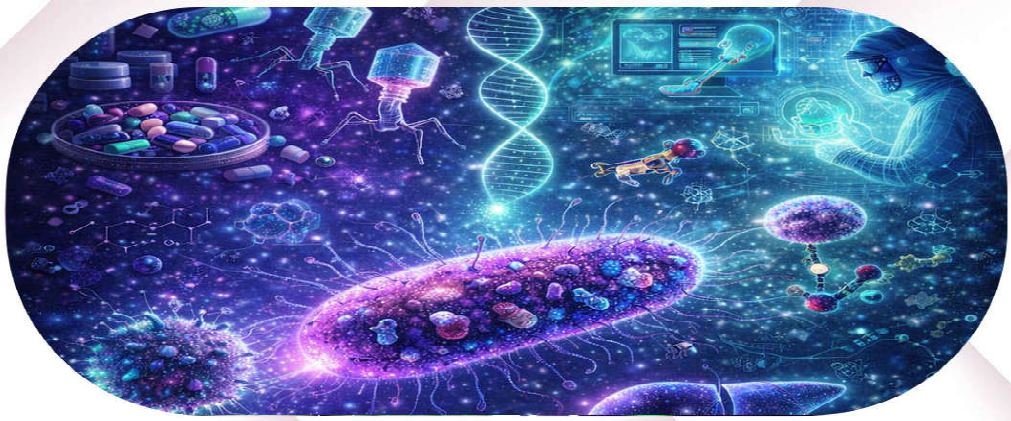
NEMPSule

THE E-BULLETIN OF NEMPS

North Eastern Medical Pharmacological Society



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NEMPS
(NORTH EASTERN MEDICAL PHARMACOLOGICAL SOCIETY)

Design by **Ashish Debnath** on behalf of **Creative Design,** Dibrugarh, Assam

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Obituary

FOREVER IN OUR HEARTS

DR. ANJU LAMA SAIKIA

Born : 14th March, 1975 ~ Departed : 1st November, 2025

"Those we love don't go away,
They walk beside us every day,
Unseen, unheard, but always near,
Still loved, still missed and very dear."

Your thoughts, words & deeds will
continue to inspire us... Rest in Peace.

~ Editor, NEMPS
on behalf of entire NEMPS family

MESSAGE FROM THE PRESIDENT

It is with great pride and enthusiasm that I present this edition of the NEMPSULE e-bulletin. This e-bulletin stands as a testament to the intellectual curiosity, creativity, and dedication of our members, who continue to strive for excellence in learning, research, and service.

NEMPSULE is more than a publication—it is a platform for ideas, dialogue, and innovation. Through the articles, reflections, and studies featured in this issue, readers are invited to engage with diverse perspectives and thoughtful insights that address both academic interests and real-world challenges. Each contribution reflects careful effort, critical thinking, and a commitment to growth.

I commend the editorial board, contributors, and advisors for their hard work, discipline, and teamwork in bringing this e-bulletin to life. Their commitment ensures that NEMPSULE remains a credible and inspiring voice within our academic community.

As we move forward, may this e-bulletin continue to encourage inquiry, integrity, and collaboration. I hope this edition inspires readers to think deeply, question boldly, and contribute meaningfully to their fields and to society.

Thank you for your continued support of NEMPSULE.

With best regards,

Dr. B.K. Bezbaruah
President, NEMPS

MESSAGE FROM THE
GENERAL SECRETARY

"Share your knowledge. It's the only way to achieve immortality."

- Dalai Lama

Dear colleagues and the members of the North Eastern Medical Pharmacological Society (NEMPS), a warm welcome and congratulations on the publication of the latest issue of NEMPSULE, the official bulletin of NEMPS.

I find immense pleasure in witnessing NEMPS take remarkable leap in disseminating information and the best advancements in the field of Pharmacology. Through its regular publication of insightful bulletins, NEMPS has sparked a deep interest in young minds and inspired my fellow pharmacologists to engage more meaningfully with the subject.

I would like to thank and congratulate the editor Dr. Gayatri Sarma, the members of the scientific committee, Dr. Meghali Chaliha and Dr. Chinmoyee Deori on successful publication of NEMPSULE. I would also like to extend my gratitude to all the authors for their contribution, without whom this issue of NEMPSULE wouldn't have seen the light of the day.

Swapnanil Gohain

Dr. Swapnanil Gohain
General Secretary, NEMPS

From The Desk of The Editor

"In the New Year, never forget to thank your past years because they enabled you to reach today! Without the stairs of the past, you cannot arrive at the future."

- Mehmet Murat Ildan

Season's greetings and best wishes for 2026 ! As we embrace a fresh New Year , bidding adieu to the old, it is indeed imperative that we pause a moment in introspection of our accomplishments in the preceding year. It has been two years since I took up responsibility as the founder editor of the NEMPSule; and the journey since then, though strenuous, has been extremely enlightening and fulfilling. The NEMPSule, the official e-bulletin of the North Eastern Medical Pharmacological Society (NEMPS), is more than an assemblage of articles: it is a reflection of our shared vision, collective creativity and unwavering commitment to excellence. Each contribution echoes the spirit of curiosity, resilience and innovation that drives us forward even in the face of challenges and impediments.

As the year 2026 ushers in bringing with it renewed hopes, dreams and aspirations, I, on behalf of NEMPS, take immense pride in presenting this edition of the NEMPSule. The previous four issues of the e-bulletin have been warmly accepted and appreciated and I am sure the present issue will be equally successful in keeping you awestruck till the last pages. The contribution of articles to the NEMPSule , this time, have been overwhelming and I take this opportunity to thank all the contributors from the deepest core of my heart.

This edition of NEMPSule boasts of some amazing articles like the role of Hypoxia inducible factor-prolyl hydroxylase inhibitors in anemia of chronic kidney disease, Digital Pills in pharmacotherapy and Role of digital therapeutics in healthcare system. We also have some interesting articles on Neurobiological perspective on digital behaviours and health, Pharmacomicrobiomics, Ecopharmacology, Apomorphine and Evolution of therapeutic strategies in Pharmacology. There is an article glorifying the role of Pharmacology in the betterment of human existence while another article stresses on the significance of deprescribing of Proton Pump Inhibitors.

On the recent advances realm, there ia an article on Zavegepant: a novel intranasal CGRP-antagonist for acute attack of migraine and another highlighting the recent advances in antimicrobials. A case report on Olanzapine- induced DRESS syndrome and an article depicting the reflections of a resident pharmacologist on the scope and challenges encountered during District Residency Program (DRP) posting, adds variety to the Contents section of the bulletin.

I extend my deepest gratitude to all the contributors and the readers of this e-bulletin for their unwavering support. I also thank the President, NEMPS, Dr. B. Bezbaruah Sir for his persistent guidance and mentorship. I thank the General Secretary, NEMPS, Dr. Swapnanil Gohain, as also the members of the scientific committee, Dr. Meghali Chaliha and Dr. Chinmoyee Deori for their support and advice.

May the New Year empower us to transform ideas into action and aspirations into lasting impact. In the words of Eleanor Roosevelt - "The future belongs to those who believe in the beauty of their dreams" and we, at NEMPS, dream to achieve big !

Warm regards,

Dr.Gayatri Sarma
Editor NEMPSule.

Dr. Anju Lama Saikia- A tribute

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Dr Anju Lama Saikia, aged 50 years , of Jorhat, Assam, passed away on 1st Nov 2025. She left behind her two beautiful kids and a lovable husband. I pray, that God gives them strength to move forward in life.

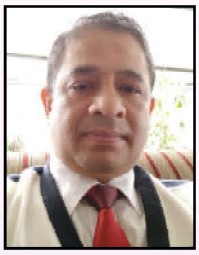
Anju was known for her warm, friendly personality and her instinctive readiness to help anyone in need. Whether offering a comfort word, a practical solution, or simply her quite presence, she had a way of making people feel cared for and understood.

She was born on 14th March 1975 and did her schooling in Arunachal Pradesh. I met her only in the year 2004, when I came to Assam Medical College, Dibrugarh to do my post-graduation. Even though, it was a three-year session where we were together, Anju became my close friend forever. After postgraduation, we went in different directions, but she was there for me whenever I needed her. She was very hardworking in the Department and a loving mother and wife. Despite her illness, she never neglected her duty till the end. Anju's optimistic outlook sometimes amazed me. And I believe, because of her optimisms, family will overcome the great loss one day and move forward. Her absence leaves an ache that words cannot fully capture, but her memory will continue to guide and comfort all who loved her.

She will be deeply missed by her friends, colleagues, neighbours, and all who had the privilege of knowing her. May her soul rest in peace and stay happy wherever the soul goes.

■■■

Role of Hypoxia Inducible Factor-Prolyl Hydroxylase Inhibitors (HIF-PHIs) in anemia of Chronic Kidney Disease.



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Introduction:

Anemia plays an important role in the progression of Chronic Kidney Disease (CKD) because it worsens the quality of life and increases the risk of cardiovascular complications. The causes of anemia in CKD patients are deficiency of endogenous erythropoietin (EPO), absolute iron deficiency, resulting from blood loss or impaired iron absorption, and functional iron deficiency, resulting from the impaired release of iron from its stores following elevated hepcidin values (1). It is also associated with chronic inflammation, co-morbidities (e.g., diabetes, cancer), inhibition of the bone marrow response to EPO by uremic toxins and vitamin B12 and folic acid deficiencies (2).

Erythropoiesis-stimulating agents (ESAs) along with iron are the standard treatment for anemia in chronic kidney disease (CKD) since 1989. They increase haemoglobin (Hb) levels, lessen the need for transfusion, and improve patients' quality of life (3). However, treatment to higher Hb targets in clinical trials has resulted in higher rates of thrombosis, cerebrovascular events, cardiovascular events and higher mortality (4). Also, ESAs are used parenterally & so inconvenient for the patients.

So, investigators are in search of an anemia therapy agent that would increase Hb levels, improve quality of life, reduce transfusion requirements, and avoid adverse events. HIF-PHIs are new oral agents for anemia in CKD. These medicines increase the production of endogenous EPO, prevent inflammation and optimize iron mobilization from its stores by influencing the HIF-PH system (5).

Mechanism of action:

In normoxic conditions, HIF-α is hydroxylated on proline residues by HIF-Prolyl Hydroxylase. Prolyl-hydroxylated HIF-α is then degraded easily by the proteasomal degradation system.

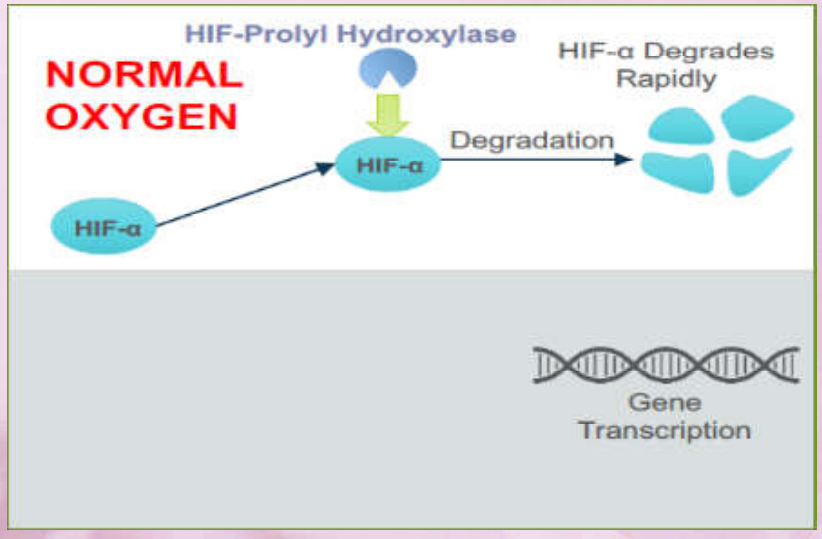

Fig 1: Fate of Hypoxia Inducible Factor-a (HIF-α) in normoxic condition (6).

In hypoxic conditions or during HIF-PHI treatment, HIF α is not degraded and translocates to the nucleus and forms a heterodimer with HIF-ß. The heterodimer binds to hypoxia-response elements and stimulates erythropoietin (EPO) production, iron absorption and iron transport to the bone marrow. They also decrease the synthesis of hepcidin.

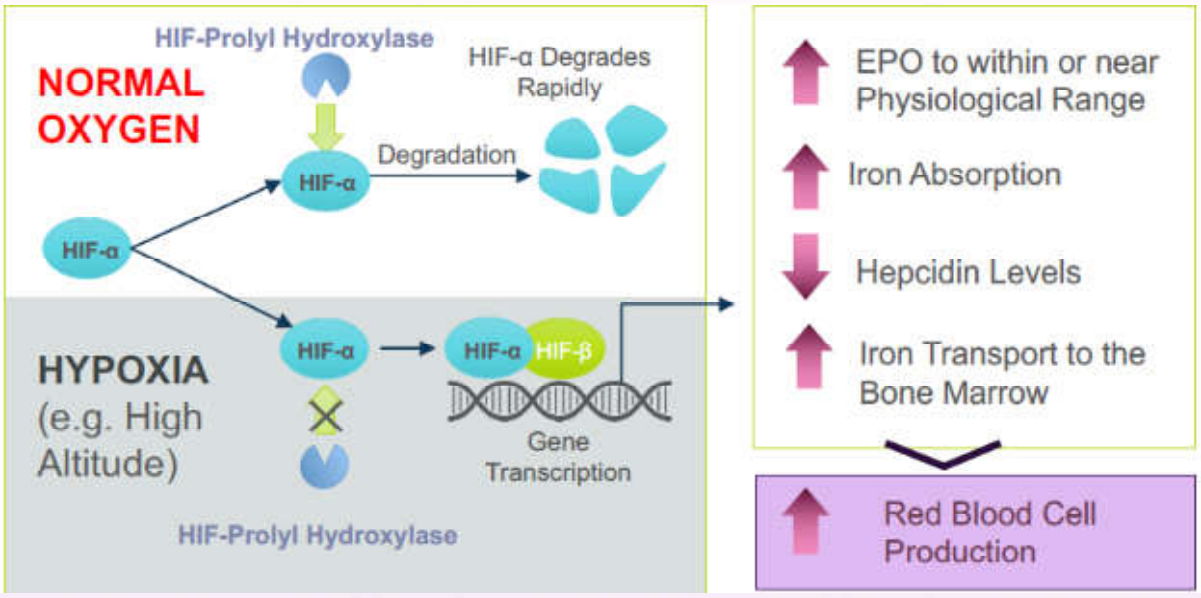

Fig 2: Role of HIF-α in hypoxic condition or during HIF-PHI treatment (6).

Effect on iron absorption & mobilization: In the intestine, Fe3+ is reduced to Fe2+ by duodenal cytochrome b reductase 1 (DCYTB), and then Fe2+ enters intestinal cells via divalent metal transporter 1 (DMT1). Intracellular Fe2+ exits cells through ferroportin (FPN), and then Fe3+ is used for erythropoiesis.

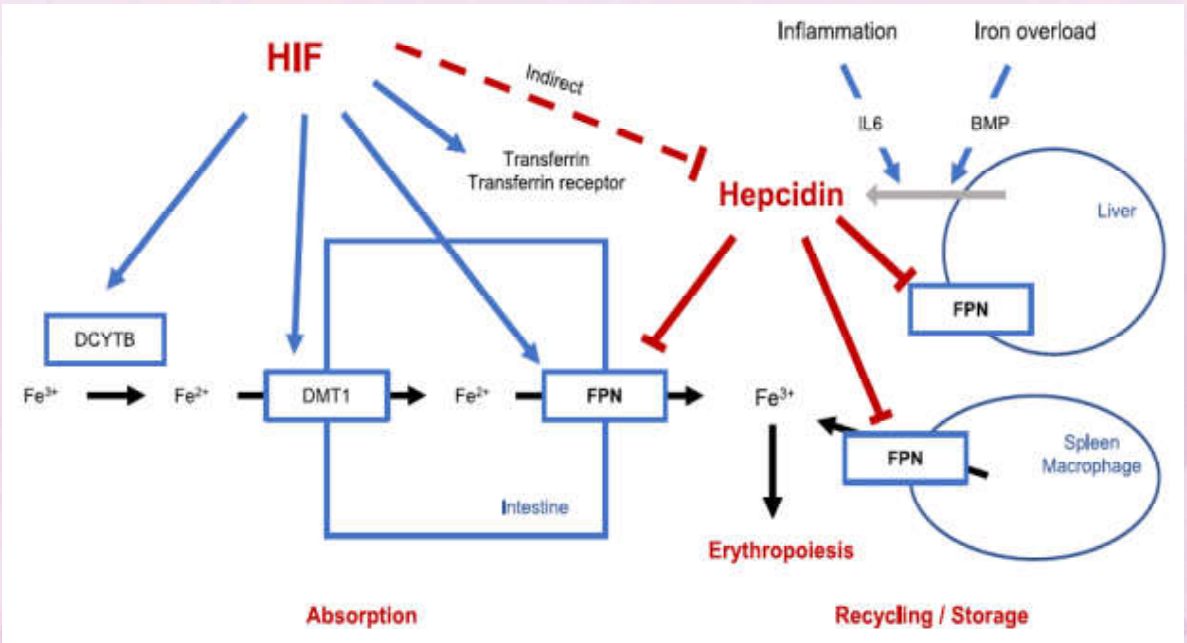

Fig 3: Effect of HIF on iron absorption and mobilization (7).

