with AI capabilities holds the key to unlocking a new paradigm of healthcare excellence.

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First AI drug enters Phase II IPF trial

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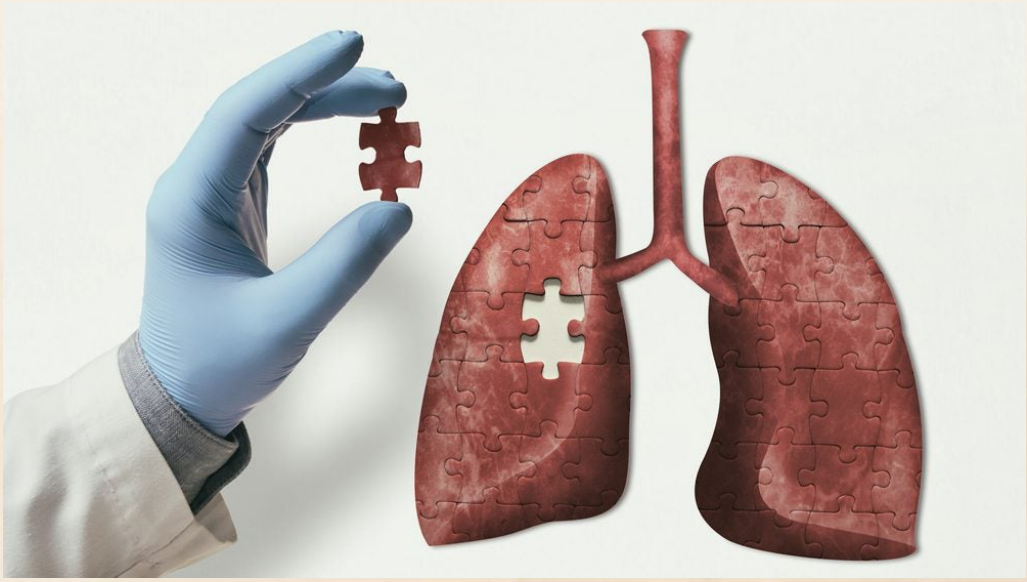
Disease modeling and target identification are the most crucial initial steps in drug discovery, and influence the probability of success at every step of drug development. Traditional target identification is a time-consuming process that takes years to decades and usually starts in an academic setting. Given its advantages of analyzing large datasets and intricate biological networks, artificial intelligence (AI) is playing a growing role in modern drug target identification.

Hong Kong-based artificial intelligence (AI)-powered drug discovery company Insilico Medicine has completed administering the first dose of its AI-discovered drug in a Phase II clinical trial.

The company is evaluating its INS018_055 on lung function in patients with idiopathic pulmonary fibrosis (IPF).

INS018_055 is potentially the **first-in-class anti-fibrotic small molecule inhibitor** discovered and designed by Insilico's AI platforms, according to the company.



(Insilico completed the first dose of its AI-generated drug in patients with IPF. Credit: SvetaZi via Shutterstock)

The randomised, double-blind, placebo-controlled, clinical trial will assess the safety, tolerability, pharmacokinetics (PKs), and preliminary efficacy of a 12-week oral dosage of INS018_055 in patients with IPF (idiopathic pulmonary fibrosis) . This trial will have four cohorts, with patients receiving 30mg once-daily (OD), 30mg twice-daily (BID), 60mg (OD) doses or placebo.

Insilico plans to recruit 60 patients at 40 sites in China and US. The company initiated enrolment in China-based sites in April 2023 and received approval from the US Food and Drug Administration (FDA) for a simultaneous clinical trial in the US in June 2023.

Phase I trial results:

In January, Insilico announced positive topline data from a Phase I healthy volunteer trial. The study utilised single-ascending dose (SAD) and multiple-ascending dose (MAD) to evaluate the safety, tolerability, PK profile, food effect, and drug-drug interaction of INS018_055.

Based on subjective and objective examination, the primary endpoint measured the number of participants with treatment-related adverse events. The study recruited 78 healthy volunteers residing in New Zealand.

The data analysis showed that the observed PK profile was favorable and in line with preclinical modeling, with no significant accumulation after a week. The drug was generally safe and well tolerated, with no deaths or serious adverse events reported in the study.

In February, the FDA granted orphan drug designation (ODD) to INS018_055 for the treatment of IPF.

IPF(idiopathic pulmonary fibrosis) landscape:

IPF is the most common subtype of idiopathic interstitial pneumonias (IIPs), characterised by damaged and scarred lung tissue. A GlobalData competitive landscape report estimates that in 2028 the highest diagnosed prevalent cases of IPF will be in China and India.

A recently published expert insight from GlobalData noted only a few approved therapies for IPF. Even though the late-stage clinical pipeline is small, it is slowly growing with several Phase III trials investigating drugs for this indication that has an unmet need.

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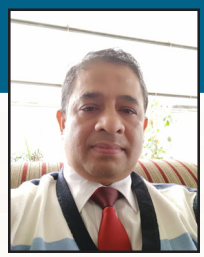
   (a healthcare reporter for Clinical Trials Arena)

Monoclonal Antibodies:
their nomenclature and uses



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Monoclonal antibodies are antibodies produced by a single clone of B-cells. They are monospecific and homogenous. Their names may sound difficult but are in reality very logical. Monoclonal antibodies are an integral part of targeted therapy approach for various diseases now-a-days. The nomenclature and different therapeutic uses of monoclonal antibodies are presented here.

1. Nomenclature:

a) All monoclonal antibodies have suffix "**mab**." Example: Cetuxi**mab**.

b) The one or two letters before "mab" indicate source. There may be three sources of monoclonal antibodies as follows:

i. Animal (rodent, more antigenic): Indicated by "o". Example: Murom**o**nab.

ii. Mixed (mixture of animal & human):

- Chimeric (more animal part): Indicated by "xi". Example: Ritu**xi**mab, cetu**xi**mab.
- Humanized (more human part): Indicated by "zu". Example: Trastu**zu**mab, Bevaci**zu**mab, Palivi**zu**mab.

iii. Human (pure human origin, least antigenic): Indicated by "u". Example: Denos**u**mab.

c) Target: The 5th & 6th letter from the end indicates target.

i. "tu" indicates that the target is tumour cell. Example: Ri**tu**ximab, Ce**tu**ximab.

ii. "vi" indicates that the target is virus. Example: Pali**vi**zumab

iii. "ci" indicates that the target is circulation. Example: Ab**ci**ximab, Beva**ci**zumab.

iv. "os" indicates that the target is osteo. Example: Den**os**umab

v. "oc" indicates that the agents are used to reduce " Over cholesterol." Example Alir**oc**umab

vi. "li" indicates that the agents are used to lower immunity. Example: Ada**li**mumab

2. Therapeutic uses:

Monoclonal Antibodies	Source	Targets	Therapeutic uses:
Ce-tu-xi-mab	Chimeric	Tu=Tumour	Cancer chemotherapy.
Ri-tu-xi-mab	Chimeric	Tu=Tumour	Cancer chemotherapy.
Tras-tu-zu-mab	Humanized	Tu=Tumour	Cancer chemotherapy.
Per-tu-zu-mab	Humanized	Tu=Tumour	Cancer chemotherapy.
Pali-vi-zu-mab	Humanized	Vi=Virus	Respiratory Syncytial Viral infection.
Ab-ci-xi-mab	Chimeric	Ci=Circulation	Antiplatelet agent
Beva-ci-zu-mab	Humanized	Ci=Circulation	To prevent metastasis
Den-os-u-mab	Human	Os=Osteo	Osteoporosis
Alir-oc-u-mab	Human	Oc=Over cholesterol	Dyslipidaemia
Evol-oc-u-mab	Human	Oc=Over cholesterol	Dyslipidaemia
Ada-li-mu-mab	Human	Li=Lower immunity	Inhibits TNFα and used in Rheumatoid arthritis, & Crohn's disease as Immunosupressant
Certo-li-zu-mab	Humanized	Li=Lower immunity	
Etanercept	Fusion protein#	Li=Lower immunity	
Inf-li-xi-mab	Chimeric	Li=Lower immunity	
Go-li-mu-mab	Human	Li=Lower immunity	Inhibits IL-2 & used in organ transplantation
Dac-li-zu-mab	Humanized	Li=Lower immunity	Psoriasis
Basi-li-xi-mab	Chimeric	Li=Lower immunity	
Efa-li-zu-mab	Humanized	Li=Lower immunity	

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Oral Micronized Progesterone: A Versatile Tool in Women's Health

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Progesterone is a natural progestogen, the main hormone of the corpus luteum and the placenta. It acts on the endometrium by converting the proliferating phase to the secretory phase.Oral micronized progesterone (OMP) has established itself as a valuable therapeutic option for various conditions in women's health. From regulating menstrual cycles to supporting fertility and managing perimenopausal symptoms, its applications are diverse. Micronised progesterone is absorbed by the digestive tract. Pharmacokinetic studies conducted in healthy volunteers have shown that after oral administration of 2 capsules (200mg), plasma progesterone levels increased to reach the Cmax of 13.8ng/ml +/- 2.9ng/ml in 2.2 +/- 1.4 hours. The elimination half-life observed was 16.8+/- 2.3 hours.Progesterone is approximately 96%-99% bound to serum proteins, primarily to serum albumin (50%-54%) and transcortin (43%-48%).

