KASTURBA MEDICAL COLLEGE
MANIPAL
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THE DRUG TIMES

Newsletter from the Department of Pharmacology,

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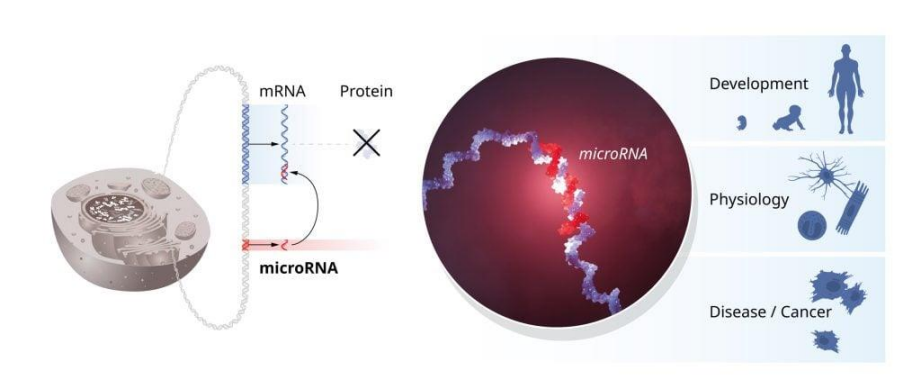
The current issue of THE DRUG TIMES provides information about Nobel prize in discovery of microRNA and its role in post-transcriptional gene regulation, smart insulin, made in India antibiotic, advances in the treatment of Schizophrenia, Phytovigilance, report on National Pharmacovigilance week celebration 2024 and USFDA's new drug approvals.

Nobel Prize 2024

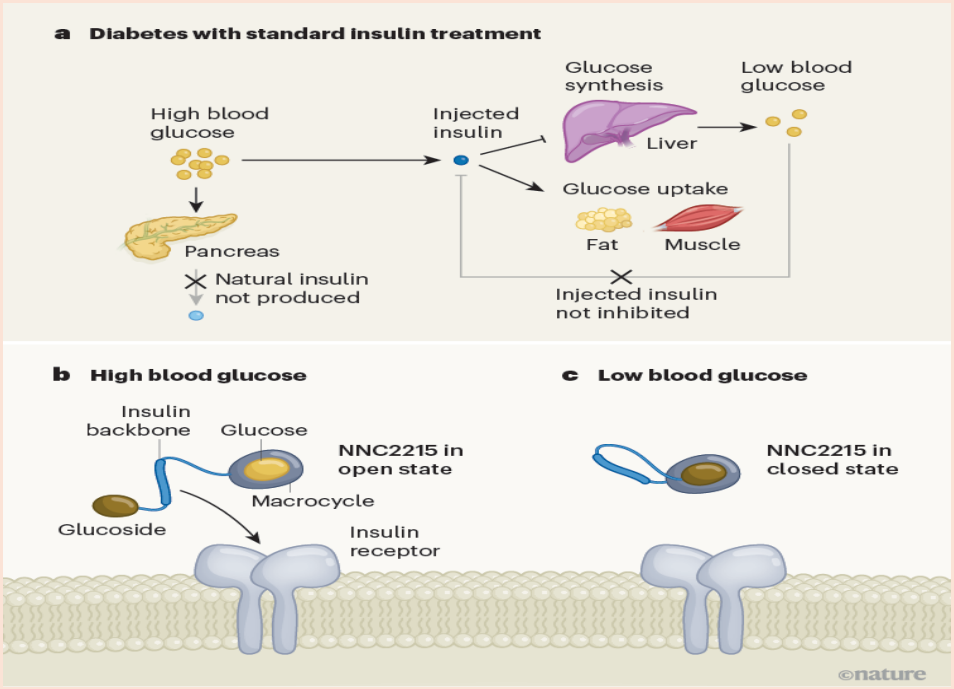
The 2024 Nobel Prize in Physiology or Medicine was awarded to Victor Ambros and Gary Ruvkun for "the discovery of microRNA and its role in post-transcriptional gene regulation". Chromosomes contain genetic information which provides instruction for all cells in our body. As the number of chromosomes in each cell is identical, the genetic information or the instructions in each cell will be the same. Then how do the differences arise say, between a muscle or nerve cell? The answer lies in microRNA, a new group of small RNA molecules, which are critical in gene regulation. They precisely regulate gene activity so that only the right set of genes is active in each specific cell type and thus each cell type is able to perform its specialized functions. More than 1,000 microRNAs are encoded by the human genome. Intriguingly, a single microRNA can regulate the expression of many different genes, and conversely, a single gene can be regulated by multiple microRNAs, thereby coordinating and fine-tuning entire networks of genes. Cells and tissues do not develop normally without microRNAs. Hence if gene regulation goes awry, it can lead to serious diseases such as cancer, diabetes, or autoimmunity. Thus the discovery of gene regulation by microRNA has been at work for millions of years but was first revealed to the world by Ambros and Ruvkun.



https://www.nobelprize.org/prizes/medicine/2024/press-release/

Can Insulin be smart?