DMT1, DCYTB, FPN, transferrin and transferrin receptor have been demonstrated to be target genes of HIF. Stabilizing HIF is associated with reduced levels of hepcidin. Hepcidin suppression increases FPN, which enhances iron absorption and utilization.

Approved HIF-PHIs - Formulations, frequency & Indications:

The different HIF-PHIs, their region of approval, their dosage forms with strength, frequency of administration and their indication are depicted in the table below:

Generic Name	Region of Approval	Formulation & Frequency	Indication
Roxadustat	Japan, China, EU, UK, Chile	20, 50, 70, 100, 150 mg tablets 3 times weekly	Anemia in CKD (dialysis and non-dialysis)
Daprodustat	Japan, US (2023), EU, UK	1, 2, 4, 6 mg tablets Once daily	Anemia in CKD (dialysis and non-dialysis)
Vadadustat	Japan, EU (2023), UK	150, 300 mg tablets Once daily	Anemia due to CKD (mainly dialysis)
Enarodustat	Japan	1, 2, 4 mg tablets Once daily	Anemia in CKD (dialysis and non-dialysis)
Molidustat	Japan	5, 12.5, 25, 50 mg tablets Once daily	Anemia in CKD (dialysis and non-dialysis)
Desidustat	India	25, 50, 75, 100 mg tablets 3 times weekly	Anemia in CKD (dialysis and non-dialysis)

Table 1: Different approved HIF-PHIs.

HIF-PHIs in Treating Renal Anemia:

1. The HIF-PHIs effectively increase Hb in both the Non-dialysis dependant CKD (NDD-CKD) and Dialysis dependant CKD (DD-CKD).
   A total of 4277 patients with NDD-CKD were randomized (roxadustat, n=2391; placebo, n=1886). Roxadustat was more effective than placebo at increasing Hb in patients with NDD-CKD and anemia, while decreasing transfusion rate [Fig 4] and being non-inferior to placebo with respect to risk of major adverse cardiovascular events (MACE) (8).

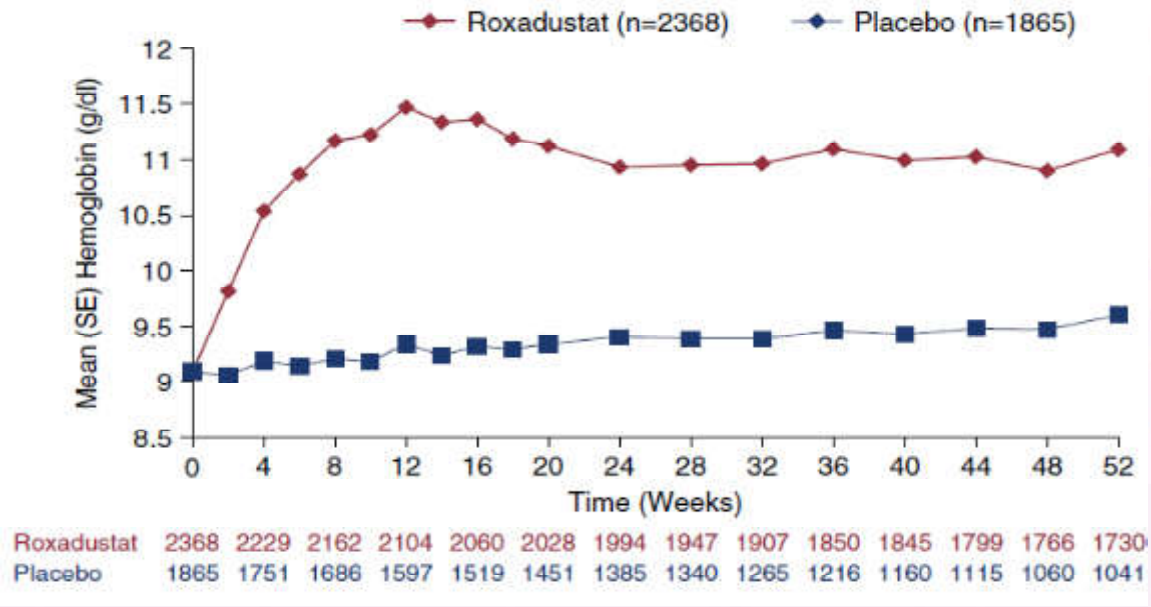

Fig 4: Hemoglobin levels in the NDD-CKD patients over time (weeks 0–52).

2. The different HIF-PHIs have shown their non-inferiority to ESAs in improving and maintaining Hb levels in different randomized clinical trials. A Cochrane database Meta analysis included 51 studies randomizing 30,994 adults and these studies compared HIF stabilizers to either placebo or an ESA. The Meta analysis showed that there was no statistical difference in improving Hb level by HIF-PHIs as compared to ESA [Fig 5].

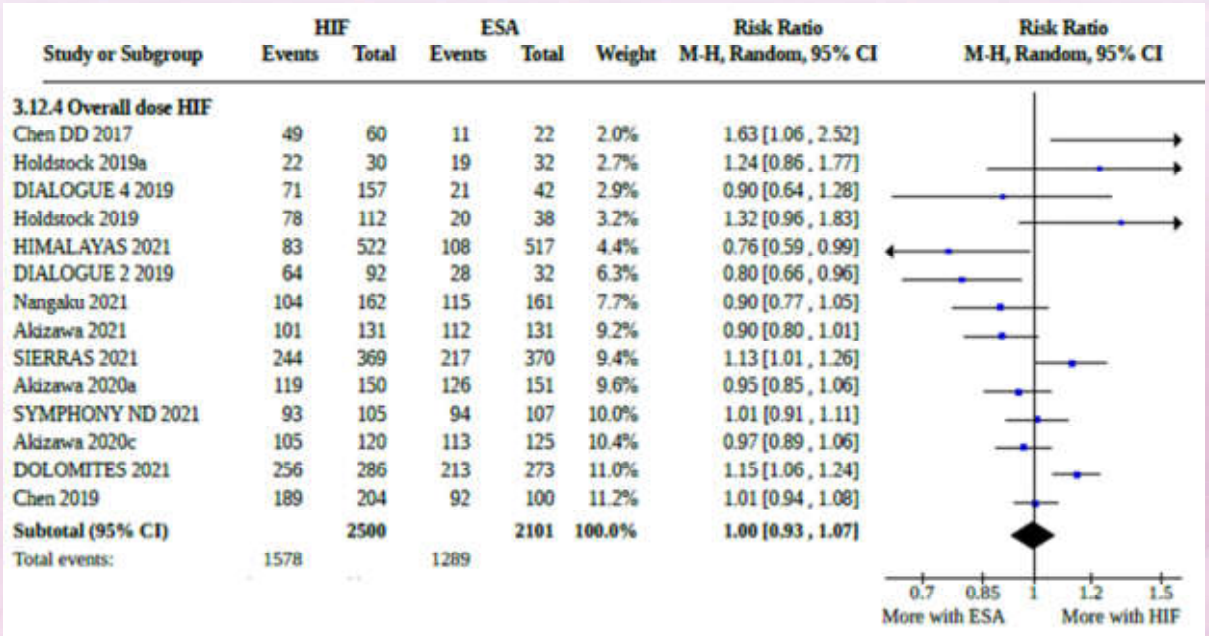

Fig 5: Forest plot showing HIF-PHIs versus ESA in reaching target haemoglobin (9).

Major Advantages of HIF-PHIs:

1. HIF-PHIs are orally effective.
2. They produce endogenous EPO with maintenance of its physiological level.
3. They improve iron metabolism.
4. HIF-PHIs are effective in elevated inflammatory states and have pleotropic effects.
5. They have potential cholesterol lowering effect.

Safety profile of HIF-PHIs:

1. **All-cause mortality:** A meta-analysis of 46 studies including 27,338 patients across all the currently available HIF-PHIs found no significant differences in mortality compared with placebo or ESAs in both the DD-CKD and NDD-CKD subgroups (10).
2. **Cardiovascular safety:** The majority of phase 3 trials demonstrated non-inferiority of HIF-PHIs to placebo and ESA therapy for major cardiac events in NDD-CKD and DD-CKD patients (11).
3. **Thrombotic events:** In a pooled analysis of trials in NDD-CKD patients, roxadustat was associated with an increased incidence of arteriovenous (AV) access thrombosis (1.5 versus 0.9 per 100 patient-years), deep vein thrombosis (DVT) (0.7 versus 0.2 per 100 patient-years) and pulmonary thromboembolism (0.3 versus 0.1 per 100 patient-years) compared with placebo (12).
4. **Retinopathy:** The neo-vascularization effect of HIF-PHIs has been postulated to worsen ocular pathology, such as diabetic retinopathy (13). For this reason, most of the phase 3 clinical trials excluded patients with severe retinopathy. The pooled Japanese daprodustat analysis of trials in NDD-CKD and DD-CKD patients found no increased risk for retinal events or aggravation of underlying retinal disease (14). The SYMPHONY-ND study demonstrated increased Vascular Endothelial Growth Factor (VEGF) levels and increased retinal adverse events of enarodustat compared with ESAs (3.7% versus 0.9%) (15).
5. **Hypertension:** Although hypertension is an established complication of ESA therapy, comparator trials of HIF-PHIs versus ESAs in NDD-CKD patients have not shown significant differences in the development of hypertension (16). A meta-analysis of NDD-CKD roxadustat trials noted a higher incidence of hypertension in the roxadustat group compared with placebo [RR 1.37 (95% CI 1.13–1.65)] (12) . However, another meta-analysis of NDD-CKD patients has reported a lower risk of hypertension with HIF-PHIs compared with ESAs [RR 0.89 (95% CI 0.81–0.98)] (17).
6. **Hyperkalemia:** Hyperkalaemia is reported in different clinical trials.
7. **Liver injury:** Reports of liver injury is uncommon in clinical trials.

Suggestions for clinical practice (18):

Consider use of HIF-PHI:

1. Patient preference for oral treatment (accessibility, convenience, ease of administration, no storage requirements).
2. Challenges to starting or receiving ESAs (needle-phobia, unable to self-administer ESAs).
3. Challenges to administer iron therapy or when increased iron availability is desired.
4. ESA hypo responsiveness or intolerance.
5. Chronic inflammatory states (CRP =3 mg/l).

Use with caution:

1. Vascular access with a high risk of thrombotic complications.
2. Retinals disorders - Consider close ophthalmology follow-up if used in retinal disorders.
3. Autoimmune diseases.
4. History of cured malignancy or without recurrence for at least 5 years.
5. Kidney transplant recipients.

Avoid or use with extreme caution:

1. Patient with a cardiovascular or thrombotic event in the previous 3 months.
2. History of malignancy in the last 5 years.
3. Polycystic kidney disease.
4. Untreated proliferative diabetic retinopathy, macular degeneration and retinal vein occlusion.
5. Idiopathic pulmonary arterial hypertension.

Administration key points:

1. Ensure adequate iron stores prior to initiating treatment (ferritin >100 µg/l, TSAT >20%).
2. Individualize dose to achieve and maintain target Hb levels of 10–12 g/dl.

Monitoring key points:

1. Avoid rapid rises in Hb, e.g. >2 g/dl over 4 weeks, or very high Hb levels (>12 g/dl) because these can be associated with an increased risk of thrombotic complications. In the case of Hb overcorrection, consider treatment discontinuation for Hb levels >13 g/dl and dose decreases for Hb levels of 12–13 g/dl.
2. Monitor haemoglobin levels at least monthly until the target haemoglobin level of 10–12 g/dl is achieved and stabilized, thereafter, as clinically indicated.
3. Monitor potassium and liver function tests.

References:

1.Pergola PE, Fishbane S, Ganz T. Novel oral iron therapies for iron deficiency anemia in chronic kidney disease. Adv. Chronic Kidney Dis 2019; 6: 272–91.

2.Gluba-Brzóska A, Franczyk B, Olszewski R, Rysz J. The influence of inflammation on anemia in CKD patients. Int J Mol Sci 2020; 21: 725.

3.Stone WJ, Graber SE, Krantz SB, et al. Treatment of the anemia of predialysis patients with recombinant human erythropoietin: a randomized, placebo-controlled trial. Am J Med Sci 1988; 296(3) : 171-79.

4.Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006; 355(20):2085-98.

5.Kurata Y, Tanaka T, Nangaku, M. Hypoxia-inducible factor prolyl hydroxylase inhibitor in the treatment of anemia in chronic kidney disease. Curr Opin Nephrol Hypertens 2020; 29: 414–22.

6.Locatelli F, Fishbane S, Block GA. Targeting Hypoxia-Inducible Factors for the Treatment of Anemia in Chronic Kidney Disease Patients. Am J Nephrol 2017;45:187-99.

7. Li J, Haase VH, Haoa CM. Updates on Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors in the Treatment of Renal Anemia. Kidney Dis 2023; 9:1–11.

8.Provenzano R, Szczech L, Leong R et al. Roxadustat for CKD-Related Anemia; CJASN 16: 1190–1200, August, 2021

9.Natale P, Palmer SC, Jaure A et al. Hypoxia-inducible factor stabilizers for the anemia of chronic kidney disease. Cochrane Database Syst Rev 2022; 8: CD013751.

10.Takkavatakarn K, Thammathiwat T, Phannajit J et al. The impacts of hypoxia-inducible factor stabilizers on laboratory parameters and clinical outcomes in chronic kidney disease patients with renal anemia: a systematic review and metaanalysis. Clin Kidney J 2023; 16:845–58.

11.Fishbane S, El-Shahawy MA, Pecoits-Filho R et al. Roxadustat for treating anemia in patients with CKD not on dialysis: results from a randomized phase 3 study. J Am Soc Nephrol 2021;32:737–55. https://doi.org/10.1681/ASN.2020081150.

12.Provenzano R, Szczech L, Leong R et al. Efficacy and cardiovascular safety of roxadustat for treatment of anemia in patients with non–dialysis-dependent CKD: pooled results of three randomized clinical trials. Clin J Am Soc Nephrol 2021;16:1190–200. https://doi.org/10.2215/CJN.16191020.

13.Portolés J, Martín L, Broseta JJ et al. Anemia in chronic kidney disease: from pathophysiology and current treatments, to future agents. Front Med (Lausanne) 2021;8:642296. https://doi.org/10.3389/fmed.2021.642296.

14.Xiong L, Zhang H, Guo Y et al. Efficacy and safety of vadadustat for anemia in patients with chronic kidney disease: a systematic review and meta-analysis. Front Pharmacol 2022;12:795214. https://doi.org/10.3389/fphar.2021.795214.

15.Akizawa T, Nangaku M, Yamaguchi T et al. A phase 3 study of enarodustat in anemic patients with CKD not requiring dialysis: the SYMPHONY ND study. Kidney Int Rep 2021;6:1840–9. https://doi.org/10.1016/j.ekir.2021.04.037.

16.Agrawal D, Varade D, Shah H et al. Desidustat in anemia due to non-dialysis-dependent chronic kidney disease: a phase 3 study (DREAM-ND). Am J Nephrol 2022;53:352–60. https://doi. org/10.1159/000523961.

17.Zheng Q, Wang Y, Yang H et al. Cardiac and kidney adverse effects of HIF prolyl-hydroxylase inhibitors for anemia in patients with CKD not receiving dialysis: a systematic review and meta-analysis. Am J Kidney Dis 2023;81:434–445.e1. https: //doi.org/10.1053/j.ajkd.2022.09.014.

18.Stoumpos S, Crowe K, Sarafidis P et al. Hypoxia-inducible factor prolyl hydroxylase inhibitors for anaemia in chronic kidney disease: a clinical practice document by the European Renal Best Practice board of the European Renal Association. Nephrol Dial Transplant 2024; 39: 1710–30.

Digital Pills in Pharmacotherapy: Promise, Pitfalls, and Ethical Challenges

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Introduction

Medication non-adherence, the failure to follow prescribed timing, dosage, and duration, critically undermines pharmacotherapy, affecting over 50% of patients with chronic diseases (1,2). This leads to avoidable disease progression, drug resistance, and increased healthcare costs (3). Traditional adherence assessments like self-report and pill counts are indirect and biased. Digital adherence tools, including reminders and video observation, aim to address this. Digital pills represent a significant leap forward by providing direct, objective verification of medication ingestion, moving beyond proxy measures like container opening (4). Pioneered by Proteus Digital Health, the field reached a milestone with the 2017 FDA approval of Abilify MyCite, an aripiprazole tablet with an ingestible sensor for psychiatric conditions (5,6). Platforms like the ID-Cap system have since expanded the technology's application to infectious and chronic diseases (7).

Technology and Components

A digital pill system integrates three core elements: an ingestible sensor, a wearable receiver, and a digital platform (8,9). The sensor, constructed from biocompatible metals like copper and magnesium, acts as a miniature galvanic cell. Upon reaching the acidic gastric environment, gastric fluid activates the cell, generating a brief, low-power radio signal with a unique ingestion identifier (9,10). This signal is captured by a wearable patch, which records the timestamp and transmits the data via Bluetooth to a smartphone or cloud-based platform for patient or clinician review (8). While this electrochemical method is dominant, alternative technologies using RFID, optical, or pH-sensitive mechanisms are under exploration (11). Key technical hurdles include ensuring sensor safety and biocompatibility, reliable activation across variable gastric conditions, consistent signal transmission through diverse body types, and seamless integration with digital health ecosystems (10).