Historical Perspective:

Traditionally, synthetic progestins dominated hormone therapy. However, concerns about their metabolic and safety profiles led to the exploration of bioidentical progesterone options. Micronization technology allowed for improved oral bioavailability, paving the way for OMP's introduction in the 1990s. Since then, it has gained increasing recognition for its potential benefits compared to synthetic counterparts.

Dosage Forms and Considerations:

OMP is available in various capsule strengths (100mg, 200mg, 300mg) and can be administered cyclically or continuously depending on the intended use. Individualized dosing is crucial, considering factors like the patient's medical history, hormonal profile, and treatment goals. Careful monitoring of serum progesterone levels may be necessary, especially in cases of endometrial hyperplasia or irregular bleeding.

In trials, oral micronized progesterone (OMP) has shown promise in various contexts:

- **IVF:** OMP proved as effective as intramuscular injections for luteal phase support, offering a convenient alternative (PORTIA trial).
- **Perimenopause:** Continuous OMP significantly reduced hot flashes and improved quality of life compared to placebo (Krona Women's Health Study).
- **Endometriosis:** Long-term cyclic OMP reduced pain and improved quality of life compared to placebo.
- **Breast cancer:** While inconclusive, the Women's Health Initiative (WHI) Observational study suggested a potential decrease in breast cancer risk with long-term OMP use.
- **Osteoporosis:** Early data indicates OMP's potential in preserving bone mineral density, but larger trials are needed for confirmation.

Spectrum of Uses:

OMP's versatility shines through its diverse applications:

- **Menstrual cycle regulation:**
  - **Amenorrhea:** Cyclic OMP (10-20mg/day for 10-14 days per month) induces withdrawal bleeding, mimicking a natural menstrual cycle.
  - **Irregular cycles:** OMP can regulate ovulation and establish a predictable cycle by balancing estrogen's proliferative effects (e.g., 100-200mg/day from cycle day 15 to the expected period).
  - **Premenstrual syndrome (PMS):** Continuous low-dose OMP (100-200mg/day) may alleviate symptoms like mood swings, bloating, and breast tenderness by reducing excess estrogen activity.
- **Endometrial protection in hormone replacement therapy (HRT):**
  - When combined with estrogen in HRT, OMP (100mg/day) protects the endometrium from excessive proliferation, thereby reducing the risk of endometrial cancer associated with unopposed estrogen therapy.
- **Support during fertility treatments:**
  - **Luteal phase support for assisted reproductive technologies (ART)**: OMP (200-300mg/day) starting after ovulation or embryo transfer promotes endometrial receptivity and improves implantation rates in conditions like IVF.
- **Management of perimenopausal symptoms:**
  - OMP effectively reduces hot flashes, night sweats, and other vasomotor symptoms associated with perimenopause (e.g., 100-200mg/day cyclically or continuously). It offers a potentially safer alternative to synthetic progestins with fewer side effects like weight gain and mood changes.
- **Off-label uses:**
  - **Breast cancer prevention:** Early research suggests OMP's potential to reduce breast cancer risk in high-risk women, but larger studies are needed.
  - **Osteoporosis:** OMP may improve bone mineral density and reduce fracture risk, but data is limited.
  - **Endometriosis symptoms:** Some studies indicate OMP's efficacy in managing pain and other symptoms associated with endometriosis, but its role requires further investigation.

Adverse Effects:

OMP is generally well-tolerated, but potential side effects include:

- Common:
  - Breast tenderness (20-30%)
  - Headaches (10-20%)
  - Mood swings (5-10%)
  - Irregular bleeding (5-10%)
  - Weight gain (less common than with synthetic progestins)
- Less common:
  - Fatigue
  - Dizziness
  - Nausea
  - Skin changes (acne, rash)
  - Sleep disturbances

Precautions and Contraindications:

A thorough medical history and appropriate investigations are crucial before prescribing OMP. Contraindications include:

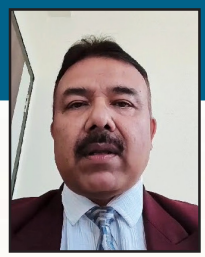
- Undiagnosed abnormal uterine bleeding
- Active breast cancer
- Hypersensitivity to progesterone

Caution is advised in patients with:

- Liver or kidney disease
- Epilepsy
- History of thromboembolic events

OMP has earned its place in women's healthcare due to its bioidentical nature, favourable safety profile, and diverse applications. Healthcare professionals should stay updated on the evolving evidence base and utilize OMP judiciously while considering individual patient needs and potential risks.

Assessment in Pharmacology



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CBME in India has changed the assessment process of medical education. Both undergraduate and postgraduate graduate students are now following the curriculum based medical education (CBME). The National Medical Commission of India is the regulator of quality medical education and directions from the NMC are implemented in all the medical institutes within the country. As faculty of Pharmacology all of us should be acquainted with the curriculum and follow it. Pharmacology is a dynamic subject and keeps changing with time. Many new drugs are added and few get deleted. Updated knowledge is required to mentor and teach the upcoming students. The quality of teaching and learning by the students obviously is not uniform everywhere. Multiple factors determine the level of education in a medical college. However the university offering the degrees lay down minimum criteria which is needed for the students to fulfill and appear in the summative assessment. It's our responsibility to conduct the assessments over a period of time. It may be a formative assessment or OSCE or skill station or oral exam. The focus is on the feedback which is normally reflected from the tests undertaken. It's an indicator of the teachers as well. The students who are very bright may do exceptionally well. They need to be encouraged. Alongside the poor students need special attention and more thrust from the department to grab the subject better. It is true for all the subjects but in pharmacology many students find it difficult to memorize the names of the Drugs. The lucidity of teaching and making the subject better acceptable is our challenge. After every system internal assessment is to be done. The objective of the assessment is to make the students conversant with the topic. Text books are essential for the students to read. Every skill is needed to be certified by conducting an appropriate test. Spelling of the medicine is to be written correctly. Students should know the art of writing a prescription in pharmacology. The power of choosing the P drug which is appropriate for a particular condition is vital for the students to learn. Pupils are more inclined to multiple choice questions and it is good to make proper use of it. The Pharmacology department should emphasize and inculcate rational use of drugs and devices. The drug history of patients in hospital is needed to avoid polypharmacy and interactions. The assessment is to be modified and innovative to explore the attainment of knowledge. Knowledge of Pharmacology is applied in all the specialties of medical sciences. Sound knowledge can only make doctors better and that is indeed a great responsibility for our teachers to teach and check the input by taking reassessment if required.

■■■

Rational Polypharmacy

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Rational Polypharmacy is the integration of one or more pharmacologic agents through a systematic selection that has the most synergistic effect to manage a pathological condition. The proper mix of medications can help manage chronic conditions, treat ailments and improve a patient's quality of life. Rational polypharmacy should at least aim at avoiding the irrational. The concept of rational polypharmacy has been made use of in chronic pain, epilepsy, psychiatric disorders. The term Polypharmacy many a times indicates only the count or the number of medicines. The term appropriate polypharmacy should be adopted. The policy of Rational Polypharmacy should be to avoid the unnecessary and harmful drugs and drugs with harmful interactions with the others, not just to curtail the number.

WHO defines Polypharmacy as the administration of many drugs at the same time or the administration of an excessive number of drugs with more than 5 or 6 medications daily. John J Miller in reference to Polypharmacy quotes Albert Einstein, "Keep it as simple as possible, but no simpler".