Diabetes mellitus is a disease caused by deficiency of insulin due to insufficient production or impaired response ultimately leading to hyperglycaemia (high glucose concentration in the blood). Over half a billion people worldwide suffer from this disease which results in almost seven million fatalities annually. By controlling blood sugar, insulin helps avoid the numerous long-term consequences linked to hyperglycemia like heart disease, chronic kidney disease, stroke and blindness. From bovine and porcine insulin which were potentially antigenic and occasionally produced injection site lipodystrophy, we have now shifted to human insulin which are much safer. However, the most feared complication of insulin therapy is hypoglycaemia (low blood glucose). Injected insulin remains active even after glucose levels normalize, potentially lowering glucose levels which can cause anxiety, weakness and confusion at the least to even loss of consciousness, coma and death. In order to avoid this, many strategies have been tried to develop a system that can automatically regulate insulin activity based on the amount of glucose in a person's blood. Making a substance with deposits that release insulin in response to an increase in glucose levels has been a popular strategy. However, this method's irreversibility once insulin is released,is a major drawback.



The latest study, published in Nature, gets around this issue by modifying insulin itself using glucose-sensitive components. The compound is called modified insulin NNC2215. This modified insulin is made of 3 parts: an insulin backbone, a glucose-binding macrocycle (ring-shaped molecule) and a glucoside (glucose-derived molecule). At high glucose concentrations, glucose binds to the macrocycle, due to which the modified insulin enters an open conformation and binds to the insulin receptor exerting its biological effects. At low glucose concentrations, the glucoside occupies the macrocycle, thereby causing a closed conformation and lowering its activity. In short, the modified insulin molecule itself switches its activity on and off in response to glucose levels in the blood. In order to simulate the consequences of diabetes, the researchers tested NNC2215 in

rats and pigs that had received glucose infusions. When NNC2215 was administered into the animals, they discovered that it was just as effective as regular human insulin at lowering blood glucose levels. Additionally, they discovered that it could stop the reduction in blood glucose levels that happened with a contemporary insulin treatment. But the glucose rise during a glucose-tolerance test in diabetic rats was only partially covered by NNC2215. In order to prevent a significant rise in blood sugar levels after meals, people would probably also need to inject rapid-acting insulin, which begins to function in approximately 15 minutes, if NNC2215 were to be used therapeutically. With the potential to lessen the debilitating effects of diabetes, glucose-sensitive insulin is going to be a promising field of study.

https://doi.org/10.1038/s41586-024-08042-3

Imatinib – Novel Formulation

The FDA approved a novel liquid formulation of Imatinib, a tyrosine kinase inhibitor, on November 25, 2024. This new preparation is beneficial for treating Philadelphia chromosome-positive Chronic Myeloid Leukemia, Myelodysplastic Syndrome, and Myeloproliferative Disease. Although Imatinib was originally approved as Gleevec by Novartis in May 2001, the recently developed strawberry-flavored liquid formulation is specifically designed for individuals who have difficulty swallowing or require doses tailored to their body surface area. Remarkably, this new formulation does not need refrigeration, making it a patient-friendly alternative that can encourage compliance and adherence to therapy.

Additionally, this liquid formulation has been approved for the treatment of unresectable metastatic dermatofibrosarcoma protuberans and for Kit-positive Gastrointestinal Stromal Tumors (GIST). It also serves as an adjuvant treatment following the surgical resection of Kit-positive GIST.

Shorla Oncology announces FDA approval of IMKELDI (imatinib) oral solution, an oral liquid for the treatment of certain forms of leukemia and other cancers. News release. Shorla Oncology. Accessed November 25, 2024

FDA Approves Zepbound (Tirzepatide) for Obstructive Sleep Apnea

The FDA has approved Zepbound (tirzepatide) as the first medication specifically designed to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity. This groundbreaking approval provides a new option for managing OSA, which has traditionally relied on lifestyle changes or CPAP machines.