Clinical Applications and Evidence

Mental health is the most established application. Studies on Abilify MyCite confirm

reliable ingestion detection and safety in schizophrenia and bipolar disorder (6). However, patient reactions are mixed; some appreciate enhanced self-management, while others report discomfort from perceived surveillance or stigma (12). Notably, large-scale randomized controlled trials demonstrating improved clinical outcomes are still lacking.

In cardiovascular care, pilot studies using digital pills to monitor diuretic adherence in heart failure patients show high technical accuracy and feasibility, suggesting potential to prevent acute decompensation and hospital readmissions (13). For infectious diseases like tuberculosis and HIV, digital tools are gaining traction, though cost and logistics make video-based monitoring more common than ingestible sensors (7). Transplant medicine is another promising area, with early studies indicating digital pills can reliably track immunosuppressant intake (14). Sample sizes remain small, however, and long-term outcome data is absent. Across all domains, digital pills offer superior objective data compared to simpler tools, but at a higher cost and technological complexity (15).

Benefits and Potential

The primary advantage of digital pills is the generation of highly accurate, objective adherence data, overcoming the flaws of self-report and refill metrics (1). This enables precise correlation between drug exposure and therapeutic response, crucial for medications with narrow therapeutic indices and in clinical trials. Real-time data transmission allows for timely interventions when doses are missed, potentially breaking cycles of non-adherence and preventing clinical deterioration (13). Furthermore, objective data fosters more constructive conversations between clinicians and patients about adherence barriers. While long-term economic data is needed, improved adherence could reduce costly emergency visits and hospitalizations (1).

Challenges and Ethical Issues

Despite their promise, digital pills face multifaceted challenges. Technical issues include communication failures between the sensor and patch, signal dropouts, and rare false positives (16). Integration with electronic health records remains problematic, hindering clinical workflow integration. Patient acceptability is a major hurdle, with concerns ranging from skin irritation from the patch to anxiety over continuous monitoring. For stigmatized populations, such as those with mental illness, perceived surveillance can damage trust and autonomy (12).

Privacy and data governance are paramount ethical concerns. Ingestion data is highly sensitive, requiring robust safeguards against misuse by insurers, employers, or other third parties (17). Regulatory frameworks are underdeveloped, creating grey areas for combined drug-device-software products, especially in countries like India (18). High cost is a critical barrier (15) , and without deliberate equity-focused planning, implementation risks exacerbating the digital divide in low-resource settings (19).

The Indian and Low- and Middle-Income Countries (LMIC) Context

India's high burden of communicable and non-communicable diseases makes adherence a public health priority. National programs have adopted simpler digital tools like video-based monitoring for tuberculosis (4). However, the feasibility of ingestible sensors in India and similar settings is limited by high costs, uneven digital literacy and network access, and heightened sensitivity to surveillance in stigmatized conditions (19). Ethical challenges may be amplified by existing power imbalances in patient-provider relationships. Prior to adoption, these regions require locally generated pilot data, real-world implementation research, rigorous cost-benefit

analyses, and the development of context-specific ethical and regulatory guidelines (18).

Future Directions

The field is evolving rapidly. Integration with artificial intelligence could enable predictive analytics for non-adherence and personalized interventions (20). Advances in material science may yield biodegradable sensors and patchless transmission systems, improving patient comfort and acceptability. Future iterations may combine adherence monitoring with targeted, site-specific drug delivery in the gastrointestinal tract (21). Critical research priorities include long-term outcome studies, comprehensive cost-effectiveness analyses, and qualitative research into patient and provider perspectives across diverse socio-cultural contexts. Clinical pharmacologists in India and other LMICs are pivotal in guiding this research and ensuring the ethical integration of the technology.

Conclusion

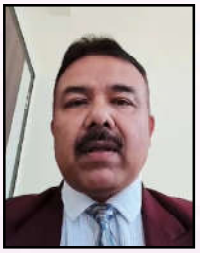
Digital pills represent a transformative convergence of pharmaceutics, engineering, and digital health, offering unparalleled objective adherence monitoring. They hold significant potential to enhance treatment outcomes, personalize therapy, and advance clinical research. However, responsible adoption must be guided by robust evidence, strong ethical frameworks, stringent data protections, and an unwavering commitment to equity. Technical reliability, patient privacy, cultural acceptability, and regulatory clarity are substantial hurdles that must be overcome. Successful implementation, particularly in resource-limited environments, will depend on sustained interdisciplinary collaboration, thoughtful policy, and a primary focus on preserving patient trust and autonomy.

Reference:

1. Figueiredo T, Alcântara L, Carrilho J, Paúl C, Costa E. Understanding Adherence to Digital Health Technologies: Systematic Review of Predictive Factors. J Med Internet Res. 2025 Nov 17;27:e77362–e77362.
2. Brown MT, Bussell JK. Medication Adherence: WHO Cares? Mayo Clin Proc. 2011 Apr;86(4):304–14.
3. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. BMJ Open. 2018 Jan;8(1):e016982.
4. Subbaraman R, De Mondesert L, Musiimenta A, Pai M, Mayer KH, Thomas BE, et al. Digital adherence technologies for the management of tuberculosis therapy: mapping the landscape and research priorities. BMJ Glob Health. 2018 Oct;3(5):e001018.
5. U.S. Food and Drug Administration. ABILIFY MYCITE (aripiprazole tablets with sensor) [Internet]. Silver Spring , MD; 2017 [cited 2025 Dec 1]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207202lbl.pdf
6. Alipour A, Gabrielson S, Patel PB. Ingestible Sensors and Medication Adherence: Focus on Use in Serious Mental Illness. Pharmacy. 2020 June 16;8(2):103.
7. Flores GP, Peace B, Carnes TC, Baumgartner SL, Buffkin DE, Euliano NR, et al. Performance, Reliability, Usability, and Safety of the ID-Cap System for Ingestion Event Monitoring in Healthy Volunteers: A Pilot Study. Innov Clin Neurosci. 2016;13(9–10):12–9.

8. Kalantar-zadeh K, Ha N, Ou JZ, Berean KJ. Ingestible Sensors. ACS Sens. 2017 Apr 28;2(4):468–83.
9. Martani A, Geneviève LD, Poppe C, Casonato C, Wangmo T. Digital pills: a scoping review of the empirical literature and analysis of the ethical aspects. BMC Med Ethics. 2020 Dec;21(1):3.
10. Chai PR, Vaz C, Goodman GR, Albrechta H, Huang H, Rosen RK, et al. Ingestible electronic sensors to measure instantaneous medication adherence: A narrative review. Digit Health. 2022 Jan;8:205520762210831.
11. Steiger C, Abramson A, Nadeau P, Chandrakasan AP, Langer R, Traverso G. Ingestible electronics for diagnostics and therapy. Nat Rev Mater. 2018 Dec 17;4(2):83–98.
12. Chevance A, Fortel A, Jouannin A, Denis F, Mamzer MF, Ravaud P, et al. Acceptability of and Willingness to Take Digital Pills by Patients, the Public, and Health Care Professionals: Qualitative Content Analysis of a Large Online Survey. J Med Internet Res. 2022 Feb 18;24(2):e25597.
13. Lee-Riddle GS, Schmidt HJ, Reese PP, Nelson MN, Neergaard R, Barg FK, et al. Transplant recipient, care partner, and clinician perceptions of medication adherence monitoring technology: A mixed methods study. Am J Transplant. 2024 Apr;24(4):669–80.
14. Eisenberger U, Wüthrich RP, Bock A, Ambühl P, Steiger J, Intondi A, et al. Medication Adherence Assessment: High Accuracy of the New Ingestible Sensor System in Kidney Transplants. Transplantation. 2013 Aug 15;96(3):245–50.
15. GoodRx [Internet]. 2024 [cited 2025 Dec 1]. Abilify MyCite (aripiprazole with sensor) - pricing page. Available from: https://www.goodrx.com/abilify-mycite
16. Divya R, Sadana Shree S, Sakthiganesh V, Gokulkumar K, Monisha A. Digital Pills: Enhancing patient outcomes through innovative medication management. Comput Biol Med. 2025 Sept;196:110907.
17. Out-Law (Pinsent Masons) [Internet]. 2017 [cited 2025 Dec 1]. New “digital” pills pose data protection and cybersecurity challenges for drugs manufacturers and health bodies, says expert. Available from: https://www.pinsentmasons.com/out-law/news/new-digital-pills-pose-data-protection-and-cybersecurity-challenges-for-drugs-manufacturers-and-health-bodies-says-expert
18. Sheikh A, Anderson M, Albala S, Casadei B, Franklin BD, Richards M, et al. Health information technology and digital innovation for national learning health and care systems. Lancet Digit Health. 2021 June;3(6):e383–96.
19. B Capital BCG. A Digital Pill for Revolutionizing Healthcare [Internet]. B Capital and Boston Consulting Group; 2023 Nov [cited 2025 Dec 1]. Available from: https://b.capital/wp-content/uploads/2023/11/BCG-x-B-Capital_DHP_vF_Compressed.pdf
20. Varma N, Han JK, Passman R, Rosman LA, Ghanbari H, Noseworthy P, et al. Promises and Perils of Consumer Mobile Technologies in Cardiovascular Care. J Am Coll Cardiol. 2024 Feb;83(5):611–31.
21. Thwaites PA, Yao CK, Halmos EP, Muir JG, Burgell RE, Berean KJ, et al. Review article: Current status and future directions of ingestible electronic devices in gastroenterology. Aliment Pharmacol Ther. 2024 Feb;59(4):459–74.

Apomorphine



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Apomorphine was initially synthesized from morphine and sulfuric acid. Adolf Edvard Arppe, in 1845 , first synthesized the compound ,while Laurent and Gerhardt, classified the compound as an amide and named it as sulphomorphide. Matthiessen and Wright, in 1869 , used hydrochloric acid instead of sulphuric acid and named it apomorphine.

Historically, apomorphine has been tried for a variety of uses, including as a way to relieve anxiety and craving in alcoholics; an emetic, for treating repetitive behavior and more recently in treating erectile dysfunction. Currently apomorphine is used in the treatment of Parkinson's disease. It is a potent emetic and should not be administered without an antiemetic like domperidone. The emetic properties of apomorphine are exploited in veterinary medicine to induce therapeutic emesis in canines that have recently ingested toxic or foreign substances . Apomorphine was used in the treatment of heroin addiction, a purpose for which it was championed by the author William S. Burroughs. Burroughs and others claimed that it was a metabolic regulator with a restorative dimension to a damaged or dysfunctional dopaminergic system. Despite anecdotal evidence that this offers a plausible route to an abstinence-based mode, no clinical trials have been tested.

A recent study indicates that apomorphine might be suitable marker for assessing central dopamine system alterations associated with chronic heroin consumption. There is no clinical evidence that apomorphine is an effective and safe treatment for regimen for opiate addiction. The use of apomorphine to treat the 'shakes' was first suggested by Weil in France in 1884, although seemingly not pursued until 1951. Its clinical use was first reported in 1970 by Cotzias et al. Although its emetic properties and short half-life made oral use impractical, a later study found that combining the drug with the antiemetic domperidone improves the result significantly. The commercialization of apomorphine for Parkinson's disease followed its successful use in patients with refractory motor fluctuations using intermittent rescue injection and continuous infusions. Apomorphine is used in advanced Parkinson's disease intermittently where a decreased response to an anti parkinsonian drug like levodopa causes muscle stiffness and loss of muscle control; while apomorphine can be used in combination with levodopa. The intention is usually to reduce L-dopa dosing, as at this stage the patient often has many dyskinesias caused by L-dopa and hypermobility periods. When an episode sets in, apomophine is injected subcutaneously or applied sublingually and signs subside. It is used at average of three times a day. Some people use portable mini pumps that

continuously infuse them with apomorphine, allowing them to stay in “on” state and using apomorphine as an effective monotherapy. Nausea, vomiting are common side effects. Others include orthostatic hypotension, fainting, sleepiness, dizziness, running nose, sweating, paleness, flushing. More serious side effects include dyskinesia, fluid accumulation, suddenly falling asleep, confusion, hallucination, increasesd heart rate, heart palpitation and priapism. The priapism is caused by apomorphine increasing arterial blood supply to the penis. This side effect has been exploited in studies attempted in erectile dysfunction.

Apomorphines are enantiomers and is an agonist of both D 1 and D2 dopamine receptor with higher activity at D2; D3 and D4 receptors are inhibited. The D4, in particular, is an important target in the signaling pathway and is connected to several neurological disorders. Shortage or excess of dopamine can prevent proper functioning and signaling of these receptors, leading to disease states. Apomorphine improves motor function by activating dopamine receptors in the niagrostrial pathway, the limbic system, and the hypothalamus and the pituitary gland. It also increases blood flow to the supplementary motor area to the dorsolateral prefrontal cortex. Parkinson's has been found to have excess iron at the sites of neurodegeneration. Both the R and S enantiomers of apomorphine are protein iron chelators and radical scavengers. Apomorphine also decreases the breakdown of dopamine in the brain. It is an upregulator of certain neural growth factors. Apomorphine causes vomiting by acting on dopamine receptors in the chemoreceptor trigger zone of the medulla which activate nearby vomiting centre. Apomorphine is used sublingually or subcutaneously under the brand name Aposan, Apotab, Erovia in India.

References :

1. Stibe CM, Lees AJ, Kempster PA, Stern GM. Subcutaneous apomorphine in Parkinsonian on-off oscillations. Lancet. 1988 Feb; 1(8582): 403-406.
2. Clayton BD, Willihnganz M (2016).Basic pharmacology for nurses (e-book). Elsevier Health Sciences.p.210-211.ISBN 978-0-323-37697-6.
3. Choudhuri KR. Clough C. Subcutaneous apomorphine in Parkinson’s disease. BMJ. 1998 February; 316 (7132): 641.

Ecopharmacology and Green Pharmacy

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Ecopharmacology is an evolving discipline that investigates the environmental impact of pharmaceuticals throughout their lifecycle—from synthesis and consumption to disposal. Though Pharmaceuticals are essential to modern medicine, their unintended entry into the environment has emerged as a significant public health and ecological challenge. Wastewater treatment plants are not fully equipped to remove many Active Pharmaceutical Ingredients (APIs), leading to the accumulation of drugs and their metabolites in surface water, soil, and living organisms. Green pharmacy complements this concept by promoting environmentally responsible drug design, production, use, and disposal without compromising therapeutic efficacy or patient safety.

Sources of Pharmaceutical Pollution

Pharmaceutical residues enter the environment through multiple pathways:

- Human and veterinary excretion of unmetabolized drugs.
- Improper disposal of unused/expired medicines.
- Hospital and industrial pharmaceutical effluents.
- Agricultural runoff from medicated animal farms.
- Leaching from landfills containing medical waste.

Environmental and Public Health Impacts

1. Antimicrobial Resistance (AMR)

Antibiotic residues in water bodies create selective pressure that promotes the development of resistant microorganisms.

2. Endocrine Disruption

Endocrine disruption refers to the alteration of the normal hormonal balance of organisms due to exposure to chemicals by:

1. Hormone mimicry – binding to hormone receptors and causing exaggerated responses (e.g., estrogenic activity).

2. Hormone antagonism – blocking receptors and inhibiting natural hormone action.

3. Altering synthesis, metabolism, or clearance of hormones.

4. Interfering with endocrine feedback loops and neurotransmitter pathways.

Common endocrine-disrupting pharmaceuticals include:

- Oral contraceptive steroids (ethinyl estradiol, progesterone).
- Hormone replacement therapy drugs
- Corticosteroids.
- Anti-androgens and anabolic steroids.
- Antidepressants influencing serotonin–melatonin pathways.

3. Ecotoxicity

Ecotoxicity refers to the toxic effects of chemical substances on living organisms within ecosystems, including plants, animals, and microorganisms. Pharmaceuticals can cause toxicity in ecosystems through:

- **Bioaccumulation –** progressive accumulation of drugs in tissues of organisms.
- **Biomagnification** – increasing drug concentration along the food chain.
- **Interference** with biochemical pathways (e.g., neurotransmission, endocrine regulation).
- **Selective pressure leading** to antimicrobial resistance in microorganisms.

Drug / Class	Ecotoxic Effect	Species Affected
Ethinyl estradiol (oral contraceptives)	Feminization, reproductive failure	Fish
Diclofenac	Liver and kidney toxicity	Vultures, fish
Antibiotics	Antibiotic resistance, disturbance of microbiota	Bacteria, soil microbes
SSRIs (antidepressants)	Behavioral changes	Fish, amphibians
Beta-blockers	Reduced heart rate, impaired swimming	Fish
Anticancer drugs	Genotoxicity, mutagenicity	Aquatic organisms

4. Bioaccumulation and Food Chain Transfer

Bioaccumulation refers to the gradual build-up of chemical substances—such as pharmaceuticals, pesticides, or heavy metals—in the tissues of living organisms over time, because the rate of uptake exceeds the rate of elimination. Bioaccumulation occurs because:

- Drugs are lipophilic (fat-soluble) - stored in fatty tissues.
- Poorly biodegradable - remain for long durations.
- Slow metabolism and excretion in exposed organisms.

Consequences of bioaccumulation

- Chronic toxicity.
- Organ damage (liver, kidneys, nervous system).
- Reproductive and developmental abnormalities.
- Behavioral changes.
- Increased mortality.

Example: Diclofenac accumulated in vultures-renal failure and massive population decline.

Food chain transfer, also called biomagnification, refers to the progressive increase in chemical concentration along the food chain, from lower to higher trophic levels.