There are multiple causes of Polypharmacy

1) Multiple diseases particularly in the elderly age group with comorbidities, altered PK, PD status, hypochondriac patients
2) Poor prescriber skill leading to symptom based treatment versus diagnosis based treatment
3) Multiple prescribers, the primary care providers, specialists, physician's assistants and nurses.
4) Transition of care taking place during transfer between different health care providers/setting. Poor communication among the different levels of health care providers leads to unintended changes in medication
5) Reflex prescribing/ prescribing cascade occurring when a medication is provided to treat an adverse reaction of a prescribed drug as a new disease.
6) Over the counter drugs/self drug prescribing behaviour: combination of prescription drugs, OTC drugs and herbal supplements.

Irrational polypharmacy can lead to grave consequences. It might lead to duplication of therapy, exponential increase in the rate of adverse drug events with increase in the number of drugs, increase in drug-drug, drug-disease, drug-food, drug-alcohol, drug-herbal product interaction, decreased adherence and compliance, impairment of quality of life, increased cost burden and worsening of patient doctor relationship.

Some commomly encountered drug interactions are Furosemide with Metoprolol leading to hypertriglyceridemia and hyperglycaemia, Furosemide and Pantoprazole leading to hypomagnesemia, manifesting in tremors, convulsions, delirium and even coma, Beta blockers with Calcium Channel blockers may precipitate CCF, hypotension, bradycardia and cardiogenic shock.

Some measures can be taken to decrease the manace of irrational polypharmacy.

SAIL Technique which emphasizes on **Simple** regimen, adequate knowledge of **Adverse** effects **Indication** of each drug clearly defined, **List** of names and dose of each medication written on the chart and shared with the patient.

TIDE Technique which emphasizes on adequate **Time** for discussion of medication issues, **Individualize** dose and medications based on PK/PD profile of patients, **drug-drug and drug-disease** interaction and **Education** of patients and caregiver.

Medical Reconciliation compares all the medication orders to all the medications the patient has been taking. It helps to avoid commission, omissions, duplications, dosing errors or drug interactions.

Deprescribing WHO defines it as patients receiving medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time and at the lowest cost to them and their community

It is important that the **Right patient** gets the **Right drug** at the **Right dosage** and at a **Right cost**.

The fulfillment of **SANE criteria, Safety, Affordability, Need and Efficacy** is also of utmost importance in rational prescribing.

Beer's Criteria developed by Mark H. Beers in 1991 and revised in 1997 is a list of criteria which determines the list of pharmacological agents inappropriate for utilization among the elderly population based on their possible risk and benefits.

The principle underlying rational polypharmacy is that combination of two medications with different mechanisms of action may result in supra additive or synergistic effects and infra additive toxicity and may overcome refractoriness to treatment. Polypharmacy is also rational for diseases with polygenic origin. Polytherapy should be resorted to in select individuals, after a careful discussion of risks and benefit. Synergistic combinations allow lower doses and therefore less adverse effects than individual drugs in hypertension. Supplemental drug like anticholinergics may decrease adverse effect of initial drug like dopamine agonists in parkinsonism. Additional drug of other groups may improve outcome in congestive heart failure. Some disease

conditions like tuberculosis, require multi drug therapy to prevent development of resistance. Some anti cancer chemotherapy are polypharmacy to attack different phases of the cell cycle. Diuretics are sometimes given in combination to avoid diuretic resistance. Combination drug therapy is given for BPH (á blockers to correct the dynamic component and 5 á reductase inhibitors to correct the static component). Combination of drug therapy for rheumatoid arthritis, Alzheimers disease, for chronic pain management, epilepsy and psychiatry are all justified and rational polyharmacy.

Use of drugs when none is needed, compulsive prescription of vitamins and tonics, use of drugs not related to the disease, selection of wrong drug, prescribing drugs of doubtful efficacy, incorrect route of administration, dose and duration, unnecessary use of drug combinations, unnecessary use of expensive medications can all lead to irrational polypharmacy.

"Cured Yesterday of my disease, I died last night of my physician". Quoting Mathew Prior, it can be concluded that all physicians should take utmost care not to be the cause of a patient's death, of which irrational polypharmacy is a major concern.

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■■■

Clovibactin: A Novel Antibiotic

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Antimicrobial resistance is one of the most important challenges being faced by mankind in its fight against infectious diseases. Most of the antibiotics currently being used originate from natural products that were discovered by screening soil-dwelling bacteria. This was a very successful technique ushered by Waksman from 1940 to 1960, also called the Golden Age of antibiotics discovery.[1] This technique has given us antibiotics like streptomycin, tetracycline-vancomycin, etc. However, the traditional sources of antibiotics have slowly and steadily worn out in the subsequent time. The pipeline of new antibiotic research and development at present is very narrow and only a few antibiotics have been marketed over the last decades and they often resemble older, already known antibiotics. Researchers have been looking at various sources for new antibiotics globally. A hopeful development has been made by scientists in the fight against drug-resistant bacteria in recent times with the discovery of Clovibactin, a novel antibiotic discovered from bacteria that were previously thought to be unconquerable, i.e. isolated from uncultured soil bacteria. Scientists have observed the amazing effectiveness of clovibactin in eliminating drug-resistant Gram-positive bacterial infections without detectable resistance development which provides a glimmer of hope in our struggle against dangerous bacteria and multi-resistant "superbugs."

SOURCE OF CLOVIBACTIN

The majority (99%) of all bacteria cannot be cultured conventionally could not be grown in laboratories previously, and could not be used for discovery of new antibiotics[2,3]. However, using the new technique called iCHip, the U.S. researchers discovered Clovibactin in a bacterium isolated from a sandy soil from North Carolina.[4,5]

ANTIBACTERIAL SPECTRUM

It exhibited antibacterial activity against a broad range of Gram-positive pathogens, including methicillin-resistant S. aureus (MRSA), daptomycin-resistant as well as vancomycin-intermediate resistant (VISA) strains, and difficult-to-treat vancomycin-resistant *Enterococcus faecalis* and *E. faecium* (VRE).[6] However, it has shown weak activity against *E. coli*.

MECHANISM OF ACTION

It is a bactericidal agent. The mode of action of clovibactin from traditional antibiotics is different against resistant bacteria. It attacks the bacterial cell wall, causing structural integrity to be compromised and finally causing cell death. It blocks cell wall synthesis by targeting the pyrophosphate of multiple essential peptidoglycan precursors (C55PP, lipid II, and lipid IIIWTA).[5]

It uses an unusual hydrophobic interface to tightly wrap around pyrophosphate, but bypasses the variable structural elements of precursors, accounting for the lack of resistance. Selective and efficient target binding is achieved by the irreversible sequestration of precursors into supramolecular fibrils that only form on bacterial membranes that contain lipid-anchored pyrophosphate groups.[5]

It has shown promising results in various animal models as well as in vitro studies.

CONCLUSION

Antibiotics have been used successfully to fight a wide range of bacterial infections. However, overuse and misuse led to the development of antibiotic-resistant bacteria, known as "superbugs". Scientists are now working in a war-footing manner to discover new antibiotics that can defeat these bacteria. While this has been a difficult task, the discovery of clovibactin has renewed hope that we can fight our way out of this antibiotic resistance crisis. However, an unfortunate, yet common, example is that antibiotics that appear safe in animals may turn out to be toxic at the higher doses required to treat humans. Such unforeseen complications during the development phase are one part of the reason why more than 98.5% of newly discovered antibiotics never make it out of the lab. It is too early to comment on whether clovibactin is the savior we've been longing for.