How It Works:
Zepbound targets hormone receptors to regulate appetite, helping reduce hunger and promote weight loss—a key factor in easing OSA symptoms.

Study Highlights:
In two studies involving 469 adults (without type 2 diabetes), participants who took Zepbound for 52 weeks experienced significant improvements in sleep apnea symptoms, with many achieving remission or milder forms of the condition.

Potential Side Effects:
Common side effects include nausea, diarrhea, and abdominal pain. Serious risks, like thyroid tumors (observed in animal studies), mean it's not suitable for those with certain thyroid conditions. Individuals with pancreatitis, kidney issues, or on specific medications should consult their doctor before use.

With its Fast Track and Breakthrough Therapy designations, Zepbound represents a major step forward for OSA treatment, offering new hope for better health and quality of life.

Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity [published correction appears in N Engl J Med. 2024 Oct 17;391(15):1464. doi: 10.1056/NEJMx240005].

Made in India Antibiotic - Nafithromycin

Nafithromycin is the country's first indigenously developed antibiotic aimed at tackling antimicrobial resistance(AMR). Nafithromycin, a first in class lactone ketolide has a novel chemical structure. Its effectiveness in comparison to other ketolide antibiotics is attributed to its dual action of binding to ribosomes that inhibit protein synthesis and also overcome resistance that are due to ribosomal protein mutations . It possess potent activity against various macrolide resistant strains of typical and atypical bacteria.

In clinical trials nafithromycin demonstrated efficacy and safety in treating community acquired bacterial pneumonia and acute bacterial skin and skin structure infections(ABSSI) This antibiotic is expected to improve patient outcomes and reduce healthcare costs associated with prolonged hospital stays and ineffective treatments. Its oral bioavailability with once daily dosing regimen and favourable tolerability profile makes it a valuable treatment option for respiratory infections. The drug has been developed by Wockhardt Limited, in collaboration with Biotechnology Industry Research Assistance Council (BIRAC) and is awaiting final approval for marketing from the Central

Drugs Standard Control Organization(CDSCO) representing a significant advancement in India's battle against AMR.

Bhawsar, S., Tadiparthi, R., Kayastha, A.K. et al. Nafithromycin (MIQNAF®): ultramodern lactone ketolide designed to treat community acquired bacterial pneumonia (CABP). Med Chem Res 33, 1715–1733 (2024). https://doi.org/10.1007/s00044-024-03281-5IRAC)

FDA New Drug Approvals

(Aug 2024 – Dec 2024)

Sl. No.	Drug Name	Active Ingredient	Approval date	FDA-approved use
1.	Nemluvio	Nemolizumab-ilto	12/8/2024	Prurigo nodularis
2.	Livdelzi	Seladelpar	14/8/2024	Primary Biliary Cholangitis (PBC)
3.	Niktimvo	Axatilimab-csfr	14/8/2024	Chronic Graft-versus-Host-Disease (cGVHD)
4.	Lazcluze	Iazertinib	19/8/2024	Non-small cell lung cancer
5.	Ebglyss	Lebrikizumab-lbkz	13/9/2024	Moderate-to-severe atopic dermatitis
6.	Miplyffa	Arimoclomol	20/9/2024	Niemann-Pick disease type C
7.	Aqneursa	Levacetylleucine	24/9/2024	Niemann-Pick disease type C
8.	Cobenfy	Xanomeline & trospium chloride	26/9/2024	Schizophrenia

9.	Flyrcado	Flurpiridaz F 18	27/9/2024	Evaluation of myocardial ischemia & infarction
10.	Itovebi	Inavolisib	10/10/2024	Locally advanced or metastatic breast cancer
11.	Hympavzi	Marstacimab-hncq	11/10/2024	Prevent or reduce haemophilia (A or B) -related bleeding
12.	Vyloy	Zolbetuximab-clzb	18/10/2024	Gastric or gastroesophageal junction adenocarcinoma
13.	Orlynvah	Sulopenem etzadroxil, probenecid	25/10/2024	uncomplicated Urinary Tract Infections (uUTI)
14.	Revuforj	Revumenib	15/11/2024	Relapsed or refractory acute leukaemia
15.	Ziihera	Zanidatamab-hrii	20/11/2024	Unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer
16.	Attruby	Acoramidis	22/11/2024	Cardiomyopathy of wild-type or variant transthyretin-mediated amyloidosis
17.	Rapiblyk	Landiolol	22/11/2024	Supraventricular tachycardia
18.	Iomervu	Iomeprol	27/11/2024	As a radiographic contrast agent
19.	Bizengri	Zenocutuzumab-zbco	4/12/2024	Non-small cell lung cancer & pancreatic adenocarcinoma
20.	Unloxcyt	Cosibelimab-ipdl	13/12/2024	Cutaneous squamous cell carcinoma
21.	Crenessity	Crinecerfont	13/12/2024	Classic congenital adrenal hyperplasia
22.	Ensacove	Ensartinib	18/12/2024	Non-small cell lung cancer
23.	Tryngolza	Olezarsen	19/12/2024	Familial chylomicronemia syndrome
24.	Alyftrek	Vanzacaftor, Tezacaftor & Deutivacaftor	20/12/2024	Cystic fibrosis
25.	Alhemo	Concizumab-mtci	20/12/2024	Prophylaxis of bleeding in Hemophilia A & B