Although environmental drug concentrations may be very low, organisms at the top of the food chain may accumulate higher concentrations due to feeding on contaminated prey.

Process of Food Chain Transfer

- Water/soil contains trace pharmaceutical residues.
- Algae and plankton absorb residues.
- Small fish feed on plankton - drug levels increase.
- Bigger fish feed on smaller fish - higher concentration.
- Birds, animals or humans consume contaminated fish - highest concentration in top predators.

Non-biodegradable drugs may accumulate in tissues and enter the human food chain, posing unknown long-term risks.

Principles of Green Pharmacy

Stage	Environmentally Responsible Approach
Drug discovery	Green chemistry, biodegradable drug design
Production	Waste minimization, solvent recycling, energy-efficient manufacturing
Distribution	Sustainable packaging, digital prescriptions
Drug therapy	Rational use, prescribing stewardship
Disposal	Safe take-back systems, proper medical waste management

Strategies for Eco-friendly Pharmaceutical Practice

At Healthcare System Level

- Implementation of drug-take-back programs.
- Hospital wastewater treatment and API-removal technologies.
- Antibiotic stewardship to minimize unnecessary antibiotic exposure.
- Formulary policies favoring environmentally safer drugs when therapeutically equivalent.

At Pharmacy Level

- Patient education on safe disposal of medicines.
- Promotion of minimal-waste packaging.
- Pharmacists as leaders in eco-friendly medicine campaigns.

At Industry and Research Level

- Development of biodegradable APIs and green chemistry synthesis.
- Life-cycle environmental assessment (LCA) of pharmaceuticals.
- Eco-labeling of medicines based on environmental impact.

Future Directions

- Biopharmaceutical innovations that minimize persistent residues.
- Policies linking reimbursement to environmental sustainability.
- Artificial intelligence for predicting environmental toxicity of new drugs.
- Microbial and nanotechnology-based wastewater purification systems.

Conclusion

Eco-pharmacology and green pharmacy represent a paradigm shift from traditional drug-centric healthcare toward planetary health. Reducing pharmaceutical pollution is not solely the responsibility of industry. The prescribers, pharmacists, policymakers, and the public must collaborate. Sustainable drug development and responsible usage can preserve both human health and ecological integrity.

References

1.Kummerer K. “Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks.” Springer, 2016.

2.Boxall ABA et al. “Pharmaceuticals and personal care products in the environment.” Environmental Science & Technology, 2012; 46(14): 7279-7281.

3.WHO–UNEP Report. “Antimicrobial Resistance and Pharmaceutical Waste.” World Health Organization, 2022.

4.Aus der Beek T et al. “Global occurrence of pharmaceuticals in freshwater environments.” Environmental Pollution, 2016; 214: 416-423.

5.European Medicines Agency (EMA). “Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use.” 2021.

6.Daughton CG, Ruhoy IS. “Green pharmacy and the responsible management of pharmaceuticals.” Journal of Hazardous Materials, 2013; 2: 37-42.

Role of Digital Therapeutics in Healthcare System

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INTRODUCTION

Digital therapeutics (DTx) are a rapidly evolving class of medical interventions that deliver evidence-based treatments through software to prevent, manage, or treat medical disorders and diseases (1). Unlike consumer wellness apps, which primarily promote general health behaviours, DTx products undergo clinical validation and regulatory review, and many are prescribed or recommended by clinicians as medical treatments or adjuncts to existing therapies (2). The field sits at the intersection of behavioural science, clinical medicine, data science, and regulated product development, and is increasingly regarded as a distinct category of therapeutic modality within modern healthcare.

Digital therapeutic companies should publish trial results inclusive of clinically meaningful outcomes in peer-reviewed journals (3). The treatment relies on behavioural and lifestyle changes usually spurred by a collection of digital impetuses (4,5). Because of the digital nature of the methodology, data can be collected and analysed as both a progress report and a preventative measure (6). Treatments are being developed for the prevention and management of a wide variety of diseases and conditions, including type 1 & type II diabetes, congestive heart failure, obesity, Alzheimer's disease, dementia, asthma, substance abuse, ADHD, hypertension, anxiety, depression, and several others (7). Digital therapeutics often employ strategies rooted in cognitive behavioural therapy (8).

The global digital therapeutics (DTx) market was valued at approximately USD 1.8 billion in 2018 and is projected to reach USD 7.1 billion by 2025 (9). Recent reports suggest that the largest applications of DTx in the near future will be in the management of diabetes and weight loss. Other promising areas of application include chronic obstructive pulmonary disease (COPD), developmental disorders (utilizing computer-based games), and post-traumatic stress disorder (PTSD), where virtual reality (VR) technologies are being explored as therapeutic tools (10).

HISTORY OF DIGITAL THERAPEUTICS

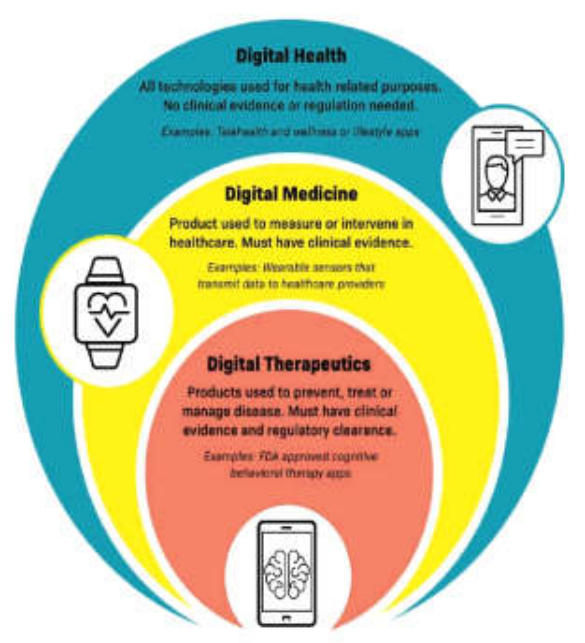
In 1995, Dr. Joseph Kvedar from Boston, USA, initiated a pioneering program aimed at exploring the development and application of technology to deliver healthcare beyond traditional hospital and clinic settings, introducing the concept of a “one-to-many model of care.” This model sought to expand physicians’ reach by overcoming the constraints of time, location, and personnel that typically limit healthcare delivery. The initiative emphasized enhancing access, convenience, and efficiency—enabling better patient care with fewer

resources (11). Dr. Kvedar's work is regarded as one of the earliest contributions to the field of digital health and digital therapeutics (DTx).

Evidence from the literature suggests that the use of digital tools to improve health outcomes dates back to as early as 2000 (12). The term "e-patient" was coined by Dr. Tom Ferguson in 1999 (13) but gained wider recognition nearly a decade later (14). The formal use of the term "digital therapeutics (DTx)" has been observed since 2012 (15).

RELATIONSHIP BETWEEN DIGITAL HEALTH, DIGITAL MEDICINE AND DIGITAL THERAPEUTICS

Digital health can be broadly defined as the integration of healthcare and technology. Differentiating between digital health, digital medicine, and digital therapeutics (DTx) is essential to prevent confusion among stakeholders, manufacturers, and developers in the digital health ecosystem. Such distinctions facilitate the appropriate positioning, regulation, and utilization of these products within the healthcare market (16).



Digital health serves as an umbrella term encompassing digital medicine, which in turn includes digital therapeutics (DTx). Products within these categories vary in terms of intended use, level of clinical claims, associated risks, and the degree of regulatory oversight required.

Digital health represents the broadest category, comprising a wide range of technologies, platforms, and systems that engage consumers in lifestyle management, wellness promotion, and general health-related activities. These technologies can capture, store, and transmit health data to support clinical operations and healthcare decision-making. Examples include health information technologies, telehealth systems, consumer health information platforms, and clinical care administration tools, among others.

Digital medicine, on the other hand, consists of software or hardware products that are typically supported by clinical evidence and are designed to measure or intervene in the service of human health. Examples include digital diagnostics, digital biomarkers, and remote patient monitoring devices, which contribute to precise and continuous health assessment (16).

Digital therapeutics (DTx) represent a distinct subset of digital medicine that provides evidence-based therapeutic interventions to prevent, manage, or treat medical disorders or diseases (6). DTx solutions deliver therapeutic benefits through scientifically validated mechanisms, often in conjunction with or as alternatives to conventional treatments. Examples of DTx applications include digital sensors, wearable devices, and certain virtual reality (VR) and artificial intelligence (AI)-based platforms designed to produce measurable clinical outcomes (16).

KEY CHARACTERISTICS OF DIGITAL THERAPEUTICS

- **Evidence-based —** Supported by clinical trials demonstrating safety and efficacy.
- **Regulated —** May require approval from bodies like the FDA, EMA, or CDSCO (in India).
- **Personalized —** Often adapt to a user's symptoms, behaviours, or biometrics.
- **Data-driven —** Use real-time monitoring and feedback loops for continuous improvement.
- **Standalone or adjunct —** Can work alone or alongside drugs, devices, or therapy.

EXAMPLES OF DIGITAL THERAPEUTICS

Condition	Example	Description
Type 2 Diabetes	**Omada Health, BlueStar**	Apps for glucose monitoring, diet, and lifestyle coaching.
Insomnia	**Somryst**	FDA-approved app delivering CBT-I (Cognitive Behavioral Therapy for Insomnia).
Substance Use Disorder	**reSET / reSET-O**	Prescription apps supporting addiction recovery.
Hypertension	**Hello Heart, Lark**	Personalized coaching to lower blood pressure.
ADHD	**EndeavorRx**	A video game-based therapy approved by the FDA for pediatric ADHD.

BENEFITS

- Accessible anytime, anywhere.
- Encourages self-management and patient engagement.
- Reduces healthcare costs.
- Supports long-term behaviour change.
- Enables data collection for precision medicine (17).

CHALLENGES AND LIMITATIONS

Despite gains, several challenges limit the full realization of DTx potential:

1. Adherence and engagement: Many trials report high drop-off rates; users often fail to engage with DTx long-term (18).
2. Heterogeneity in trial design: Differences in outcome measures, control groups, follow-up durations, and populations make comparisons difficult (2,19).
3. Regulation and reimbursement: Regulatory frameworks are uneven across countries. Many DTx are not FDA-regulated or equivalent elsewhere, which affects oversight. Reimbursement models are still evolving (17,20).
4. Evidence at launch: Some DTx products reach market without published efficacy or effectiveness studies pre-launch, particularly non-regulated ones (21).
5. Data privacy, security, and digital literacy: Handling sensitive health data raises privacy and cybersecurity risks; population-level differences in digital literacy can limit access or proper use.

DIGITAL THERAPEUTICS VS. WELLNESS APPS

Feature	Digital Therapeutics (DTx)	Wellness Apps
Clinical validation	Yes	Usually no
Regulatory oversight	Yes (FDA/EMA/CDSCO)	No
Prescription required	Sometimes	No
Evidence-based outcomes	Proven in trials	Rarely validated
Medical claims	Permitted	Not permitted

CONCLUSION

Digital therapeutics represent a transformative evolution in how healthcare is delivered, especially for conditions amenable to behavioural or software-mediated interventions. The current evidence base is growing rapidly, particularly via Randomised controlled trials (RCTs), but variable across products and regions. As regulatory frameworks mature and methodological standards improve, DTx may become essential complements—or alternatives—to traditional medical treatments. The next critical phase will require delivering consistent evidence, protecting user privacy, ensuring access, and embedding DTx into healthcare ecosystems.

REFERENCES

1. Armeni, P., Polat, I., de Rossi, L. M., Diaferia, L., Meregalli, S., & Gatti, A. (2024). Exploring the potential of digital therapeutics: An assessment of progress and promise. Digital Health, 10, 1-16. https://doi.org/10.1177/20552076241277441 (iris.unibocconi.it)
2. Huh, K. Y., Oh, J., Lee, S., & Yu, K.-S. (2022). Clinical evaluation of digital therapeutics: Present and future. Healthcare Informatics Research, 28(3), 188-197. https://doi.org/10.4258/hir.2022.28.3.188 (PMC)
3. "Understanding DTx: A New Category of Medicine". Digital Therapeutics Alliance.
4. Sepah SC, Jiang L, Peters AL (April 2015). "Long-term outcomes of a Web-based diabetes prevention program: 2-year results of a single-arm longitudinal study". Journal of Medical Internet Research. 17 (4): e92
5. Duffy S (17 April 2014). "What If Doctors Could Finally Prescribe Behavior Change?". Forbes. Retrieved 19 October 2016
6. Dignan L (18 November 2015). "Ready for digital therapeutics? Andreessen Horowitz hopes so". ZDNet. Archived from the original on November 19, 2015. Retrieved 19 October 2016
7. Kvedar JC, Fogel AL, Elenko E, Zohar D (March 2016). "Digital medicine's march on chronicdisease". NatureBiotechnology. 34 (3): 239-246. doi:10.1038/nbt.3495. PMID 26963544. S2CID 1515998.
8. Gebremedhin D, Schuster M (29 August 2016). "Overview: Health tech startups innovating the behavioral health space". Mobi Health News. Retrieved 19 October 2016
9. Catalani C, Farese C. Can digital therapeutics revolutionize medicine? [monograph on the Internet]. Ideo Journal. Available from: https://www.ideo.com/journal/can digital therapeutics revolutionize medicine. [Updated 2019 Oct 02; Cited 2020 Jan 09]
10. Moar J. Digital therapeutics and wellness [homepage on the Internet]. Juniper Research. Availablefrom: https://www. juniperresearch.com/researchstore/innovation disruption/digital therapeutics wellness. [Updated 2019 May 15; Cited 2020 Jan 09].
11. Makin S. The emerging world of digital therapeutics. Nature 2019;573:S106 9.
12. Capobianco E. On Digital Therapeutics. Front Digit Humanit 2015;2:6.
13. Tom Ferguson, M.D. [homepage on the internet]. Doctom. Available from: http://www.doctom.com/. [published 2006 Apr 14; Cited 2020 Jan 09].
14. Fox S. The engaged e patient population. [monograph on the internet]. Pew Research Centre. Available from: https://www.pewresearch.org/internet/2008/08/26/the engaged e patient population/. [Published 2008 Aug 26; Cited 2020 Jan 09].

15. United States Patent and Trademark Office. [homepage on the internet]. 2012. Available from:http://tsdr.uspto.gov/documentviewer?caseId=sn85765357&docId=FTK20121101070417#docIndex=4&page=. [Cited 2020 Jan 09].
16. Goldsack J, Coder M, Fitzgerald C, Navar Mattingly N, Coravos A, Atreja A. HealthXL. Digital health, digital medicine, digital therapeutics (DTx): What's the difference? [monograph on the interent]. HealthXL. com Available from: https://www.healthxl.com/blog/digital health digital medicine digital therapeutics dtx whats the difference. [Updated 2019 Nov 07; Cited 2020 Jan 09].
17. Thorndike, F. P. (2024). Prescription digital therapeutics: Evidence. Health Affairs, [Letter]. https://doi.org/10.1377/hlthaff.2024.00068
18. Koller, C., Blanchard, M., & Hügle, T. (2025). Assessment of digital therapeutics in decentralized clinical trials: A scoping review. PLOS Digital Health, 4(6), e0000905. https://doi.org/10.1371/journal.pdig.0000905
19. Yao, H., Liao, Z., Zhang, X., Zhang, X., Li, M., You, L., & Liu, Y. (2024). A comprehensive survey of the clinical trial landscape on digital therapeutics. Heliyon, 10(16), e36115. https://doi.org/10.1016/j.heliyon.2024.e36115
20. Crisafulli, S., Santoro, E., Recchia, G., & Trifirò, G. (2022). Digital therapeutics in perspective: From regulatory challenges to post-marketing surveillance. Frontiers in Drug Safety & Regulation, 2022. https://doi.org/10.3389/fdsfr.2022.900946
21. Amyx, M., Phi, N. T. T., Alebouyeh, F., Ravaud, P., & Tran, V. T. (2024). Mapping the evidence supporting digital therapeutics: A review. JAMA Internal Medicine, 184(11), 1388-1390. https://doi.org/10.1001/jamainternmed.2024.4972

Rethinking Long-Term PPI Use: A Framework for Safe Deprescribing

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Introduction

Proton pump inhibitors (PPIs) have revolutionized the treatment of acid-related disorders since their introduction in the late 1980s. Acid-related gastrointestinal disorders affect more than 25% of the global population, making PPIs among the most frequently prescribed medications worldwide. These medications, which include omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole, work by irreversibly blocking the hydrogen - potassium ATPase enzyme system in gastric parietal cells, effectively reducing stomach acid production by up to 90%.[1][2] While PPIs have proven highly effective for appropriate clinical indications, their widespread availability and perceived safety profile have contributed to extensive overuse, raising significant concerns about unnecessary exposure to potential adverse effects and healthcare costs. It has been found that approximately 25-70% of PPI prescriptions lack appropriate clinical indication, representing a significant public health concern with potential adverse effects associated with chronic use.[3]

The Scope of PPI Overuse

PPIs are indicated for several well-established gastrointestinal conditions supported by robust clinical evidence which include Gastroesophageal reflux disease, Peptic ulcer disease, whether associated with Helicobacter pylori infection or nonsteroidal anti-inflammatory drug (NSAID) use, Zollinger-Ellison syndrome and other hypersecretory conditions, Barrett's esophagus, and eosinophilic esophagitis. Recent evidence also supports PPI use in preventing stress ulcers in critically ill patients.[4]

Despite clear clinical guidelines, numerous studies from the past ten years demonstrate alarming rates of inappropriate PPI use across diverse healthcare settings. Several factors contribute to this epidemic of overuse. Prescribing inertia—the tendency to continue medications once started—plays a major role, as does the misconception among both patients and providers that PPIs are completely harmless. Hospital stress ulcer prophylaxis protocols often initiate PPIs inappropriately, and these prescriptions frequently continue after discharge without clear rationale.[5] Additionally, inadequate documentation of indication, failure to reassess necessity during routine visits, and patient reluctance to discontinue medications all perpetuate unnecessary use.