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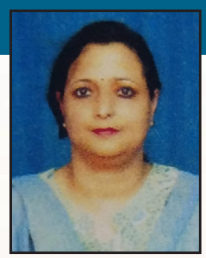
Pharmacogenomics holds Promise for Personalized Dementia Therapies



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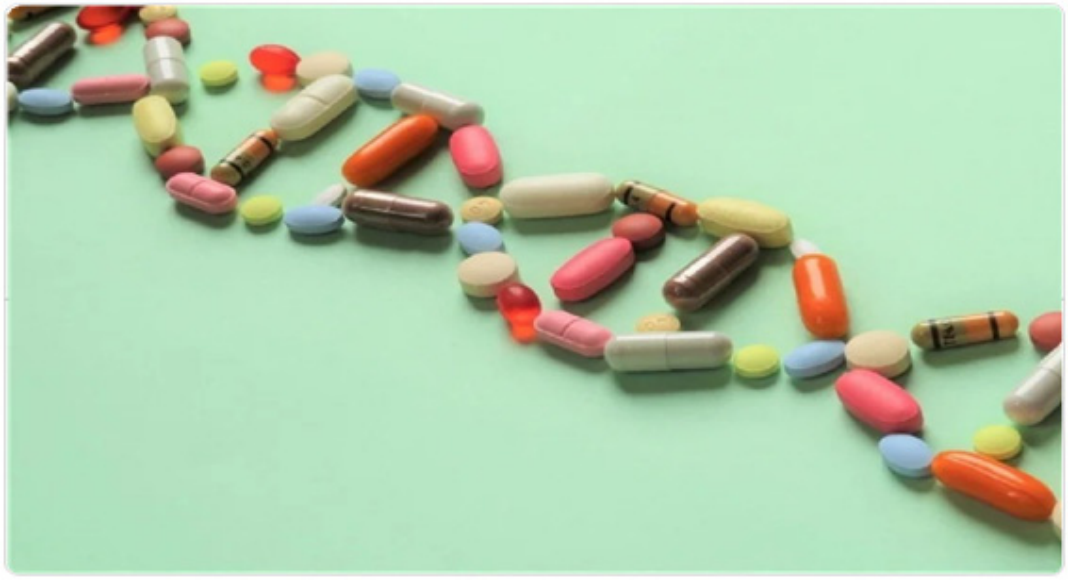

Pharmacogenomics of Dementia : Personalizing the Treatment of Cognitive and Neuropsychiatric Symptoms.

Background

Dementia is a complex progressive disorder represented by cognitive decline. Dementia pathogenesis and clinical manifestation are complex and involve more than 200 genes. Given its complexity, dementia patients, especially older ones, typically simultaneously receives 9 to10 drugs per day which mainly include psychotropic drugs, such as antipsychotics, antidepressants, anticonvulsants, anxiolytics, hypnotic, and sedative drugs.

Indeed, no single pharmacotherapy provides a comprehensive long-term remedy for dementia. Several complementing approaches are needed to broaden the available options for managing this

condition and enhance the quality of life for individuals with dementia.

Pharmacogenomics, which addresses the genome-wide interaction of many genes affecting drug efficacy and safety of dementia therapeutics, could help with patient stratification, resulting in more effective therapy and reduced drug adverse effects among dementia patients. However, so far, it has remained challenging to apply it to dementia patients.

Therapeutic strategies in dementia

The primary focus of any dementia pharmacotherapy is treating the impairment of cholinergic and glutamatergic systems involved in cognitive dysfunctions triggered by Alzheimer's Disease (AD) and other types of dementia.

N-methyl-d-aspartate (NMDA) receptor antagonists, e.g., memantine and AChE inhibitors,e.g., donepezil, have received the Food and Drug Administration (FDA) approval for aging AD-related cognitive symptoms; however, they do not effectively slow down the progression of the disease.

Some monoclonal antibodies have been shown to effectively slow down the progression of mild dementia due to AD, for example, aducanumab and lecanemab.

Since single-target therapeutics have remained ineffective in slowing the progression of dementia, several multi-target compounds are currently undergoing investigation for AD treatment. For example, Ladostigil. This AChEI and a monoamine oxidase (MAO)- A and B inhibitor combines the mechanisms of actions of drugs like Rivastigmine and Rasagiline into a single molecule.

Pharmacogenomics of anti-dementia drugs

Different cytochrome P4502D6 (CYP2D6) genetic variants influence the safety and efficacy of donepezil, the most prescribed AChE inhibitor drug. rs1080985single nucleotide polymorphism of the CYP2D6 gene is the most studied polymorphism in studies evaluating the clinical efficiency of donepezil. Its allele defines the CYP2D6*2A variant, potentially associated with a higher drug metabolism rate. Poor metabolizers of CYP2D6, thus, show a 32% slower clearance rate of donepezil compared to ultra-rapid metabolizers.

Several other genes, e.g., ATP-binding cassette (ABC) transporters and apolipoprotein E (APOE), modulate the efficiency of donepezil.

Evidence also suggests a potential association between estrogen receptor 1 (ESR1) gene variants and the therapeutic effects of donepezil, especially ESR1 polymorphisms rs2234693 and rs9340799.

Likewise, the rs1803274 polymorphism of the butyrylcholinesterase (BCHE) gene or K-variant has been associated with poor treatment response in patients receiving donepezil.

Other potential candidates in the pharmacogenetics of donepezil are the polymorphisms in the cholinergic receptor nicotinic alpha7 subunit (CHRNA7) gene and rs662 related to paraoxonase-1 (PON-1). The former likely affects acetyl choline binding to neuronal nicotinic acetylcholine receptors (nAChRs). At the same time, the latter was found in higher frequency in patients showing a good response to donepezil treatment.

Likewise, different gene variants of APOE, BCHE, presenilin, and UDP glucuronosyl transferase2B7 (UGT2B7) genes explain the observed variability in rivastigmine efficiency.

Similarly,CYP2D6 genetic variants have been associated with galantamine treatment's outcome and side effects. Ma et al. found that CYP2D6*10 rs1065852 carriers reported fewer adverse side effects to galantamine and better treatment response.

Pharmacogenetic studies focused on galantamine efficacy have also highlighted the involvement of genetic variants of CHRNA7.

Unlike AChEIs, studies focused on the pharmacogenetics of memantine efficacy are fewer. However, studies have highlighted the role of genetic variants of membrane transporter genes in variability observed in memantine pharmacokinetics.

Ovejero Benito et al. investigated the association of 67 single nucleotide polymorphisms (SNPs) in 21 genes encoding for different neurotransmitter receptors, including CYP2D6 and ABCB1.

However,they found no significant association with memantine and donepezil pharmacokinetics or adverse drug reactions.

Pharmacogenomics of multifactorial dementia treatments

Pharmacogenomics-based studies have thoroughly described the therapeutic effects of multifactorial therapy related to APOE and CYP2D6 variants.

A study investigating the effects of APOE variants on multifactorial treatment found APOE 3/4 carriers as the best and APOE 4/4 carriers as the worst responders to multifactorial therapy.

Likewise, a study investigating the influence of CYP2D6 variants showed that CYP2D6-extensive and intermediate metabolizers were the best responders to multifactorial therapy.

Consequently,they showed improved cognition after a year,while CYP2D6-poor and ultra-rapid metabolizers showed no improvement in cognitive functions.

Pharmacogenomics of antipsychotic, antidepressant, antiepileptic, anxiolytic, hypnotic, and sedative drugs

Majority of antipsychotics, antidepressants and anticonvulsants are metabolized by enzymes of the cytochrome P450 family, e.g., CYP2B6, CYP2D6, and CYP3A4.

Over 100 different alleles of CYP2D6 enzyme show deficient, normal, intermediate,or increased enzymatic activity against these classes of drugs, implying all patients need different dosages. Accordingly,10-20% of Caucasians carrying defective CYP2D6 variants display aberrant metabolism of psychotropics.

In addition, the metabolism of these drugs also depends on groups of enzymes, receptors (serotonin receptors), transporters (ATP-binding cassettes), and channels (sodium channels), which are genetically variable. Polymorphisms in these serotonin receptor gene (5HTR2A) are associated with a better response to clozapine, olanzapine, or risperidone, all atypical antipsychotics.

Benzodiazepines, prescribed for the treatment of dementia- related anxiety and sleep disorders, are metabolized by CYP2C19 and CYP3A4/5, with over 40 polymorphic variants of the CYP2C19 gene generating 35 enzyme isoforms with CYP2C19*2 to CYP2C19*8 alleles associated with poor metabolism of benzodiazepines.

Conversely, the CYP2C19*17 variant increases the activity of benzodiazepines. Studies have also implicated CYP1A2, CYP2C9, and CYP2B6 genes in the metabolism of benzodiazepines.

Conclusions

Pharmacogenomics-based methods could help offer safer and more effective personalized medications for dementia patients in the future. These methods could also facilitate the identification of early detection markers for dementia diagnosis and improve understanding of its underlying causes. However, further studies should investigate the functional consequences of genetic polymorphisms in other crucial genes, including neurotransmitter receptors, transporters, etc.

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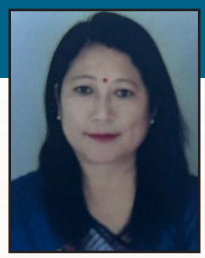
Antimicrobial Resistance and Its Clinical Significance



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INTRODUCTION :

The role of antimicrobial agents in controlling and curing infectious diseases is undeniable, serving as essential tools in modern medicine. Since the discovery of the first antibiotic, a new challenge emerged – antibiotic resistance. These agents employ various mechanisms against bacteria, aiming to prevent their pathogenesis, and can be categorized as either bactericidal or bacteriostatic. Antibiotics, a prominent class of antimicrobial agents, consist of several subclasses, each targeting specific aspects of bacterial function.