https://www.fda.gov/drugs/novel-drug-approvals-fda/novel-drug-approvals-2024

Advances in the treatment of Schizophrenia: Xanomeline and Trospium Chloride as a Promising Substitute for Conventional Therapies

USFDA approved Xanomeline and Trospium chloride, a novel cholinergic combination medications to treat adult schizophrenia in Sept 2024. After decades of treatment that primarily relied on atypical and conventional antipsychotics, the new class was finally approved. Schizophrenia affects 24 million people worldwide, and the prevalence in adults is 1 in 222.

Schizophrenia patients often go through a cycle of stopping and switching treatments. According to studies, nearly 60% of individuals with schizophrenia experience unpleasant adverse effects or show partial improvement during therapy, and about 40% remain unresponsive. Traditionally, antipsychotic medications approved for the treatment of schizophrenia have depended on the dopaminergic and serotonergic pathways in the brain. However, adverse effects of these drugs including muscle dystonia's and other extrapyramidal side effects causes discontent among patients. This drug combination presents a new option for managing this challenging condition by utilizing a novel pathway.

Clinical studies have demonstrated the Xanomeline and Trospium chloride combination can reduce both the positive and negative symptoms of schizophrenia. The two clinical studies (NCT04659161 and NCT04738123) established the safety and efficacy of the drugs compared to placebo in adults with schizophrenia. The combination drugs, demonstrated reduction of positive and negative syndrome scale (PANSS) at week five. Further, the study found reduction in clinical global impression-severity score.

Mechanism of action: Xanomeline has agonistic action at muscarinic M1 and M4 in central nervous system and trospium is anticholinergic at M1, M2 and M3 receptors in periphery.

Pharmacokinetics: Xanomeline is metabolized by cyp450 enzymes including CYP2D6, CYP2B6, CYP1A2, CYP2C9, and CYP2C19 - as well as flavin monooxygenases (FMO1 and FMO3). Eliminated in urine with T1/2=5hr. Trospium is likely metabolized via ester hydrolysis and glucuronic acid conjugation, elimination in renals with T1/2=6hr.

Recommended dose and administration: Administered orally twice daily, one hour before or two hours after food. Treatment initiated with the dosage of 50 mg/20 mg capsule (Xanomeline 50mg+ Trospium chloride2 0mg) for two days. The dosage increased to 100 mg/20 mg capsule for five days with a maximum recommended dose of 125 mg/30 mg.

Adverse Events: Risk of urinary retention, hepatic impairment, decreased gastrointestinal motility, angioedema, tachycardia, urinary retention, dizziness, confusion, hallucinations, somnolence, dry mouth, constipation, dyspepsia.

Contraindications: Urinary retention, moderate or severe hepatic/renal impairment(eGFR <60mL/min), angioedema, untreated narrow-angle glaucoma.

Khandker R, Shepherd J, Chekani F, et al. Atypical Treatment Switches in Schizophrenia Patients: Drivers and Associated Outcomes. Neuropsychiatr Dis Treat. 2022 May 18;18:1057-1067. doi: 10.2147/NDT.S358392.

Diniz E, Fonseca L, Rocha D, et al. Treatment resistance in schizophrenia: a meta-analysis of prevalence and correlates. Braz J Psychiatry. 2023;45(5):448-458. doi: 10.47626/1516-4446-2023-3126 7.

Phyto vigilance: Ensuring Safety in Natural Therapies

Herbal medicines, long considered a cornerstone of traditional healthcare, are gaining popularity worldwide due to their perceived safety, cultural acceptability, and potential therapeutic benefits. The use of herbs today has been shaped by a blend of European, Chinese, Ayurvedic, and other traditional medicinal practices around the world. Despite their natural origins, herbal medicines are not devoid of risks. They can cause adverse reactions, interact with other drugs, or be contaminated, necessitating robust pharmacovigilance systems.