Understanding the Need for Deprescribing

The inappropriate use of PPIs contributes to increased pill burden, leading to nonadherence, medication errors, and more frequent emergency department visits and hospitalizations. While short-term PPI use demonstrates excellent tolerability, observational studies increasingly associate prolonged therapy with various adverse outcomes.[6]

PPI-induced hypochlorhydria permits bacterial colonization and increases susceptibility to enteric infections. Multiple studies demonstrate associations between PPI use and increased risk of both initial and recurrent Clostridioides difficile infections. Community-acquired pneumonia risk may also increase, potentially through aspiration of bacteria proliferating in hypochlorhydric gastric content. [6][7][8] Studies suggest associations between long-term PPI use and increased risk of bone fractures, hypomagnesemia, and vitamin B12 deficiency, possibly related to impaired calcium absorption and altered bone mineral density[8][9][10]. A 2024 meta-analysis of twelve studies involving 700,125 participants demonstrated PPI use associated with increased chronic kidney disease risk. Acute interstitial nephritis, though rare, represents a recognized idiosyncratic reaction to PPIs. [11][12]

Clinical Implications and Deprescribing Strategies

The emerging safety profile necessitates judicious prescribing practices and systematic deprescribing approaches. The 2022 American Gastroenterological Association Clinical Practice Update on deprescribing PPIs provides comprehensive best practice advice, emphasizing that all patients taking PPIs should undergo regular review of on-going indications, with primary care providers assuming responsibility for documentation and reassessment. Deprescribing should be considered for all patients without definitive indications for chronic PPI use.[13]

Collaborative efforts involving multiple healthcare professionals, utilization of clinical decision-making algorithms, and active patient involvement in the deprescribing process are key elements of successful deprescribing strategies.[2]

The Canadian deprescribing guideline, developed by Farrell and colleagues, provides a comprehensive algorithm to assist healthcare providers in the deprescribing process. The algorithm begins by determining why the patient is taking a PPI to assess whether they qualify for deprescribing. Once eligibility is established, three approaches can be considered: decreasing to a lower dose, stopping and using on-demand therapy, or completely stopping the PPI. [5]

Practical Deprescribing Methods

Evidence regarding optimal deprescribing methods remains limited. Both gradual dose tapering and abrupt discontinuation can be considered, with tapering potentially reducing rebound symptoms in patients with mild disease. [2]

A systematic approach includes slowly tapering off the PPI over 2-4 weeks, with longer tapers for higher doses. During the taper, bridge therapies can reduce symptoms of rebound hyperacidity, including nutritional modifications (avoiding alcohol, caffeine, chocolate, cow's milk, animal fat, and orange juice), regular aerobic exercise, and relaxation techniques. The Canadian guideline recommends follow-up at four (4) weeks to assess symptom control and at 12 weeks to evaluate on-demand use frequency and need for continuous treatment reinitiation. [13,5]

The Challenge of Rebound Acid Hypersecretion

A critical challenge in PPI deprescribing is rebound acid hypersecretion, a physiologic phenomenon occurring in 10-50% of patients following prolonged PPI therapy. This compensatory increase in gastric acid production results from hypergastrinemia induced by chronic acid suppression. Rebound symptoms typically persist for 2-8 weeks after discontinuation, though enterochromaffin-like cells and parietal cell mass may require up to 6 months to fully regress. Patients should be counselled about potential transient upper gastrointestinal symptoms to prevent premature resumption of therapy. [14]

Contraindications to Deprescribing

Importantly, deprescribing decisions should be based solely on lack of appropriate indication, not

on concerns about potential adverse effects. Patients at high risk for upper gastrointestinal bleeding, those with complicated gastroesophageal reflux disease, Barrett's oesophagus, eosinophilic esophagitis, or idiopathic pulmonary fibrosis should generally not be considered candidates for deprescribing.[15]

Patient Education and Multidisciplinary Approaches

Patient education materials are key elements in the deprescribing process. Development of user-friendly brochures following national reference methodologies, with iterative testing for content understandability, can improve deprescribing success. When counselling about discontinuing a PPI, patients should be informed that they will likely experience symptoms of reflux for approximately two weeks after stopping the medication.[14][16]

General practitioners call for a multifaceted approach to improve deprescribing feasibility, involving patient-centered approaches, systemic optimizations, support from other healthcare professionals, and provider-centered strategies emphasizing the importance of deprescribing. Using comprehensive deprescribing protocols along with multidisciplinary approaches demonstrates strong potential for successful implementation throughout the medical community.

Conclusion

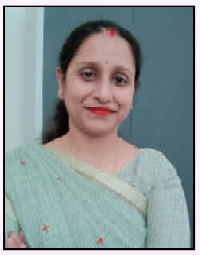
PPIs represent one of gastroenterology's most significant therapeutic advances, offering superior efficacy for acid-related disorders. However, their widespread availability and perceived safety have contributed to extensive inappropriate use. Healthcare providers must balance undeniable PPI benefits against potential risks through thoughtful prescribing, regular reassessment, and commitment to evidence-based deprescribing when appropriate.

References

1. Strand DS, Kim D, Peura DA. 25 Years of Proton Pump Inhibitors: A Comprehensive Review. Gut Liver. 2017 Jan 15;11(1):27-37. doi: 10.5009/gnl15502. PMID: 27840364; PMCID: PMC5221858.
2. Rossi A, Perrella L, Scotti S, et al. Approaches to Deprescribing Proton Pump Inhibitors in Clinical Practice: A Systematic Review. J Clin Med. 2024;13(20):6283. doi: 10.3390/jcm13206283.
3. Nirwan JS, Hasan SS, Babar ZU, Conway BR, Ghori MU. Global Prevalence and Risk Factors of Gastro-Oesophageal Reflux Disease (GORD): Systematic Review with Meta-Analysis. Sci Rep. 2020;10:5814.
4. Tripathi KD. Essentials of Medical Pharmacology. 8th ed. New Delhi: Jaypee Brothers Medical Publishers; 2018.
5. Farrell B, Pottie K, Thompson W, et al. Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline. Can Fam Physician. 2017;63(5):354-364.
6. Gupta R, Garg P, Kottoor R, Munoz JC, Jamal MM, Lambiase LR, Vega KJ. Overuse of acid suppression therapy in hospitalized patients. South Med J. 2010 Mar;103(3):207-11. doi: 10.1097/SMJ.0b013e3181ce0e7a. PMID: 20134378.
7. Scarpignato C, Gatta L, Zullo A, Blandizzi C. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. BMC Med. 2016;14:179.
8. Jaynes M, Kumar AB. The risks of long-term use of proton pump inhibitors: a critical review. Ther Adv Drug Saf. 2018 Nov 19;10:2042098618809927. doi: 10.1177/2042098618809927. PMID: 31019676; PMCID: PMC6463334.

9. Lehault WB, Hughes DM. Review of the Long-Term Effects of Proton Pump Inhibitors. Fed Pract. 2017 Feb;34(2):19-23. PMID: 30766253; PMCID: PMC6372031.
10. Othman F, Card TR, Crooks CJ. Review of the Long-Term Effects of Proton Pump Inhibitors. Cureus. 2019;11(2):e4209.
11. Casula M, Ardoino I, Pierini L, et al. Inappropriate prescribing of drugs for peptic ulcer and gastro-esophageal reflux disease remains a matter of concern: Results from the LAPTOP-PPI cluster randomized trial. Front Pharmacol. 2025;15:1430879. doi:10.3389/fphar.2024.1430879.
12. Ang SP, Chia JE, Valladares C, Patel S, Gewirtz D, Iglesias J. Association between Proton Pump Inhibitor Use and Risk of Incident Chronic Kidney Disease: Systematic Review and Meta-Analysis. Biomedicines. 2024 Jun 25;12(7):1414. doi: 10.3390/biomedicines12071414. PMID: 39061988; PMCID: PMC11274577.
13. Targownik LE, Fisher DA, Saini SD. AGA Clinical Practice Update on De?Prescribing of Proton Pump Inhibitors: Expert Review. Gastroenterology. 2022;162(4):1334-1342. doi: 10.1053/j.gastro.2021.12.247.
14. Namikawa K, Björnsson ES. Rebound Acid Hypersecretion after Withdrawal of Long-Term Proton Pump Inhibitor (PPI) Treatment—Are PPIs Addictive? Int J Mol Sci. 2024;25(10):5459. doi: 10.3390/ijms25105459.
15. Targownik LE, Fisher DA, Saini SD. AGA Clinical Practice Update on De Prescribing of Proton Pump Inhibitors: Expert Review. Gastroenterology. 2022;162(4):1334-1342. doi: 10.1053/j.gastro.2021.12.247.
16. Nguyen-Soenen J, Rat C, Letellier E, Fournier JP. Development of Patient Education Material for Proton Pump Inhibitor Deprescribing: A Mixed-Methods Study. J Patient Exp. 2021;8:23743735211043110. doi: 10.1177/23743735211043110.

Evolution of Therapeutic Strategies in Pharmacology: From Conventional Drugs to Integrated Therapeutic Systems



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Introduction

Pharmacology has traditionally been taught as the science of drugs and their actions on the body, with emphasis on receptors, dose–response relationships, and adverse effects. This framework remains fundamental for understanding basic drug action and for rational prescribing. However, clinicians and teachers working in tertiary care settings increasingly encounter therapies that cannot be fully understood or applied using this conventional approach alone.

In present-day clinical practice, therapeutic decision-making often extends beyond selecting a drug from a standard list. Many modern therapies require prior biological characterization of disease, consideration of patient-specific variability, specialized delivery systems, and continued monitoring that may extend well beyond the period of drug administration. Consequently, therapeutic outcomes are influenced not only by the pharmacological agent, but also by how, when, and in whom the drug is used.

This shift is particularly evident with the growing use of targeted therapies, pharmacogenomic-guided prescribing, immunotherapy, and advanced drug delivery systems. These approaches reflect a broader evolution in pharmacology—from drug-centred treatment to system-based therapeutics. Understanding this evolution is especially important for postgraduate students, early-career faculty, and clinicians involved in tertiary-level healthcare.

Targeted Therapy: From Drug Action to Disease Dependency

Conventional drugs generally act on physiological processes that are shared by both normal and diseased tissues. This lack of selectivity explains their dose-related toxicity and limited therapeutic margins. In contrast, targeted therapies exploit disease-specific molecular dependencies, particularly in cancers and immune-mediated disorders.

Many diseases develop reliance on specific signalling pathways for survival or progression. When such dependency exists, interruption of that pathway can produce meaningful clinical benefit while sparing normal tissues that possess biological redundancy. However, targeted therapy cannot be separated from diagnostics. Molecular characterization of disease is essential to identify patients who are likely to benefit.

Loss of response to targeted therapy is frequently due to adaptive changes in disease biology, such as activation of alternative pathways or modification of the original target. This should be viewed as an expected biological response rather than failure of pharmacological treatment. In tertiary hospitals, targeted therapy therefore functions as a therapeutic system involving

diagnostics, pharmacology, and multidisciplinary clinical decision-making.

Pharmacogenomics: Making Drug Response Predictable

A major limitation of conventional pharmacology is the assumption that patients will respond similarly to standard drug doses. Pharmacogenomics provides a mechanistic explanation for the variability commonly observed in clinical practice by linking genetic differences to drug metabolism, target sensitivity, and immune response.

From a practical standpoint, pharmacogenomics is most useful as a drug safety and risk-prediction tool. Genetic variations affecting drug-metabolising enzymes may result in excessive drug exposure or therapeutic failure at conventional doses. Similarly, certain genetic markers are associated with severe immune-mediated adverse drug reactions, where drug avoidance rather than dose adjustment is necessary.

In tertiary care settings, where polypharmacy and high-risk drugs are common, pharmacogenomic information can help reduce preventable adverse drug reactions and improve confidence in prescribing. Its role is not personalization for its own sake, but rational and safer use of existing therapies.

Immunotherapy: Benefit and Toxicity from the Same Mechanism

Immunotherapy represents a significant departure from traditional pharmacological concepts. Immune checkpoint inhibitors do not act directly on tumour cells; instead, they modify immune regulation by removing inhibitory signals that normally maintain self-tolerance. This mechanism explains the durable responses observed in some patients with advanced disease.

At the same time, the same mechanism accounts for immune-related adverse events that resemble autoimmune disorders and may involve multiple organ systems. These toxicities are on-mechanism effects, not off-target reactions, and may occur independently of dose. They can appear late and may persist even after discontinuation of therapy.

For clinicians, this necessitates a different approach to monitoring and management. Early recognition of immune-mediated toxicity and timely initiation of immunosuppressive treatment are often more important than dose modification. Immunotherapy therefore functions as controlled immune dysregulation and requires system-level preparedness and multidisciplinary involvement.

Advanced Drug Delivery Systems: Improving Adherence and Outcomes

In routine clinical practice, treatment failure often occurs not because a drug lacks efficacy, but because it is not delivered effectively. Poor adherence, fluctuating drug levels, and unacceptable toxicity remain important challenges. Advanced drug delivery systems address these issues by modifying the pharmacokinetic behaviour of drugs.

Technologies such as insulin pumps, smart inhalers, nanocarrier-based formulations, and implantable delivery devices regulate the rate, timing, and site of drug release. By stabilising drug exposure and simplifying dosing schedules, these systems improve adherence through design rather than relying solely on patient behaviour.

From a healthcare system perspective, advanced drug delivery systems can reduce emergency admissions, improve long-term disease control, and enable remote monitoring. Although they may involve higher initial costs, they often result in improved outcomes and reduced long-term healthcare utilisation, particularly in chronic diseases.

Table 1. Comparison between conventional pharmacology and integrated therapeutic systems

Feature	Conventional Drugs	Integrated Therapeutic Systems
Focus	Drug and receptor	Drug + biology + delivery
Diagnostics	Often optional	Essential
Monitoring	Dose and labs	Mechanism-based
Role of patient	Passive	Actively supported

Table 2. Examples illustrating systems-based therapeutic approaches

Therapeutic approach	Key system component	Clinical implication
Targeted therapy	Molecular diagnostics	Selective efficacy
Pharmacogenomics	Genetic risk profiling	Improved safety
Immunotherapy	Immune regulation	Durable response with immune toxicity
Drug delivery systems	Pharmacokinetic control	Better adherence

Conclusion

Therapeutic strategies in pharmacology have evolved beyond conventional drugs acting in isolation. Contemporary treatments increasingly function as integrated therapeutic systems that link pharmacological agents with diagnostics, patient-specific factors, delivery technologies, and structured monitoring. For clinicians and educators working in tertiary care settings, adopting a systems-based perspective is essential for rational prescribing, patient safety, and effective translation of therapeutic advances into everyday clinical practice.

REFERENCES

1. Relling MV, Evans WE. Pharmacogenomics in the clinic. Nature. 2015;526:343–350.
2. Daly AK. Pharmacogenomics of adverse drug reactions. Genome Med. 2022;14:70.
3. Blumenthal GM, Pazdur R. Precision oncology and targeted therapies. Clin Cancer Res. 2024;30:215–220.
4. Sawyers CL. Targeted cancer therapy. Nature. 2004;432:294–297.
5. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359:1350–1355.
6. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events. N Engl J Med. 2018;378:158–168.
7. Kabbani D, Zgheib NK. Clinical implementation of pharmacogenomics. Front Pharmacol. 2023;14:1189976.
8. Aronson JK. Systems pharmacology. Br J Clin Pharmacol. 2021;87:3890–3898.
9. Darrow JJ. The future of drug development. Clin Pharmacol Ther. 2022;111:36–43.
10. Langer R. Drug delivery and targeting. Nature. 1998;392:5–10.
11. Patra JK, et al. Nano-based drug delivery systems. J Nanobiotechnology. 2018;16:71.
12. Shaikh S, et al. Smart drug delivery systems. Pharmaceutics. 2023;15:462.
13. Hood L, Friend SH. P4 medicine. Nat Rev Clin Oncol. 2011;8:184–187.
14. Atkinson AJ Jr, et al. Principles of Clinical Pharmacology. 4th ed. Academic Press; 2020.
15. Michot JM, et al. Immune-related adverse events. Eur J Cancer. 2016;54:139–148.

Pharmacomicrobiomics: The Gut Microbiome's Emerging Role in Drug Efficacy and Toxicity – A Primer for Medical Pharmacologists

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Introduction

Inter-individual variability in drug response remains a significant challenge in clinical practice, contributing to treatment failure and adverse drug reactions (ADRs). While host genetic factors (pharmacogenomics) have long been studied, the contribution of the gut microbiome to this variability is a burgeoning field of research termed "pharmacomicrobiomics" [1] . The gut microbiota harbors a vast enzymatic repertoire, far exceeding that of the host, capable of metabolizing a wide array of xenobiotics, including many commonly prescribed drugs [2]. Understanding these interactions is paramount for medical pharmacologists aiming to optimize drug therapy and minimize ADRs.