Despite the initial success of antibiotics, bacteria continuously evolve and employ diverse mechanisms to counteract the effectiveness of these drugs. This adaptability has led to the development of antibiotic resistance, a phenomenon that poses a significant threat to public health worldwide. Bacteria employ various strategies, including genetic mutations, horizontal gene transfer, and the production of enzymes, to evade the impact of antibiotics and continue their survival .Over time, the use of antimicrobials, often inappropriately, has been on the rise. In the United States, antibiotic resistance results in approximately 23,000 patient deaths annually and incurs over $20 billion in additional medical expenses. To counteract this alarming trend, antibiotic stewardship was established and acknowledged in 1996 to address the increasing incidents of mortality and morbidity associated with the inappropriate use of antibiotics. Antimicrobial agents play a significant role in the development of serious infections, including but not limited to Staphylococcus aureus, vancomycin-resistant enterococci, extended-spectrum â-lactamase-producing Enterobacteriaceae, and other infectious agents. The primary objectives of stewardship programs are to enhance clinical outcomes, reduce antibiotic resistance, and lower healthcare costs. In 2007, stewardship programs gained national recognition and support with the publication of guidelines by the Infectious Disease Society of America (IDSA) in collaboration with the Society of Healthcare Epidemiology of America (SHEA). These guidelines proved instrumental in the establishment of institutional programs aimed at bolstering antimicrobial stewardship efforts.Antibiotics, potent medications employed to combat once-lethal diseases, come with a broad array of adverse effects, typical of powerful drugs. The proper utilization of these agents yields significant benefits that outweigh the associated risks.

However, when antibiotics are used unnecessarily, patients undergo no therapeutic advantages, while still being susceptible to potential side effects. Additionally, antibiotics disturb the composition of the infectious agent, inducing bacterial adaptation or mutations, resulting in the emergence of new strains resistant to the current antibiotic regimen. The improper use of antibiotics in a single patient may give rise to a resistant strain, posing a substantial public health concern as it can spread to non-antibiotic-using patients. Notably, in 2015, 30% of outpatient antibiotic prescriptions were considered unnecessary, with acute respiratory infections accounting for the highest percentage of inappropriate antibiotic use at 50%. Antibiotics, potent medications crucial for treating once-deadly diseases, come with a spectrum of adverse effects. Despite the risks, their judicious use offers significant benefits. However, when antibiotics are employed unnecessarily, patients gain no advantages while remaining susceptible to potential side effects. Furthermore, the use of antibiotics disturbs the composition of the infectious agent, fostering bacterial adaptation or mutations that result in the emergence of new strains resistant to the current antibiotic treatments. This misuse of antimicrobial in one patient can give rise to a resistant strain, posing a serious public health concern as it may spread to other patients not using antibiotics. In 2015, a staggering 30% of outpatient antibiotic prescriptions were deemed unnecessary, with acute respiratory infections accounting for 50% of these instances. This review examines the considerations surrounding antimicrobial use and emphasizes the role of the interprofessional team in educating both patients and providers about the appropriate circumstances for antimicrobial use and the situations where they should be avoided.

KEYWORDS : Antimicrobial , antibiotic , resistance , patient

MECHANISM OF ANTIBIOTIC RESISTANCE :

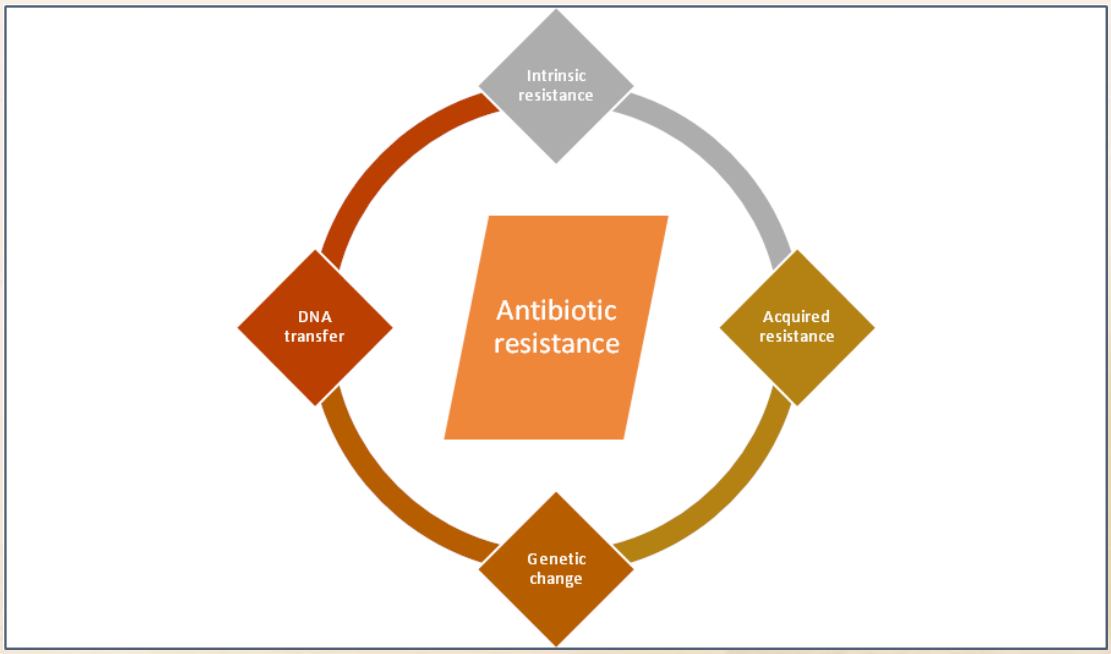

FIGURE 1: Mechanism of antibiotic resistance

MECHANISM OFANTIMICROBIAL RESISTANCE	EXAMPLE
Intrinsic	Penicillin
Acquired	Rifamycin
Genetic	Trimethoprim
DNA Transfer	Methicillin

CHART 1: MECHANISM OF ANMICROBIAL RESISTANCE WITH EXAMPLE

CLINICAL SIGNIFICANCE :

Understanding antimicrobial resistance in clinical practice is a complex and relative phenomenon. Effective engagement with patients plays a crucial role in successful antimicrobial stewardship to mitigate rates of antibiotic resistance. Part of this engagement involves educating patients on actions they can take to ensure their safety, including raising awareness about the adverse effects of antibiotics and the potential consequences of unnecessary antibiotic use. Additionally, employing different diagnostic tools, such as the Overlap2 Method, which assesses the synergistic effects of antibiotics on various antimicrobials, can be highly advantageous. While the clinical approach to antimicrobial stewardship may vary between outpatient and inpatient settings, the overarching objective remains consistent—improving antibiotic use is a fundamental aspect of combating antibiotic resistance.

CONCLUSION:

Antibiotic resistance demands urgent attention and collaborative efforts from the scientific community, healthcare professionals, policymakers, and the public. Without decisive action, we risk returning to an era where common infections become life-threatening, and medical advancements achieved through the use of antibiotics are compromised. It is imperative that we prioritize research, implement effective policies, and raise awareness to safeguard the effectiveness of antibiotics for current and future generations. Only through a concerted global effort can we hope to mitigate the clinical significance of antibiotic resistance and preserve the invaluable role of antibiotics in modern medicine.

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Recent advances in local anaesthesia - A review of literature of Articaine and Centbucridine

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Articaine and Centbucridine are two relatively recent medications that have been shown to be as effective as or perhaps more effective than lignocaine.

Articaine:

Mechanism of action of Articaine:

Articaine is a local anaesthetic that is a member of the amide family. Articaine has an exponential half life and is eliminated over an extended period of time- plasma esterase is mostly responsible for metabolism in the liver and plasma.

Adverse effect of Articaine :

Articaine has the potential to produce neuropathies and methglobinemia. Articaine if used for intraorbital nerve block causes eye problems.

Centbucridine:

Centbucridine is a local anaesthetic molecule created in 1983 in Lucknow. It is a quinoline derivative local anaesthetic. It contains antihistaminic and vasoconstricting effects. Centbucridine has an anaesthetic power 4-5 times larger than that of 2% lignocaine; can be used successfully for infiltration , nerve block and spinal anaesthesia at a concentration of 0.5%.

Centbucridine is comparable to lignocaine and can be used as a substitute in cases of hypersensitivity in patients aged 12 - 14, as well as in cases of cardiac and thyroid diseases.