Why Pharmacovigilance for Herbal Medicines or Phytovigilance is Crucial?

Issue	Description	Examples
Adverse Reactions	Side effects range from mild allergic reactions to severe organ toxicity.	Aristolochic acid, found in traditional remedies, can cause **nephrotoxicity** and **carcinogenicity**.
Drug-Herb Interactions	Interact with conventional drugs, altering their pharmacokinetics or pharmacodynamics.	St. John's Wort induces **CYP3A4 enzymes**, reducing the efficacy of oral contraceptives.
Quality Issues	Contamination, adulteration, or incorrect identification of plant species.	Heavy metal contamination, such as **lead and mercury**.
Lack of Regulation	Variability in quality, potency, and safety as there is no rigorous testing	Aloe vera gel labeled products contained little to **no active Aloe constituents**

Some of the challenges in Phytovigilance are adverse events related to herbal medicines are often underreported due to the misconception that "natural" equates to "safe." Herbal products contain multiple active constituents, making it challenging to identify the causative agent. The diverse nomenclature and regional variations in herbal medicine names complicate pharmacovigilance efforts. A lack of clinical trials and robust safety data for many herbal products hampers evidence-based pharmacovigilance.

Strategies to Enhance Herbal Pharmacovigilance

1. Encourage healthcare providers, consumers, and manufacturers to report adverse events associated with herbal medicines, including details on the dosage, duration of use, and concomitant medications.
2. Regulation on standardization, labeling, and quality assurance of herbal medicines.
3. Public awareness about the potential risks, emphasizing the importance of consulting healthcare professionals before use.
4. Integration with conventional pharmacovigilance, collaboration between traditional medicine practitioners and conventional healthcare providers can bridge knowledge gaps.
5. Research and evidence generation by conducting systematic studies on the safety, efficacy, and interactions of herbal medicines. These studies should include post-marketing surveillance to track real-world usage.

While herbal medicines hold immense therapeutic potential, ensuring their safe use is a shared responsibility of healthcare providers, regulators, manufacturers, and consumers. A robust pharmacovigilance system tailored to the unique challenges of herbal medicines can mitigate risks and foster trust in these age-old remedies.

Wal P, Wal A, Gupta S, Sharma G, Rai A. Pharmacovigilance of herbal products in India. J Young Pharm. 2011 Jul;3(3):256-8. doi: 10.4103/0975-1483.83780

Memişoğlu M, Otlatıcı G. The Safety of Herbal Medicines (Phytovigilance) from Community Pharmacists' Perspective: A Cross-Sectional Study. Turk J Pharm Sci. 2022 Jun 27;19(3):280-286. doi: 10.4274/tjps.galenos.2021.77178.

Pharmacovigilance Week Celebration 2024

The 4th National Pharmacovigilance Week was celebrated by the Adverse Drug Reaction Monitoring Centre (AMC) Department of Pharmacology, Kasturba Medical College, Manipal, with a series of activities aimed at raising awareness and strengthening adverse drug reaction (ADR) reporting among healthcare professionals and patients. Event flyers and posters were released and displayed in the department to promote the celebration. The AMC participated in the national-level competition conducted by PVPI on the theme, “You Share, We Care: Know How to Report Adverse Drug Reactions,” which was highlighted in a poster shared via email and on social media platforms. A patient education program aimed at promoting ADR reporting was successfully conducted in the Medicine and Dermatology OPDs at Kasturba Hospital, Manipal, empowering patients to take an active role in ensuring medication safety. An engaging awareness session on pharmacovigilance and the importance of ADR reporting was conducted specifically for second-year MBBS students, fostering their understanding of drug safety practices. An academic and industry collaboration was done by arranging a guest talk on Signal Detection in Pharmacovigilance which was delivered by Dr. Bino Ebin Singh, Medical Advisor, and Deputy QPPV at Exeltis, Mumbai, and attended by the faculty and post-graduates of Kasturba Medical College, Manipal. Community-level initiatives featured awareness sessions on ADR reporting, informative poster displays, and sensitization programs for healthcare providers at PHC Kumbashi and CHC Hebri in Karnataka. To foster engagement, a range of competitions were organized, including an essay competition on the theme “Strengthening ADR Reporting for Patient Safety,” along with quizzes and interactive games. The celebrations culminated in a formal valedictory function.

THE DRUG TIMES

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"Knowledge is power.

Sharing knowledge is the key to unlocking that power."

-Martin Uzochukwu