Mechanisms of Microbiome-Drug Interactions

The gut microbiome can influence drug disposition and action through several key mechanisms:

1. **Direct Microbial Metabolism of Drugs:**
   - **Activation:** Some prodrugs require microbial enzymes for conversion into their active forms. A classic example is sulfasalazine, used for inflammatory bowel disease, which is cleaved by bacterial azoreductases in the colon into its active components, 5-aminosalicylic acid (5-ASA) and sulfapyridine [3].
   - **Inactivation:** Conversely, gut microbes can directly inactivate drugs, reducing their efficacy. For instance, the cardiac glycoside digoxin can be inactivated by Eggerthella lenta through enzymatic reduction of its unsaturated lactone ring, leading to sub-therapeutic levels in a subset of patients [4].
   - **Toxicity Generation/Modification:** Microbial metabolism can sometimes generate toxic metabolites or alter the toxicity profile of a drug. The chemotherapeutic agent irinotecan (CPT-11) is metabolized in the liver to its active form SN-38, which is then glucuronidated (SN-38G) for detoxification and biliary excretion. However, bacterial ß-glucuronidases in the gut can deconjugate SN-38G back to SN-38, leading to severe, dose-limiting diarrhea [5].

2. Indirect Modulation of Host Drug Metabolism and Transport:

- The microbiome can influence the expression and activity of host drug-metabolizing enzymes (e.g., cytochrome P450s - CYPs) and drug transporters (e.g., P-glycoprotein) in the liver and intestine [6]. Microbial metabolites, such as short-chain fatty acids (SCFAs) or components of the

bacterial cell wall, can act as signaling molecules affecting host gene expression. For example, germ-free mice exhibit altered expression of several CYP enzymes compared to conventionally raised mice, which can be partially restored by microbial colonization [7].

3. Alteration of Drug Bioavailability:

- Microbial activity can affect drug dissolution, absorption, and enterohepatic circulation. For example, changes in gut pH or bile acid metabolism orchestrated by the microbiome can influence the solubility and absorption of certain drugs [2].

4. Modulation of Host Immune System and Drug Response:

- The gut microbiome plays a crucial role in shaping the host immune system. This is particularly relevant for immunotherapies. Studies have shown that the composition of the gut microbiota can significantly impact the efficacy of immune checkpoint inhibitors [e.g., anti-PD-1 (Programmed Cell Death Protein – 1)/PD-L1 (Programmed Death Ligand 1] in cancer treatment, with certain bacterial taxa associated with improved patient outcomes [8].

Clinical Relevance and Therapeutic Areas

The impact of pharmacomicrobiomics spans multiple therapeutic areas:

- **Oncology:** Beyond irinotecan and immunotherapy, the microbiome can affect the efficacy and toxicity of cyclophosphamide and platinum-based chemotherapies [9].
- **Cardiology:** The digoxin example highlights direct inactivation. Furthermore, trimethylamine N-oxide (TMAO), a pro-atherogenic metabolite produced by gut microbial metabolism of dietary choline and L-carnitine, has been linked to cardiovascular disease risk and may interact with cardiovascular drugs [10].
- **Gastroenterology:** Besides sulfasalazine, the microbiome influences the metabolism and toxicity of non-steroidal anti-inflammatory drugs (NSAIDs), potentially exacerbating gut damage [11].
- **Neuropsychiatry:** While direct drug metabolism is less established, the "gut-brain axis" implies that microbial dysbiosis could influence the efficacy of psychotropic medications, or conversely, these drugs could alter the microbiome [12].
- **Metabolic Diseases:** Metformin, a first-line treatment for type 2 diabetes, has been shown to alter gut microbial composition, and some of its therapeutic effects, as well as gastrointestinal side effects, may be mediated through these microbial changes [13].

Challenges and Future Perspectives

Despite rapid advancements, several challenges hinder the clinical translation of pharmacomicrobiomics:

1. **High Inter-individual Variability:** The human gut microbiome is highly diverse and dynamic, influenced by diet, genetics, age, and environment, making it difficult to establish universal microbiome-drug interaction patterns.
2. **Methodological Standardization:** Standardized protocols for sample collection, processing, sequencing, and data analysis are crucial for reproducible and comparable results.
3. **Causality vs. Association:** Many studies report associations, but establishing causal links between specific microbes or microbial functions and drug responses requires rigorous mechanistic investigation.

4. **Complexity of Interactions:** Drug-microbiome interactions are often complex, involving multiple microbial species and metabolic pathways, as well as host factors.

Future research directions and potential applications include:

- **Microbiome-based Diagnostics:** Developing biomarkers (specific taxa, genes, or metabolites) to predict drug efficacy and ADR risk.
- **Therapeutic Microbiome Modulation:** Strategies like probiotics, prebiotics, synbiotics, or fecal microbiota transplantation (FMT) could be employed to optimize drug response by "reshaping" the gut microbiome [14].
- **"Bug-Drug" Co-development:** Incorporating pharmacomicrobiomic assessments early in the drug discovery and development pipeline.
- **Personalized Dosing Strategies:** Tailoring drug choice and dosage based on an individual's microbiome profile, alongside pharmacogenomic data.

Conclusion for Medical Pharmacologists

Pharmacomicrobiomics is no longer a niche interest but an essential consideration in understanding drug action and variability. As medical pharmacologists, appreciating the profound influence of the gut microbiome on pharmacokinetics and pharmacodynamics is critical. While the field is still evolving, its potential to refine drug development, predict patient responses, minimize ADRs, and ultimately personalize medicine is immense. Staying abreast of these developments will be crucial for leveraging this new frontier to improve therapeutic outcomes. Future pharmacological research and clinical trial design should increasingly consider the gut microbiome as a significant, modifiable factor influencing drug therapy.

References

1. Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL. Mapping human drug metabolism by the gut microbiome. Nature. 2019;570(7762):462-466.
2. Wilson ID, Nicholson JK. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. Transl Res. 2017;179:204-222.
3. Peppercorn MA, Goldman P. The role of intestinal bacteria in the metabolism of salicylazosulfapyridine. J Pharmacol Exp Ther. 1972;181(3):555-562.
4. Haiser HJ, Gootenberg DB, Chatman K, Sirasamy G, Balskus EP, Turnbaugh PJ. Predicting and manipulating cardiac drug inactivation by the human gut bacterium Eggerthella lenta. Science. 2013;341(6143):295-298.
5. Wallace BD, Wang H, Lane KT, et al. Alleviating cancer drug toxicity by inhibiting a bacterial enzyme. Science. 2010;330(6005):831-835.
6. Jourova L, Anzenbacher P, Anzenbacherova E. Human gut microbiome and its influence on the bioavailibility of drugs. Drug Metab Rev. 2016;48(3):335-345.
7. Selwyn FP, Cheng SL, Klaassen CD, Cui JY. Regulation of hepatic drug-metabolizing enzymes in germ-free mice by conventionalization and probiotics. Drug Metab Dispos. 2016;44(2):262-274.
8. Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science. 2018;359(6371):91-97.

9. Gopalakrishnan V, Spencer CN, Nezi L, et al. Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. Science. 2018;359(6371):97-103.
10. Cryan JF, O'Riordan KJ, Cowan CSM, et al. The Microbiota-Gut-Brain Axis. Physiol Rev. 2019;99(4):1877-2013.
11. Wu H, Esteve E, Tremaroli V, et al. Metformin alters the gut microbiome of individuals with treatment-naive type 2 diabetes, contributing to the therapeutic effects of the drug. Nat Med. 2017;23(7):850-858.
12. Suez J, Zmora N, Segal E, Elinav E. The pros, cons, and many unknowns of probiotics. Nat Med. 2019;25(5):716-729.

Recent Advances In Antimicrobials

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INTRODUCTION:

Serious infections caused by microorganisms resistant to commonly used antimicrobials have become a major healthcare problem worldwide in the 21st century. This is responsible for the significant increase in morbidity and mortality, longer hospitalization and increased health care costs. Currently, multidrug-resistant (MDR) Gram-positive and Gram-negative bacteria in both hospital and healthcare-acquired infections are widespread. AMR now causes 700,000 or more deaths each year, which could grow to 10 million by 2050. In order to guide and promote the discovery and development of antibiotics, WHO has published a list of the twelve most important bacteria. Nine of the twelve pathogens are Gram-negative bacteria, including three critical priority pathogens: Acinetobacter baumannii, Pseudomonas aeruginosa and extended-spectrum ß-lactamase (ESBL) producing Enterobacteriaceae (covering Klebsiella pneumoniae and Escherichia coli).

A. DRUGS IN PRE-CLINICAL TRIALS:

a) Lariocidin-

Lariocidin is a Lasso peptide antibiotic. Lasso peptides are biologically active molecules with a distinct structurally constrained knotted fold, and are natural products belonging to the class of ribosomally-synthesized and post translationally modified peptides (RiPPs). Lariocidin was discovered by Gerry Wright and Manoj Jangra from McMaster University. It is produced by the bacteria, Paenibacillus, that the researchers retrieved from a soil sample collected from a Hamilton backyard.

In vitro studies: -

Lariocidin has shown potent antimicrobial activity against various Gram-positive bacteria, including drug-resistant strains of Staphylococcus aureus and Enterococcus faecalis.

In vivo studies: -

In mouse models of infection, lariocidin significantly reduced bacterial burden in various organs and demonstrated a high survival rate in infected mice.

Low toxicity: -

Lariocidin exhibits low toxicity to human cells in vitro and in vivo, making it a promising candidate for drug development.

b) Halicin-

Halicin is a c-Jun N-terminal kinase (JNK) inhibitor. It was originally developed as a compound for the treatment of diabetes and later repurposed as a potent antibiotic through deep learning

algorithms developed at Massachusetts Institute of Technology (MIT). Its mechanism involves disruption of the proton motive force across the bacterial membrane by interfering with iron homeostasis, thereby impairing ATP synthesis and essential transport processes.

In vitro studies: -

The minimum inhibitory concentration (MIC) of halicin was determined for Escherichia coli ATCC 25922 and Staphylococcus aureus ATCC 29213, using the broth microdilution method. Halicin demonstrated notable antibacterial activity, with MIC values of 16 µg/mL and 32 µg/mL against E. coli ATCC 25922 and S. aureus ATCC 29213, respectively.

In vivo studies: -

A Caenorhabditis elegans model infected by MRSA was employed to evaluate the in vivo effect of halicin against MRSA. The findings revealed the antibacterial activity of halicin against methicillin-resistant S. aureus clinical strains with MICs ranging from 2 to 4 µg/mL.

Animal Toxicology: -

The safety of halicin was evaluated by acute oral toxicity, genotoxicity and subchronic toxicity studies. The results of the acute toxicity test indicated that halicin, as a low-toxicity compound, had an LD50 of 2018.3 mg/kg. The results of sperm malformation, bone marrow chromosome aberration and cell micronucleus tests showed that halicin had no obvious genotoxicity. However, the results of the 90-day subchronic toxicity test indicated that the test rats exhibited weight loss and slight renal inflammation at a high dose of 201.8 mg/kg. Teratogenicity of zebrafish embryos showed that halicin had no significant teratogenicity. Analysis of intestinal microbiota showed that halicin had a significant effect on the intestinal microbial composition, but caused a faster recovery.

B. DRUGS IN PHASE 1 TRIALS:

a) Xeruborbactam-

Xeruborbactam is a new boron-based beta-lactamase inhibitor with activity against both serine and metallo-beta-lactamases in combination with a beta-lactam antibiotic. Qpex Biopharma is developing it. A randomized, double blind, placebo-controlled drug-drug interaction, pharmacokinetics and safety study of cefiderocol in combination with xeruborbactam in healthy adult participants is being done, where 40 participants are enrolled (NCT06547554). The study commenced on September 4, 2024, and is estimated to be completed by December 2025. Interventions used were Xeruborbactam, Cefiderocol, Xeruborbactam + Cefiderocol and Dextrose 5% in water.

b) Zifanocycline (KBP-7072)-

Zifanocycline is a novel third-generation tetracycline-aminomethylcycline antibiotic with a broad spectrum of antibacterial activity against gram-negative and gram-positive bacteria, including methicillin-resistant Staphylococcus aureus (MRSA), penicillin-resistant Streptococcus pneumoniae (PRSP), vancomycin-resistant Enterococcus (VRE), and multidrug-resistant A. baumannii (MDR-AB). Zifanocycline demonstrated efficacy in an in vivo neutropenic murine pneumonia model against S. aureus, K. pneumoniae, and S. pneumoniae and in a neutropenic thigh model against S. aureus, K. pneumoniae, and E. coli.

MICs of Zifanocycline against A. baumannii ranged from 0.06 to 0.5 mg/L, with significant activity against all 8 strains. Average daily doses of Zifanocycline to achieve a static, 1-log10 kill, and 2-log10 kill effect were projected to be 6.92, 9.63, and 13.22 mg/kg, and the mean fAUC/MIC ratios were 6.91, 9.10, and 12.60, respectively.

C. DRUGS IN PHASE 2 TRIALS:

a) Apramycin-

Apramycin is a unique octadiose-monosubstituted 2-deoxystreptamine. Apramycin

evades cross-resistance to other aminoglycosides in clinical use, utilizing a distinct chemical structure that evades enzymatic inactivation by aminoglycoside-modifying enzymes (AMEs) and can still bind and inhibit ribosomes methylated by ribosome-methyltransferases, resulting in superior coverage of highly drug-resistant bacterial pathogens. Preclinical evidence has suggested potent in vivo efficacy of apramycin against both carbapenem-resistant and aminoglycoside-resistant Gram-negative bacilli, and an improved safety profile of apramycin when compared with other aminoglycosides.

In vitro susceptibility testing of multidrug-resistant Gram-negative blood culture isolates showed all carbapenem and third-generation cephalosporin-resistant Enterobacterales, all Acinetobacter baumannii and all Pseudomonas aeruginosa isolates tested in the study to be susceptible to apramycin. Based on its high susceptibility rates and low toxicity compared to colistin, apramycin may represent a promising next-generation aminoglycoside for the treatment of MDR Gram-negative systemic infections, especially bloodstream infections.

D. DRUGS IN PHASE 3 TRIALS:

a) Zosurabalpin (RG6006)-

Zosurabalpin is a novel tethered macrocyclic peptide (MCP) antibiotic. The mechanism of action of this molecule class involves blocking the transport of bacterial lipopolysaccharide from the inner membrane to its destination on the outer membrane, through inhibition of the LptB2FGC complex. There is an accumulation of this endotoxin (lipopolysaccharide) in the bacterial cell, ultimately resulting in the death of the bacteria. Zosurabalpin showed excellent antibacterial activity against carbapenem-resistant Acinetobacter baumanni (CRAB), both in vivo and in vitro.

Phase 1 clinical trials showed that the most common treatment-related adverse events were infusion-related reactions (IRRs), which appeared to be dose-dependent, and all IRRs were fully reversible and mostly of mild intensity. Single IV doses of 10 mg to 2000 mg Zosurabalpin were safe and overall, well-tolerated, and displayed a well-behaved PK profile in healthy participants. On 26 May 2025, Roche said that the experimental antibiotic Zosurabalpin, jointly developed with Harvard University, would enter the third and last phase of testing on humans.

b) Zoliflodacin-

Zoliflodacin is the first in a new class of bactericidal agents called the spiropyrimidinetriones. Zoliflodacin inhibits DNA synthesis through inhibition of bacterial type II topoisomerases, which not only stabilizes the cleaved, double-stranded DNA complex as do fluoroquinolones but also prevents the formation of fused circular DNA required for biosynthesis. The FDA has accepted a new drug application (NDA) for Zoliflodacin on 12th June 2025.

The group of studies includes a pivotal phase 3 trial (NCT03959527) that evaluated Zoliflodacin vs a Standard Of Care (SOC) regimen (500 mg ceftriaxone intramuscular plus 1g oral azithromycin) in patients with uncomplicated gonorrhea. The trial met its primary endpoint by demonstrating that Zoliflodacin was non-inferior to the SOC regimen regarding microbiological response at the urogenital site at the test of cure visit (6 +/- 2 days following treatment). Specifically, the microbiological cure rate was 90.9% in the zoliflodacin arm vs 96.2% in the ceftriaxone/azithromycin arm, representing a difference of 5.3% (95% CI, 1.4% to 8.7%) across patients in the micro-intent-to-treat (ITT) population.

Treatment-emergent adverse events (TEAEs) occurred in 46.2% of patients in the Zoliflodacin arm vs 46.4% of patients in the ceftriaxone/azithromycin arm. The most common TEAEs in the Zoliflodacin arm included headache (9.9%), neutropenia (6.8%), and leukopenia (3.9%). There were no deaths or serious adverse events reported in either arm.

c) Cefepime-Zidebactam-

It is a ß Lactamase/ß-lactamase inhibitor combination antibiotic. Wockhardt Limited is developing it. The overall clinical efficacy in the Phase 3 Trial was 98% at the test-of-cure (TOC), which was 7-10 days after completion of treatment. In comparison, it was 100% for BSI (Bloodstream infections), HABP/VABP (Hospital-acquired bacterial pneumonia/Ventilator-associated bacterial pneumonia) & cIAI (Complicated intra-abdominal infection) and 97.3% for cUTI (Complicated Urinary Tract Infection). Notably, it also demonstrated high pathogen eradication rates (microbiological cure), including for tougher-to-treat HABP/VABP (91%) and BSI patients (100%).