Centbucridine is used in dental extraction and surgery and as an adjunct to conventional anaesthesia to reduce pain during the administration of local anaesthetics.

An Insight into Ferroptosis- A potential pharmacological development

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Ferroptosis is a recently discovered essential type of cell death that is distinguished from other types of death for its peculiar characteristics of death regulated by iron accumulation. Non-apoptic cell death is characterised by accumulation of ROS (Reactive Oxygen Species)and decrease in lipid peroxidation leading to cell death.Features of ferroptosis were not recognized as evidence of a distinct form of cell death until recently. Since new discoveries in cellular pathology as well as control of lipid peroxidation continue to emerge often, a lesser-known type of cell death - Ferroptosis has been implicated in the pathogenesis of several diseases, including neurodegenerative disorders, ischemia-reperfusion injury, digestive system, respiratory system, circulatory system, urinary system, and cancer.

The study of ferroptosis has led to advances in our understanding of lipid metabolism, iron homeostasis, and redox biology. Ferroptosis is different from apoptosis, autophagy, necroptosis and pyroptosis in terms of cell morphology, biochemistry, and genetics. In ferroptosis, the distinctive characteristics are manifested as mitochondrial atrophy as well as a reduction or even disappearance of the mitochondrial ridge, but there is no change in the size of the nucleus except for chromatin condensation.

This article reviews the characteristics and mechanism of ferroptosis and summarizes how ferroptosis participates in the pathophysiological process in various systemic diseases.

Fig: Pathophysiology of Ferroptosis, an Iron dependent cell death.

Iron may directly generate excessive ROS (reactive oxygen species) through the Fenton reaction.

$Fe2^{+} + HOOHFe3^{+} + OH^{-} + OH^{\cdot}$ thereby increasing oxidative damage.

On the other hand, mitochondria are another essential source of ROS. Oxidative phosphorylation of mitochondria leads to accumulation of lipid ROS, atrophy of mitochondria and eventually result in ferroptosis.

The regulatory mechanismof ferroptosis can be divided into three categories including:

1) The extrinsic pathway is by inhibition of the **cystine-glutamate antiporter (system X_c^-).** This affects the synthesis of glutathione (GSH). This reduction in the cell's antioxidant capacity can result in the accumulation of lipid ROS, thus promoting ferroptosis.

2)Regulation by glutathione peroxidase4 **(GPX4)**:The intrinsic pathway- GPX4 can reduce the cytotoxic lipid peroxide (L-OOH) to the corresponding alcohol (L-OH). Once the activity of GPX4 is inhibited, it will lead to the accumulation of lipid peroxide in the cell membrane resulting in ferroptosis. (Glutathione Peroxidase 4 is an enzyme, required for conversion of reduced form to oxidised form of glutathione.)

3)Regulation by lipid metabolism: **PUFA-PLs** are susceptible to oxidation induced by free radicals mediated by lipoxygenases (ALOXs), which eventually lead to the destruction of the lipid bilayer and affect the membrane function, thus triggering ferroptosis.

Implications of ferroptosis inducers and inhibitors in clinical conditions (although there are many)

Ferroptosis inhibitors in neurodegenerative diseases.

Ferroptosis inhibitors provides opportunities in neurodegenerative diseases where abnormal iron haemostasis in brain tissues induce brain cells to produce high levels of reactive oxygen species, resulting in oxidative damage to sensitive subcellular structures.In ischemic stroke mouse model, GSH level in brain was decreased, as a result GPX4 was decreased too and loss of GPX4 function results in ferroptosis. Ferroptosis inhibitors showed significantly improved prognostic outcome.

Ferroptosis inhibitors:

1.*Ferrostatins-1* are known to inhibit ferroptosis. A synthetic antioxidant, acts via a reductive mechanism to prevent damage to membrane lipids and thereby inhibits cell death. Vit E, Ferrostatin and Deferoxamine, decrease ferroptosis which helps in decreasing cluster of diseases.

2.*Liproxstatin-1***:**Liproxstatin-1 is another ferroptosis inhibitor. It functions by inhibiting lipid peroxidation and has shown efficacy in protecting cells from ferroptosis.

3.*Ferroptosis suppressor protein 1 (FSP1***):** AIFM2 (Apoptosis-Inducing Factor Mitochondria-Associated 2), acts by reducing coenzyme Q10 and regenerating alpha-tocopherol, thereby protecting cells from lipid peroxidation.

Ferroptosis Activators/ Inducers:

The classical ferroptosis activators Erastin or RSL3 inhibit the antioxidant system as they increase intracellular iron accumulation. Iron may directly generate excessive ROS through the Fenton reaction, regulation by iron metabolism. Drugs like:

1. **Erastin** :Ferroptosis inducers Erastin acts on mitochondria to induce an increase in lipid reactive oxygen species by inhibiting cystine import via **System Xc-** this is a cystine/glutamate antiporter that

plays a role in maintaining intracellular redox balance. Inhibitors of System Xc-, such as Erastinand sulfasalazine, capable of initiating ferroptotic cell death in cancer cells.

2.**RSL3** directly act on GPX4, thereby reducing the antioxidant capacity of cells, which leads to accumulation of lipid ROS and leads to ferroptosis.

Other ferroptosis inducers in tumours:

Several tumour cells are highly sensitive to drug induced ferroptosis—leading to cancer cell death, like:

1. Artesunate can specifically induce pancreatic cancer cell lines to produce ROS and activate ferroptosis thereby inhibiting pancreatic cancer occurrence.

2. Erastin induces ferroptosis in gastric cancer cells. They competitively absorbs cysteine , inhibits GSH synthesis and promotes ferroptosis.

3. Downregulation of system xc- signalling pathway induces ferroptosis and used in breast cancer thereby killing cancer cells.

Development of related diseases by regulating cell ferroptosis has become a hotspot and focus of etiological research and treatment, GPX4 activation can even be used as a novel anti-inflammatory or cytoprotective therapy. Though few clinical implications with inducers and inhibitors of ferroptosis are explored but the functional changes and specific molecular mechanisms of ferroptosis still need to be further explored. Studies are currently screening the biomarkers to study the effect of ferroptosis.

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Updates on newer drugs in the management of dyslipidemia

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Dyslipidemia, a lipoprotein disorder results in cardiovascular complications. This metabolic disorder is an imbalance of various lipids such as cholesterol, low-density lipoprotein, triglycerides, and high-density lipoprotein.[1] In Indian scenario, limited data are available for prevalence of dyslipidemia. A recent study (n = 2976) done in Southern parts of India (Tamilnadu) stated that, the prevalence rates of dyslipidemia among sub-urban and urban population were 85% and for rural it was 78.5%.[2] Dyslipidemias are classified into (i) primary or familial dyslipidemia, and (ii) secondary to other co-morbid conditions such as diabetes mellitus, thyroid diseases, obesity, or an unhealthy lifestyle.[3]

Current management of dyslipidemia

Any adult with history of cardiovascular diseases (CVA), or adult with 10 years risk of developing CVA, or adult with diabetes, or those with low-density lipoprotein cholesterol (LDL-C) level of greater than 190 mg/dL, American Heart Association recommends statin therapy. Till date, statins remains the first line of therapy.[4] If the patient needs more lowering of LDL-C, bempedoic acid or ezetimibe in combinations with statins showed good efficiency.[5] Other dyslipidemic drugs in combinations with stains or as monotherapy includes monoclonal antibodies (alirocumab and evolocumab),[6] inclisiran,[7] drugs targeting apolipoprotein (a) (Pelacarsen),[8] apolipoproteinC-III (Volanesorsen, Olezarsen),[9] apolipoproteinB (mipomersen)[10] and ANGPTL3 inhibitor (evinacumab)[11]

(1). **Statins:** These are the first line drugs for the management of dyslipidemia. Currently statins approved by the FDA includes atorvastatin, simvastatin, rosuvastatin, fluvastatin, pitavastatin, lovastatin and pravastatin. They act as antagonist for the enzyme hydroxymethylglutaryl-CoA (HMG-CoA) reductase by blocking the endogenic cholesterol synthase pathway, resulting in lower LDL cholesterol serum levels. FDA approved statins for hypercholesterolemia, hyperlipoproteinemia, and hypertriglyceridemia as an adjunct to diet and exercise.[12] Generally statins are well tolerated by the patients, but significant adverse effects includes myopathy and rhabdomyolysis. Long term use of statins might result in de novo occurrence of type 2 diabetes mellitus.[13]

(2). **Bempedoic Acid:** A prodrug, which gets activated and decreases LDL-C by inhibition of adenosine triphosphate-citrate lyase (ACL) in the liver. ACL is a lipogenic enzyme which catalyses a critical

reaction which is responsible for cellular glucose catabolism and lipogenesis. Bempedoic acid inhibits the conversion of mitochondrial ACL to cytosol ACL thereby, reducing the availability of substrate for cholesterol and fatty acid synthesis.[5] This drug is mainly used in patients who needed additional lowering of LDL-C level in spite of statin therapy. FDA approved once daily dose of 180 mg for the treatment of hypercholesterolemia. Most common adverse effects of bempedoic acid includes upper respiratory tract infection, urinary tract infection, arthralgia, muscle spasms and diarrhoea. [14]

(3). **Ezetimibe:** Ezetimibe selectively blocks the NPC1L1 protein in the jejunal brush border of the intestine and inhibits intestinal cholesterol absorption. This results in depletion of hepatic cholesterol and increase in expression of LDL receptor on the surface of hepatocytes leading to decrease in serum LDL-C level.[15] FDA has approved ezetimibe (10 mg) as a monotherapy and also as fixed combinations with different statins and with bempedoic acid (180 mg) for the treatment of hypercholesterolemia and mixed dyslipidaemia.Literature search, Ezetimibe shows a good safety profile.[16]

(4). **Monoclonal antibodies:** Monoclonal antibodies such as alirocumab and evolocumab inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme. This enzyme plays an important role in cholesterol homeostasis by interacting with hepatic LDL receptors. Alirocumab and evolocumab are both administered subcutaneously once every two weeks. Dose of these monoclonal antibodies ranges from 75mg – 300 mg and mainly recommended for patients with high cardiovascular incident risk and high LDL cholesterol levels. Patients mostly tolerate these monoclonal antibodies with most common side effects being the reaction at the injection site.[17]

Another monoclonal antibody, evinacumab inhibits angiopoietin-like proteins (ANGPTL)-3 which plays an important role in lipoprotein metabolism. FDA has approved this drug for the treatment of familial hypercholesterolemia.It is administered intravenously every four weeks at a dose of 15 mg/kg body weight.Evinacumab reported less adverse effects such as upper respiratory tract infections and flu-like syndromes but some patients shows serious allergic reactions or anaphylaxis.[18]

(5). **Inclisiran:** Inclisiran is a small interfering RNA molecule which targets PCSK9 synthesis in hepatocytes and inhibits the enzyme resulting in significant reduction of LDL-C. The basic difference between PCSK9 inhibitors and inclisiran is that inclisiran intracellularly upregulates the LDL-C receptor whereas PCSK9 inhibitors extracellularly binds and blocks the circulating PCSK9 enzyme. Inclisiran have been well tolerated among the patients. FDA has approved this drug for the treatment of mixed dyslipidaemia and hypertriglyceridemia.[19]

6. **Pelacarsen:** Apolipoprotein (a) is a risk factor for many CVD. Pelacarsenbinds to hepatocyte apo(a) mRNA and prevents the translation of apolipoprotein(a) resulting in decreased apolipoprotein(a) production and lower level of circulating apolipoprotein(a).[20] Patients reported mild to moderate side effects such as myalgia, arthralgia, malaise, or injection site reactions. Pelacarsen is still in Phase III trial.

7. **Volanesorsen, Olezarsen**: Ultra-low-density lipoprotein, Chylomicron mostly contains triglycerides which is also a risk factor for CVD. Volanesoren and olezarsen binds to the apolipoproteinC (ApoC)-III mRNA and disrupts apoC-III translation. This results in lower level of apoC and subsequently lower level of chylomicrons and triglycerides.[21] Volanesoren has currently not been approved by FDA but it is administered subcutaneously 285 mg once a week.Olezarsen is in Phase III trial.

8. **Mipomersen:**Mipomersen is an antisense oligonucleotide that binds to human apolipoproteinB100 (apoB 100) mRNA and inhibits apoB 100 protein synthesis.This drug is approved by FDA for treating patients with homozygous familial hypercholesterolemia 200 mg once a week.[10]

9. **Lerodalcibep:** This drug inhibits PCSK9 by gene editing by using CRISPR-Cas9 techniques.Lerodalcibep half-life is 12-15 days. In Phase II study, Lerodalcibep 300mg once a month showed significant decrease in LDL-C level in patients.[22]

10. **Vaccines against PCSK9** : AntiPCSK9 vaccine is a liposomal immunogenic-fused PCSK9-tetanus peptide plus alum adjuvant (L-IFPTA). This vaccine showed promising results in two animal models. AntiPCSK9 is yet to go through clinical trial.[23]

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Materiovigilance Programme Of India (Mvpi): An Invigilator Of Patient Safety For Medical Devices

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Materiovigilance is the harmonized system of identification, collection, reporting, and analysis of any untoward occurrences associated with the use of medical devices and protection of patient's health by preventing its recurrences. Monitoring the safety of these devices enables dangerous devices to be withdrawn from the market and to eradicate faults in medical devices with the intention to constantly improve the quality of the devices and providing best service to patients and consumers with increased safety. ***Materiovigilance*** refers to medical devices as well as in-vitro diagnostics wherease ***pharmacovigilance*** refers to medicines.

Medical device is defined as any instrument, equipment, material or any other article used on its own or jointly,including software required for it to function correctly.

In order to monitor the safety on the use of medical devices in the country, Ministry of Health & Family Welfare, Govt. of India approved and commenced Materiovigilance Programme of India (MvPI) in the country. The MvPIwas launched on 6th July 2015 at Indian Pharmacopoeia Commission, Ghaziabad by the Drugs Controller General India (DCGI). Indian Pharmacopoeia commission (IPC) is an autonomous institution under Ministry of Health & Family welfare and also functions as National Coordination Centre for the Materiovigilance Programme of India. Sree Chitra Tirunal Institute of Medical Sciences &Technology (SCTIMST), Thiruvananthapuram functions as a National Collaborating Centre for MvPI. Technical support for the programme is provided by the Division of Healthcare Technology, a proposed WHO collaborating centre for priority medical devices and health technology policy in the National Health Systems Resources Centre.

The MvPI aims to collect the safety data in a systematic manner so that the recommendations and regulatory decisions on safe use of medical devices can be taken based on the data generated in Indian population. The programme is meant to monitor medical device associated adverse events (MDAEs) and create awareness among healthcare professionals about the importance of MDAEs reporting in India and monitoring the benefit-risk profile of the medical devices. It is also meant to generate independent, evidence-based recommendations on the safety of medical devices and further

to communicate the findings to all the key stakeholders in the country and the stakeholders of the Pharmacovigilance Programme of India (PvPI). Currently 174 Medical Device Adverse Event Monitoring (MDAEM) Centres have been identified in order to monitor the safety of medical devices across the country.

Reporting of Medical Device associated Adverse Events (MDAEs)

What to Report

All types of suspected Medical Device associated Adverse Events (MDAEs) can be reported whether they are serious or non-serious, known or unknown, frequent or rare regardless of an established causal relationship. Any adverse events related with the use of medical devices can be reported.

Where to Report MDAEs

The Healthcare professionals (clinicians, dentists, pharmacists, nurses) and patient/consumers can report MDAEs to SCTIMST or NCC. Duly filled Medical Device Adverse Event Reporting Form can be sent to Sree Chitra Tirunal Institute of Medical Science and Technology (SCTIMST), National Collaboration Centre-Materiovigilance Programme of India, Biomedical Technology Wing, Poojappura, Thrivananthapuram-695012, Kerala, India or can directly email the duly filled form to mvpi@sctimst.ac.in.

How to Report MDAEs

Medical Device Adverse Event Reporting Form can be downloaded from the website of IPC (www.ipc.gov.in) to report adverse event associated with medical devices. MDAEs can also be reported via PvPI helpline number (1800 180 3024) on weekdays from 9:00 am to 5:30 pm.

Whom to Report MDAEs

After filling the MDAEs reporting form it can be directly submitted to NCC or SCTIMST. In case if the report is submitted directly to SCTIMST, these reports are confirmed and validated by healthcare professionals, following the entry of the case report into Vigiflow and sent to NCC for further assessment. After receiving the case report at NCC, all the cases finally reviewed and assessed at NCC and committed to WHO-Uppsala Monitoring Centre (WHO-UMC). The submission of the MDAEs report does not have any legal implication on the reporters. The confidentiality of the patient's is strictly maintained and protected to the fullest extent. Healthcare providers are encouraged to report MDAEs for better understanding of the risk associated with the use of medical devices and to safeguard the patient's health.