E. APPROVED ANTIMICROBIALS:

a) Sulbactam-Durlobactam-

This combination antimicrobial was approved by the US-FDA on 23rd May, 2023. It is manufactured by Innoviva (formerly Entasis Therapeutics). Sulbactam is a beta-lactam antibacterial and beta-lactamase inhibitor that has bactericidal activity due to its inhibition of Acinetobacter baumannii-calcoaceticus complex (ABC) penicillin-binding proteins PBP1 and PBP3, which are essential enzymes required for bacterial cell wall synthesis. Durlobactam is a diazabicyclooctane non-beta-lactam, a beta-lactamase inhibitor that protects sulbactam from degradation by serine-beta-lactamases. Durlobactam alone does not have antibacterial activity against ABC isolates.

It is indicated in patients 18 years of age and older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP), caused by susceptible isolates of Acinetobacter baumannii-calcoaceticus complex. Recommended dose is 1 g of sulbactam and 1 g of durlobactam (co-packaged product) to be administered every 6 hours by intravenous (IV) infusion over 3 hours in patients with creatinine clearance (CLcr) of 45 to 129 mL/min. The most common adverse reactions were liver test abnormalities (19%), diarrhea (17%), anemia (13%), and hypokalemia (12%). Arrhythmia (9%), Acute Kidney Injury (6%), Thrombocytopenia (6%) and Constipation (6%) were the other adverse reactions.

b) Nafithromycin-

Nafithromycin is a novel lactone ketolide (advanced generation macrolide). It overcomes all three of the macrolide resistance mechanisms—Erm, efflux and ribosomal protein mutations—in Streptococcus pneumoniae. In a global surveillance study, nafithromycin showed potent activity against respiratory pathogens, including macrolide-resistant S. pneumoniae. It also retains consistent activity against ß-lactam and quinolone-resistant S. pneumoniae and covers atypical respiratory pathogens.

On 1st January 2025, Nafithromycin tablet 400 mg was approved in India under the provisions of the New Drugs and Clinical Trials Rules, 2019, for manufacturing in the country for treatment of adults (above 18 years old) with community-acquired bacterial pneumonia (CABP), for supply only to medical colleges, tertiary care hospitals or district hospitals.

Nafithromycin has a broad spectrum of activity, making it effective against all major CABP pathogens. Its bactericidal activity, high lung penetration and prolonged post-antibiotic effect ensure effective pathogen clearance and enable an ultra-short, three-day, once-daily dosing regimen, which improves patient compliance and outcomes.

Nafithromycin stands out as a safer option compared to other antibiotics. Unlike fluoroquinolones, which carry risks of severe side effects such as tendonitis, neuropathy and cardiac issues, Nafithromycin is well-tolerated across age groups, including elderly patients, the key population vulnerable to CABP. It does not need a combination drug treatment, providing a safer alternative therapy for CABP. Further, as an

alternative to fluoroquinolones, Nafithromycin avoids concerns regarding selection of resistant Mycobacterium tuberculosis bacterial infections.

c) Contezolid-

Contezolid is an orally administered oxazolidinone antibacterial agent, is being developed by Shanghai MicuRx Pharmaceutical Co., Ltd. for the treatment of multidrug-resistant (MDR) Gram-positive bacterial infections, including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci.

It was approved by the National Medical Products Administration of China for the treatment of complicated skin and soft tissue infections (cSSTI), including, but not limited to, methicillin-susceptible S. aureus, MRSA, Streptococcus pyogenes and Streptococcus agalactiae in June 2021.

The recommended dosage of contezolid is 800 mg (i.e., two 400 mg tablets) every 12 hours for 7 to 14 days.

d) Cefepime-Enmetazobactam-

Cefepime-Enmetazobactam is an intravenous (IV) antibacterial fixed-dose combination of a 4th-generation cephalosporin and an extended-spectrum ß-lactamase (ESBL) inhibitor, being developed by Allecra Therapeutics and ADVANZ PHARMA for the treatment of infections caused by multidrug-resistant (MDR) Gram-negative bacteria.

In February 2024, cefepime/enmetazobactam was approved in the USA for use in adults with complicated urinary tract infections (cUTI), including pyelonephritis, caused by susceptible strains of Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis, and Enterobacter cloacae complex. In March 2024, Cefepime-Enmetazobactam was approved in the EU for use in adults for the treatment of cUTI, including pyelonephritis, and hospital-acquired pneumonia, including ventilator-associated pneumonia, and the treatment of patients with bacteraemia occurring in association with or suspected to be associated with any of these infections. It was approved by the DCGI in June 2024.

The recommended dosage is 2.5 grams (2 grams cefepime and 0.5 grams enmetazobactam) administered every 8 hours by intravenous (IV) infusion over 2 hours in patients 18 years of age and older with an estimated glomerular filtration rate (eGFR) between 60 and 129 mL/min. The duration of treatment is 7 days and up to 14 days for patients with concurrent bacteremia.

The most frequently reported adverse reactions were increased transaminases (20%), increased bilirubin (7%), headache (5%), and phlebitis/infusion site reactions (5%).

e) Gepotidacin-

It was approved by the US-FDA in March 2025. It is a triazaacenaphthylene bacterial type II topoisomerase inhibitor indicated for the treatment of female adult and pediatric patients 12 years of age and older , weighing at least 40 kilograms (kg) with uncomplicated urinary tract infections (uUTI) caused by Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii complex, Staphylococcus saprophyticus, and Enterococcus faecalis. The recommended dosage is 1,500 mg (two 750 mg tablets) taken orally, twice daily (approximately 12 hours apart), for 5 days.

Gepotidacin tablets should be administered after a meal to minimize the risk of gastrointestinal intolerance. The most common adverse reactions occurring in =1% of patients are diarrhea, nausea, abdominal pain, flatulence, headache, soft feces, dizziness, vomiting, and vulvovaginal candidiasis. Gepotidacin should be avoided in patients with severe renal impairment with eGFR <30 mL/min, including those receiving dialysis. It should also be avoided in patients with severe hepatic impairment (Child-Pugh Class C).

NANOPARTICLES:

Nanoparticles have a diameter ranging from 1 to 100 nm. Biofilm is the complex structure of the pathogen that may often show resistance towards foreign chemicals. These microbial aggregates can be 10-10,000 times less sensitive towards antimicrobial agents than the organism itself in suspension. Nanotherapy seems to have a

significant effect on biofilms.

In addition, Nanoparticles display potent antimicrobial effects through the generation of innate and adaptive host immune responses, inhibition of the electron transport chain, production of toxic reactive oxygen species (ROS), and stimulation of intracellular effects (e.g., enzyme disruption, DNA damage, and protein damage). Important Nanoparticles are Chitosan nanoparticles (40 nm), Silver nanoparticles (7 nm), Zinc oxide nanoparticles (30 nm), Copper oxide nanoparticles (20 nm), and Silver oxide nanoparticles (42.7 nm).

GENE-EDITING APPROACHES FOR TACKLING ANTIBIOTIC RESISTANCE:

The employment of gene editing tools, such as transcription activator-like effector nucleases (TALENs) and zinc finger nucleases (ZFNs), which may be utilized to modify drug-resistant bacteria's DNA precisely, has also contributed to the resolution of antibiotic resistance. The CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats-Cas9) gene editing system, which is currently regarded as the most inventive method, has been applied quickly to the treatment of antibiotic resistance or MDR. It can accurately target a particular sequence using just one guide RNA (gRNA) and the protein that accompanies it (Cas). This system usually acts as an adaptive immunity, shielding the body from genetic material that is not native to the body.

CONCLUSION:

Concerns arising from the high cost of new antibiotics are possible inequities in the availability of drugs between low, middle, and high-income countries. The AMR burdens vary across geographical regions, even on the same continent. Small particle size and the charged surface have provided Nanoparticles an easy route to enter the pathogenic cells, interfere with cellular contents such as protein and DNA, thereby inducing programmed cell death. Antibiotic therapy in conjunction with nanotherapy is now being considered a methodical approach to overcome microbial resistance.

The in-depth knowledge of the spectrum and mechanism of action, along with antibiotic stewardship targeting the rational use of antibiotics, can be the leading edge in the battle against multidrug-resistant pathogens, especially in healthcare settings with limited facilities and resources.

REFERENCES:

1. World Health Organization. 2023 Antibacterial agents in clinical and preclinical development: an overview and analysis.
2. Bassetti M, Vena A, Larosa B, Giacobbe DR. New antibiotics in clinical pipeline for treating infections caused by metallo-ß-lactamases producing Gram-negative bacteria. Curr Opin Infect Dis. 2024 Dec 1;37(6):582-588. doi: 10.1097/QCO.0000000000001056. Epub 2024 Sep 12. PMID: 39106036; PMCID: PMC11556884.
3. Katsarou A, Stathopoulos P, Tzvetanova ID, Asimotou CM, Falagas ME. ß-Lactam/ß-Lactamase Inhibitor Combination Antibiotics Under Development. Pathogens. 2025 Feb 8;14(2):168. doi: 10.3390/pathogens14020168. PMID: 40005543; PMCID: PMC11858600.
4. Zong TX, Silveira AP, Morais JAV, Sampaio MC, Muehlmann LA, Zhang J, Jiang CS, Liu SK. Recent Advances in Antimicrobial Nano-Drug Delivery Systems. Nanomaterials (Basel). 2022 May 29;12(11):1855. doi: 10.3390/nano12111855. PMID: 35683711; PMCID: PMC9182179.
5. Sharmin S, Rahaman MM, Sarkar C, Atolani O, Islam MT, Adeyemi OS. Nanoparticles as antimicrobial and antiviral agents: A literature-based perspective study. Heliyon. 2021 Mar 13;7(3):e06456. doi: 10.1016/j.heliyon.2021.e06456. PMID: 33763612; PMCID: PMC7973307.

A World Without Pharmacology : The Boundaries Of Modern Medicine

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Modern medicine has reached to great heights in the recent years with advances in multiple therapeutic options and newer technologies to deal with varying diseases and day to day ailments. At its very core is Pharmacology, the unsung hero that dedicatedly has been involved in newer drug development, research and varying toxicology studies, without which modern medicine would have been far from its current position. Pharmacology is a wide field that gives us knowledge about the understanding of drug action, its mechanism of action as well as ways to estimate its adverse potential (1). And yet, the role of Pharmacology has been at times overlooked. Hence, through this article, my aim is to highlight the importance of my subject by letting the world move on without us, Pharmacologists.

State of healing – Empirical :

Long back in the ancient era, empirical therapy with the help of folk medicine used to be the primary form of healing. The roots of Pharmacology can be traced back to the ancient Egyptians who used plant products as a source of healing (2). These were mainly based on trial and error methods with the roots of ritualistic or traditional systems which were based on intuition and sometimes surrounded by superstitious beliefs. The products of plant, animal and mineral origin that are currently being used undergoes proper pharmacological studies in order to establish its purity and standard dosing. But without pharmacology, even though these crude products are useful, they will lose their efficiency and might result in various toxicities when given unchecked.

Clinical practice will be highly erratic as the expectation of the treatment outcome will be highly variable. While a single product may be beneficial to one, it might not work at all in others. And what about all the unchecked interactions that will occur in the body. Without proper dose adjustments and purification of the active ingredients, there will be higher cases of toxic exposures and even accidental poisonings.

Innovation will slow, if not altogether halt. And serendipitious discovery of newer active principles will be the only hope for advancement in healing options. There will be a complete lack of reproducible treatment evidence and hence overall, the public belief will start to dwindle. Pharmacology is a rapidly evolving field which has been making significant contributions for a stronger healthcare system (3).

Infectious diseases without Pharmacology :

One of the greatest threats to humankind will continue to be infectious diseases that will significantly lower the life expectancy. The

infectious diseases will run rampant without check in the absence of antibiotics, antivirals, antifungals, vaccines and the Antibiotic Stewardship Program (AMS). It has taken modern medicine years to combat fatal diseases like tuberculosis, pneumonia, cholera and the recent pandemic of coronavirus across the globe has taken its toll. Hence, without Pharmacology these diseases will not only be wiping populations, there will be difficulty in diagnosis as well as in stopping their prevention as well.

Even simple bacterial infections which are easily cured with antibacterials may turn into a lethal experience. Minor infections needing antimicrobial cover like wound infections, dental infections may lead to sepsis and hospitals will become the active ground of transmission of diseases. Healthcare workers will be at constant risk due to the absence of healthcare. Viral diseases will travel unchecked and unbothered leading to frequent outbreaks, epidemics and pandemics. Without Pharmacology, even after ascertaining the diagnosis and identification of the causative agent, there will be no vaccines to combat this agent. Infectious diseases will reign the world.

Chronic Diseases - Untreated and often fatal :

In the current times, chronic diseases are the silent killers that are responsible for morbidity and mortality across the globe. Preventive measures and pharmacological advances to support the stable functioning of the body has resulted in a decrease and reduced mortality with these diseases and increased lifespan. However, without Pharmacology, these diseases will keep progressing, increasing disability rates and significantly decreasing the quality of life. Even symptomatic relief of some long standing conditions will not be possible.

Surgery Without Pharmacology - No Evolution:

The first prerequisite of surgery is asepsis, which itself will not be possible without Pharmacological preparations. Without a proper antibiotic coverage, the operative procedures will be limited to crude and fast procedures only. Organ transplantation will only remain a topic of theoretical discussion. Postpartum complications and maternal mortality will reach new heights. Pharmacology is not only essential for surgical procedures but also is important to improve patient outcome (4).

Another field that will completely disappear is Anaesthesia. If there are no general or regional anaesthetics or properly formulated analgesics, the very criteria of anaesthesia remains unfulfilled. Even if somehow, a surgery is successfully conducted, there will be no intravenous fluids, no anticoagulants and recovery will ultimately be a very risky business. With modern Pharmacology, however, anaesthesia has become safer and more targeted (5).

Mental Health - An Unmanaged Global Crisis :

Mental health issues are gradually increasing in our society and has become a matter of global concern (6). Without proper medication, these diseases will continue to affect people decreasing their productivity. There will be no antidepressants and hence people with severe depression will continue to deteriorate and there will be an increase in suicidal rates. There will be no treatment for anxiety, bipolar diseases and these will affect the society at a very basic level. The stigma behind these diseases will increase and people will still prefer to send the affected to asylum based confinement in order to maintain their public image.

Emergency Medicine - Complete Collapse :

Emergency medicine is heavily dependent on Pharmacology and without it, even after accurate diagnosis, it will be futile. Only supportive care can be given and there will be a complete lack of trust on the healthcare system. Poisoning cases will suffer through the adverse effects and will ultimately succumb to a very painful death; even

very treatable conditions might turn fatal. Trauma cases will continue to suffer without analgesics and eventually die due to sepsis or shock.

Toxicology - A World Without Safety :

A drug can act as a therapeutic agent as well as a poison based on its dosing and toxicology helps us understand this delicate balance. Pharmacodynamic studies gives us an idea about the rate of absorption, the clearance and excretion of drugs, indicating drugs that are more prone to accumulation. Based on these factors, we can predict the probable adverse reactions and adjust the dose accordingly. Without Pharmacology, dosing will be based on hit and trial method in order to ensure benefits without adverse effects, which will be extremely difficult to achieve. Even in current scenarios, we face toxic reactions but Pharmacology has enabled us with options to deal with these situations. If therapeutic index and drug safety studies are not conducted, physicians will not be able to accurately treat multiple conditions due to the fear of toxic reactions. Pharmacology and toxicology go hand in hand to determine the efficacy, tolerability, safety and the pharmaceutical products (7).

Biomedical Research - Halted at the Foundation :

The foundation of biomedical research is to modify the biological processes by targeting different receptors, biological molecules or pathways. Without Pharmacology, there will be no proper framework as there will be no knowledge of the various aspects of drugs in order to modulate them. Newer drugs will be discovered purely by chance and their potential will remain largely benign. Without safety and toxicity studies, the clinical trials will result in grossly variable results and multiple casualties that will eventually lead to a shutdown of research as a whole. It is because of the rapid advances in the field of Pharmacology that the process of drug discovery has become such a sophisticated work of art and newer drugs are being pushed out into the market (8).

Public Health Without Pharmacology - Severely Weakened :

The emergence of disease outbreaks can cripple the healthcare system of any nation. In order to prevent that and protect the population, vaccines play a very significant role and these products are made after stringent testing and safety and efficacy assessment involving multiple trials. Numerous infectious diseases that were a great source of burden to the community are on the verge of cure and unheard of due to proper treatment regimens made available due to the advances in our field.

Conclusion

This virtual scenario here was emphasised in order to bring into perspective the very irreplaceable role of Pharmacology. In its absence, practice of medicine will be a gamble with rationality a mere concept of fiction. The world will be dominated by ancient diseases, with epidemics sprouting in various regions every now and then. Hence, we as Pharmacologists , are making life safer and better and should always commit to keep our subject growing, because without it, humankind will be essentially lost.