Social Media : A Tool for Spreading Awareness on Pharmacovigilance

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The use of social media has grown a lot over the past few years and it has led to revolutionary shift in how people are communicating with one another today. Social media platforms and applications are fast becoming the go-to form of communication in this new era of Internet.

Within the last decade, social media has become one of the most powerful and easy sources for news updates, marketing, collaboration, networking and entertainment.

Pharmacovigilance practice has grown more over the past few years due to collection of higher data volumes, continuous evolving of regulations, increased influence of emerging markets and innovative technological advances. However, the use of internet and social media has progressed slower in medicinal safety/pharmacovigilance (PV) due to lack of awareness. This provides the healthcare industry with opportunities for appropriate and effective use of social media to make new, innovative and necessary changes in Pharmacovigilance system and to bridge the communication between patients and healthcare practitioners around the world.

Social media provides new methods that can help pharmaceutical companies to move away from the traditional systems of data collection and safety reporting methods towards more patient-centric models for reporting, analysing and monitoring of safety data.

Social media activities for Pharmacovigilance by pharmaceutical companies fall into three broad categories – listening (safety data reporting), engaging (follow up) and broadcasting (risk communication).Today, most of the Pharmacovigilance activities done using social media and internet are focused around screening of the social media sites and follow-up of reported data.

There are now multiple sites and applications by using which patient and consumers can report the data sitting in their homes using their computers and smartphones. Few such tools are WHO UMC pharmacovigilance, MedWatcher, PrimeVigilance, EudraVigilance etc. MedWatcher is a free tool that allows the patients and physicians to submit reports of adverse events following use of medication to the FDA via smartphone or tablet (MedWatcher.org). The main purpose of such websites and tools is to provide patients or healthcare professionals information on drugs, devices, interactions and other pharmaceutical information. In coming future these tools and websites will improve and grow in numbers and will be user friendly and help both the sponsors and regulators to interact to patients and consumers directly.

Pharmaceutical companies are now actively trying to engage to identify and understand the factors for developing a Pharmacovigilance social media strategy, which helps to create social media platforms to collect data to grow social media monitoring and reporting activities and further examine the progress and challenges of the different types of social media platforms which are being used.

Many companies are now engaging in providing training to their employees with social media guidance and best practices to facilitate effective safety reporting via social media. The employees are encouraged to report safety issues, adverse effects that they see on social media sites, where side effects are mentioned after taking drugs in a way which was prescribed to him/her.

Many users of social media often share their personal medical experiences online rather than to their physician or in clinical research for many reasons. Social media platform has the ability to act as an important source of adverse effects data as well as data on off-label use and impact of treatments on quality of life. If the pharmaceutical companies have the ability to use these social media data, it can transform these platforms into strategic Pharmacovigilance tools.

There are certain challenges and problems which might arise from these tools which needs to be taken care of. The information provided on social media is often less and incomplete. The credibility of the data provided needs to be checked always by following up with the patient. The most important problem that might arise and should be taken care of by the tool developers is the data safety and privacy as the data often contains personal data of the patient and also sometimes of the person reporting usually a patient's healthcare provider or a family member.

There are a number of additional challenges which needs to be addressed including: the identification of duplicate safety information with respect to data originating from digital media; use of multiple languages and how data collected in different languages relates to the standard data; data organising would also be required to reduce the risk of spreading rumours. On top of all this is the global diversity that is represented by social media and networking.

The FDA is currently trying to develop social media-based strategies, including Google search tools which will help in optimizing data gathering from communities and websites. Few similar tools like European research Project Trend Miner, WEBAE project (Web Adverse Events), etc. aims to develop a technical and policy framework for mining publicly available social media content and adopt methodologies and data mining algorithms applicable to social media content in order to find emerging, self-reported medical insights such as adverse effects associated with medicines and medical devices.

Although the new age tool of collecting and monitoring data from social media is growing rapidly, the traditional pharmacovigilance methods will certainly prevail. The combination of both these methods will help the pharmaceutical companies to generate more robust safety profiles. Also, systematic research should be conducted to investigate the feasibility of using social media for the pharmacovigilance system.

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Cosmetovigilance in India: Need of the day

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Cosmetovigilance is a new concept of safety monitoring of cosmetic products.The Federal Food, Drug, and Cosmetic (FD&C) Act defined cosmetics as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance".The products covered under this definition are skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup preparations, cleansing shampoos, permanent waves, hair colors, and deodorants, or any other substance intended for use as a component of a cosmetic product. The purpose of Cosmetovigilance is to collect, analyse and assess the adverse reactions/side effects occurring in consumers to identify any potential health risk.This allows to control or rule out potentially hazardous ingredients that may be present in cosmetic products.Initiated by the French health products safety agency as a part of pharmacovigilance system for cosmetics. Today, it is recognized globally as a concept of public health to address the safety of cosmetic products. Prior to July 2013, the safety of cosmetic products was not reviewed or approved. Since then new legislation has compelled the industry to provide data on products and ingredients before they can be marketed, however the efficacy and safety of cosmetic products are not reviewed or approved by national authorities before they are sold to the public.

In India, cosmetics are regulated as per Drugs and Cosmetics Act 1940 and Rules 1945. Part-XIII (regulates import and registration of cosmetics), part-XIV (manufacture of cosmetic for sale or for distribution) and part-XV (regulates labelling, packing and standards of cosmetics). Rule 145 and 135 prohibits the use and import of arsenic and lead containing compounds. Cosmetics containing mercury are prohibited as per provisions of rules 135A and 145D.However, the distinction between drugs and cosmetics is sometimes not clear. In India, the population is huge and similar is the market of cosmetics. Like drugs, adverse effects/side effects of cosmetics are commonly encountered.

In a study with 1609 participants, in a period of 5 years, 12.2% suffered from adverse effects of cosmetics and toiletries, out of which 63.3% were women and 36.7% were men. Most common complaint was itching (70.9%), dryness of skin (63.3%), and burning sensation in skin (50%). The duration of suffering ranged from 5.5 months to 3 years. Adverse reactions to traditional agents are also commonly reported, for example, kajal and kumkum dermatitis. Although lots of adverse effects occur at the population level, reporting to the regulatory authority is very low. A recent study published from Brazil noted that several common allergens and irritants are found in children's skin care products and

additionally were labeled as “dermatologist tested” or “hypoallergenic.”According to the Food and Drug Administration (FDA), hypoallergenic means “whatever a particular company wants it to mean” and ”manufacturers of cosmetics labeled as hypoallergenic are not required to submit substantiation of their hypoallergenicity claims to FDA.” This allows for unhindered marketing use of the terms “hypoallergenic,” “sensitive skin,” or “fragrance free” without any consequences. There are some organizations, such as the National Eczema Foundation, that perform testing on common skin care products and provide product recommendations, which have passed their testing. Unfortunately, until more consumer-friendly databases are easily available and easy to interpret, adverse skin reactions will continue to be common.

Cosmetovigilance then falls on the responsibility of the consumer and their physician. As consumers, we must be aware that drugs are not the only culprits for side effects but cosmetics like hair dyes, moisturizers,make up products and perfumes etc can also produce side effects. Family medicine physicians and primary care practitioners thus have an essential role to recognize adverse reactions induced by cosmetic products, and thus encourage patients for reporting. Increasing awareness on this new concept will be a valuable remark on global public health.Hence besides proper regulation of these agents, a proper vigilance system is also required to protect the health of the Indian population. Going with words of Vigan and Castelain, proper use of cosmetovigilance can help to control or rule out hazardous ingredients in cosmetics and thus improve our confidence on use of these agents.

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REMINISCENCES

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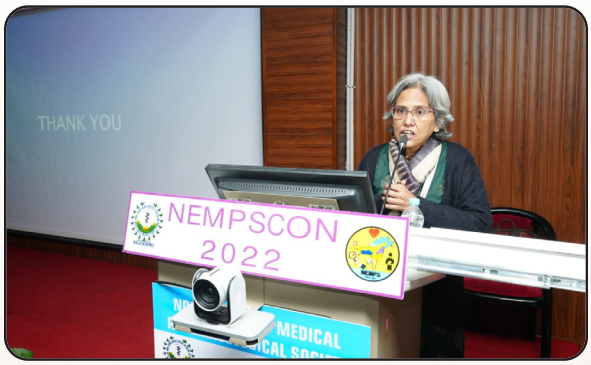

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