References

1. Li Q, Guan X, Wu P et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. NEJM. 382,1199-1207 (2020).
2. Mohebali M. Visceral leishmaniasis in Iran: review of the epidemiological and clinical features. Iran J Parasitol. 8:348-358 (2013).
3. Mohebali M, Hajjaran H, Hamzavi Y et al. Epidemiological aspects of canine visceral leishmaniosis in the Islamic Republic of Iran. Vet Parasitol. 129,243-251 (2005).
4. Nishtala, P. S., Salahudeen, M. S., & Hilmer, S. N. (2016). Anticholinergics: theoretical and clinical overview.Expert opinion on drug safety,15(6), 753-768.
5. Kearns, R., Macfarlane, A., Grant, A., Puxty, K., Harrison, P., Shaw, & Kinsella, J. (2016). A randomised, controlled, double blind, non-inferiority trial of ultrasound-guided fascia iliaca block vs. spinal morphine for analgesia after primary hip arthroplasty.Anaesthesia,71(12), 1431-1440.
6. Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. Lancet Psychiatry 2016;3:171-8.
7. Solanki M. Cytochrome P450 2J2: Potential Role in Drug Metabolism and Cardiotoxicity. Drug Metab. Dispos. 2018;46:1053–1065. doi: 10.1124/dmd.117.078964.
8. Zhou P, Liu Z, Chen Y et al. Bacterial and fungal infections in COVID-19 patientsn. Infect Control Hosp Epidemiol. 41,1124-1125 (2020)

Doom Scrolling vs Bloom Scrolling: A Neurobiological Perspective on Digital Behaviours and Health

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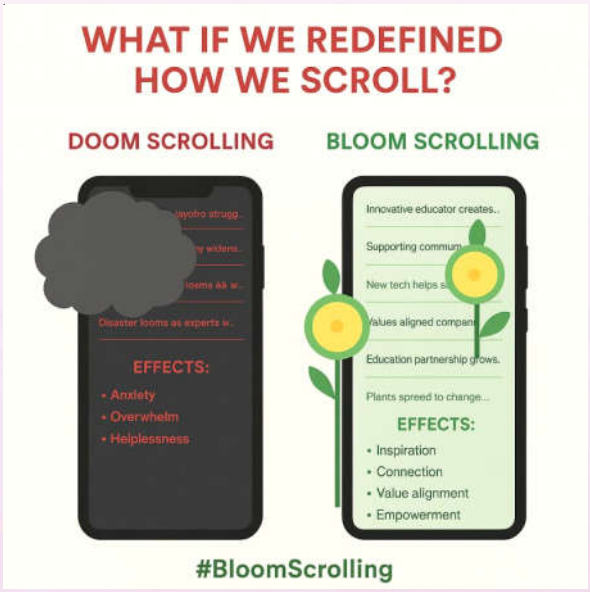
In clinical practice, I increasingly meet students and working professionals presenting with unexplained anxiety, poor sleep, and impaired concentration. A subtle yet powerful contributor is the pattern of doom scrolling — the compulsive consumption of negative digital content.



What Doom Scrolling Does to the Brain

Neuroscientific evidence shows that chronic exposure to negative online stimuli activates the amygdala, triggering a persistent threat response:

- Heightened cortisol levels and sympathetic activation (1).
- Increased anxiety and perceived stress (2).
- Sleep disruption and melatonin suppression due to screen overuse (3).
- Reinforcement of compulsive checking behaviours similar to addiction pathways (4).

A WHO report (2022) further warns that excessive negative digital exposure contributes to a measurable rise in anxiety and depressive symptoms among young adults (5).

In simple terms, the brain interprets online negativity as ongoing threat — even when the body is physically safe.

Bloom Scrolling: A Healthier Digital Habit

Intentional exposure to constructive or enriching content — learning, creativity, culture, health, spirituality — has the opposite effect:

- Activates prefrontal cortex circuits associated with calm, focus, and executive functioning (6).
- Enhances positive affect and reduces stress reactivity (7).
- Supports dopaminergic reward pathways in a non-addictive, regulated manner.
- Improves sleep quality when paired with mindful digital use (8).

This is not about "positive thinking."
It's about neurobiological regulation.

The Clinical Implication

The human brain has limited capacity to differentiate between real-world danger and digital threat cues. Chronic doom scrolling keeps the body in a near-constant fight-or-flight posture, leading to:

- Irritability.
- Difficulty concentrating.
- Low motivation.
- Emotional exhaustion.
- Somatic symptoms (tension, headaches, fatigue).

Conversely, bloom scrolling promotes neuroplastic resilience — a measurable improvement in emotional regulation and cognitive flexibility.

A Practical Framework for Patients & Professionals

Before scrolling, ask:

"Is this input elevating stress or enhancing growth?"

If it elevates stress - pause or skip.

If it enhances growth - stay.

Digital hygiene is now as essential as sleep hygiene or nutrition.

Your neural circuits become what they repeatedly consume.

References

1. Garrett PM, White JP, Lewandowsky S, Kashima Y, Perfors A. The psychological effects of engaging with COVID-19 related misinformation. Proc Natl Acad Sci U S A.2021;118(15):e2101526118. doi:10.1073/pnas.2101526118
2. Bendau A, Petzold MB, Pyrkosch L, et al. Associations between COVID-19 related media consumption and symptoms of anxiety, depression and perceived stress in the general population. J Anxiety Disord. 2021;79:102394. doi:10.1016/j.janxdis.2021.102394
3. Levenson JC, Shensa A, Sidani JE, Colditz JB, Primack BA. The association between social media use and sleep disturbance among young adults. Sleep Health. 2017;3(5):351–357. doi:10.1016/j.sleh.2017.06.001
4. Turel O, He Q, Xue G, Xiao L, Bechara A. Examination of neural systems sub-serving Facebook "addiction". J Behav Addict. 2014;3(4):1–10.doi:10.1556/JBA.3.2014.016
5. World Health Organization. Mental health and COVID-19: Early evidence of the pandemic's impact. Geneva: WHO; 2022.Available from: https://www.who.int/publications (accessed 2022)
6. Creswell JD, Taren AA, Lindsay EK, et al. Alterations in resting-state functional connectivity link mindfulness meditation with reduced interleukin-6. Proc Natl Acad Sci U S A. 2016;113(35):E3907–E3916.doi:10.1073/pnas.1603722113
7. Fredrickson BL. Positive emotions broaden and build. Am Psychol. 2013;56(3):218–226. doi:10.1037/0003-066X.56.3.218
8. Exelmans L, Van den Bulck J. Bedtime mobile phone use and sleep in adults. Sleep Med. 2019;64:146–152. doi:10.1016/j.sleep.2019.06.016

Zavegepant: A Novel Intranasal CGRP-Antagonist For Acute Attack Of Migraine

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Migraine headaches!! - A widespread and complex neurobiological disorder characterized by recurring unilateral headaches identified as second leading cause of disability throughout the world posing significant global burden with an increase incidence of 1.7% since 1990. It has both personal and socioeconomic implications along with physical pain adding to lower quality of life with peak prevalence being identified in middle life.

Are migraine headaches bothersome? The impact of migraine headache on functionality for those who experience it have higher risk of greater indirect costs related to increased work loss, short-term as well as long-term disability. In accordance with the International Classification of Headache Disorders (ICHD), the 'third edition' diagnostic criteria for chronic migraine include headache for at-least 15 days per month (with migraine-associated features for a minimum of 8 of the days), whereas the diagnostic criteria for episodic migraine involve headache for 14 or less days per month.

Migraine pathophysiology? Initially, migraine headaches were thought to cause strictly due to vasoconstriction, which was the reason for therapies such as triptans and ergotamines. However, through extensive research, it is evident that migraine phathophysiology also have component within the core brain circuits, most prominent parts being disturbance in trigeminal ganglia, trigeminal nucleus, medulla, pons, hypothalamus and thalamus, resulting in modulation of sensory activity causing migraine headaches. Release of the potent vasodilatory neuropeptide like Calcitonin Gene-related Peptide (CGRP) in trigeminovascular system is believed to be crucial for migraine generation. This provides rationale for development of newer CGRP-targeted therapies –the "Gepant" class, a novel CGRP-antagonist for migraine. Gepants are small-molecule compounds that selectively antagonize CGRP receptors, thereby preventing CGRP from binding and triggering the pro-migraine signaling cascade. The first-generation gepant developed was telcagepant but later discontinued due to hepatotoxicity concern. Second-generations oral gepants for acute migraine include ubrogepant that gained approval in 2019 followed by rimegepant in 2020. Atogepant approved in 2023 represents a distinct therapeutic advance as oral gepant in chronic migraine prevention.

Another novel calcitonin gene-related peptide (CGRP) receptor antagonist was studied in United States for several years for the purpose of treating migraine headaches. After years of rigorous trials, on 9th March 2023, Zavegepant received its first approval from the Food and Drug Administration (US FDA). It was developed by Pfizer under a license from Bristol-Myers Squibb. Branded as ZAVZPRET, a third-generation and the only intranasally administered drug in the "gepant" class, it is an advancement from the hepatotoxic

initial two generations of oral gepant drugs. It has shown quite remarkable efficacy achieving therapeutic result with 10 mg single nasal spray in 24-h period, acting as fast relief for acute attack of migraine with or without aura in adults.

Zavegepant consists of a 37-amino-acid neuropeptide that acts on calcitonin-like receptors, blocking the potentiation of the adenylate cyclase pathway. Antagonist to CGRP receptor increases inhibitory mechanisms to desensitize neuronal circuits thus leading to development of a peripherally acting drug that could modulate CGRP to act abortively and prophylactically. The summery of pathophysiological process of migraine has been highlighted in figure 1:

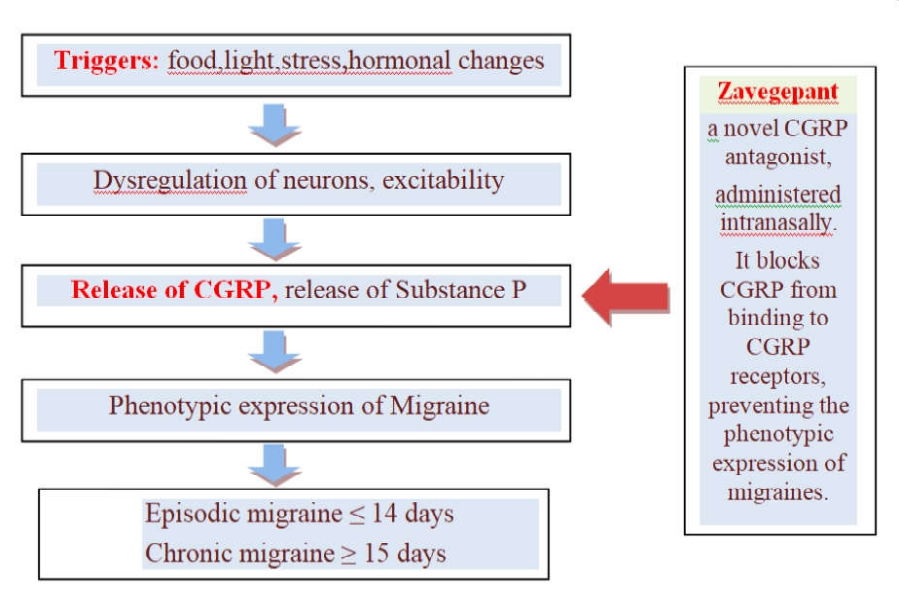

Fig 1. Summary of pathophysiology of migraine. CGRP, calcitonin gene-related peptide.

Is Zavegepant an effective and safe intranasal gepant ? A phase 2/3, double-blind, placebo-controlled, and dose-ranging randomized controlled study conducted to assess the efficacy and safety of intranasally administered single-dose Zavegepant 10mg or 20mg produced favourable effects for acute treatment of migraine in adults on specified outcomes when compared to a placebo. Zavegepant 10mg also had a favourable tolerability during long-term treatment in a 1-year, phase 2/3 open-label safety study.

Intranasal Zavegepant 10mg was found to be effective in acute migraine in adults participating in a phase 3, double-blind, placebo-controlled, multicenter randomized controlled study that demonstrated primary endpoint i.e. pain freedom 2hr post-dose and freedom from the Most Bothersome Symptoms of migraine (MBS) 2hr post-dose. Furthermore, this novel drug has a favourable safety profile, with no signs of hepatotoxicity. Common observed adverse events were dysgeusia, nasal discomfort and nausea with no severe adverse events.

Preferred over triptans? - Triptans are gold standard for migraine. However, while compared with alternative treatments for acute migraine attacks, the intranasal Zavegepant is found to be beneficial for patients who struggle with oral medication because of extreme nausea and vomiting. Nasal triptans use is limited due to its unfavorable safety profile like presence of cardiovascular contraindications. Sumatriptans

also have contraindications in patients having ischemic heart disease, hypertension, coronary artery vasospasms and adverse effects like peripheral vascular ischemia, Raynaud's syndrome, making it less favorable. Certain triptans were observed to be associated with greater incidence of adverse effects as compared to CGRP antagonists. This illustrates the benefit of using intranasally administered Zavegepant due to its safety profile, thus, having the capability of becoming the new norm for fast relief in acute migraine attacks.

Conclusion:

Migraine headaches are a complex neurobiological disorder causing significant detriment to quality of life and decreasing significant functionality during the episodes. A new and promising class of drug, CGRP-receptor antagonists, has shown efficacy in migraine treatment and has potential to improve quality of life for patients. Intranasal Zavegepant has considerable potential to be promising alternative for patients who struggle with oral medications like triptans due to its various side effects and poor tolerance. However, the long-term effects, drug-drug interactions and possible use of combination therapies of Zavegepant is yet to be explored as well as the oral route of delivery of the CGRP antagonist. Efforts are underway to achieve future approval in Europe and India as well.

References:

1. Noor N, Angelette A, Lawson A, et al. A Comprehensive Review of Zavegepant as Abortive Treatment for Migraine. Health Psychology Research.2022;10(2).
2. Larik, et al. Nasal spray (Zavegepant) for migraines: a mini-review. Annals of Medicine & Surgery.2023; 85: 2787-2790.
3. Dhillon S. Zavegepant: First Approval. Drugs. 2023; 83: 825-831.
4. Cho S, Chang K. Gepants for Migraine: An Update on long-Term Outcomes and Safety Profiles. Headache Pain Res. 2025; 26(3):184-192. https://doi.org/10.62087/hpr.2025.0012.

Olanzapine- Induced Dress Syndrome : A Case Report

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INTRODUCTION:

Psychotropic medications are notorious for causing cutaneous adverse reactions. 1 out of every 1000 inpatients is affected by cutaneous reactions-TEN and SJS are most widely reported (1). Recently, "Drug Reaction with Eosinophilia and Systemic Symptoms" abbreviated as DRESS has caught attention of clinicians due to its unique clinical features and unknown pathogenesis. Psychotropic drugs suspected to cause DRESS are amitriptyline, clomipramine, lamotrigine, mirtazapine, bupropion, benzodiazepines, carbamazepine, oxcarbazepine, olanzapine (1,2).

PATHOGENESIS (3) :

DRESS is considered to be an immunological reaction to a drug or its metabolites. Pathogenic processes are due to:-

- Immunological hypersensitivity reaction (Type IV) with genetic vulnerability determined by HLA types.
- Viral reactivation (HHV-6).
- Expansion of regulatory T-cells.

CLINICAL FEATURES :

- Typically occurs 2-6 weeks after drug intake (4).
- High grade fever and rash associated with lymphadenopathy, arthritis, general malaise. Also associated with multiple organ involvement (liver 50-87%, kidney 10-53%) (1,5,6).
- Anicteric hepatitis associated with elevated serum ALT is common (icterus signals poor prognosis) (7).
- Kidney involvement presents with increase serum-creatinine, proteinuria which is newly onset.
- **Hematological abnormalities includes-** atypical lymphocytes, eosinophilia. leucocytosis (occasionally) and thrombocytopenia (8).
- **Less involved systems -** pulmonary (non-productive cough, breathlessness, acute interstitial pneumonitis, pleuritis, ARDS).
- **Cardiovascular:** myocarditis, AV block.
- **Skeletal Muscle:** rhabdomyolysis.
- **Neurological:** headache, seizure, coma or disturbed speech.
- **Miscelleneous:** acute pancreatitis, arthritis, gastrointestinal bleeding (7,8).

DIAGNOSTIC CRITERIA:

International Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) criteria (9), Japanese consensus group criteria (10).
Differential Diagnosis: TEN, SJS, Generalized Bullous Fixed Drug Eruption (GBFDE), acute viral infections (EBV, reactivation of HHV-6) (3).

MANAGEMENT (3) :

- Complete withdrawal of the offending drug.
- Supportive care (symptomatic treatment).
- Judicious use of systemic steroids.

CASE HISTORY:-

A 49 years old married male was diagnosed as a case of paranoid schizophrenia presenting with fearfulness, suspiciousness, auditory hallucinations, wandering tendencies, decreased sleep and appetite for past three months. He was treated on OPD basis with oral Olanzapine 10mg and Lorazepam 2mg per day, following which his psychiatric symptoms improved.

After 5 weeks of the above medications, he developed high grade fever followed by rashes all over the body after 3 days. The condition deteriorated when he developed facial puffiness and erythematic lesions all around the body especially around the trunk and face after 3 days. He had no past history to adverse effect of any drug.

General presentations during time of hospital admission:- patient was drowsy, icteric, axillary lymphadenopathy, anasarca, tachycardia.

- BP: 110/80 mmHg.
- Pulse rate: 92 beats/minute.
- Respiratory rate: 22 breaths/minute.
- Chest Bilateral clear with symmetrical air entry.
- Normal heart sounds with no focal neurological deficit.
- Other systems were within their normal biological and physiological state.

LABORATORY FINDINGS:

Parameters (unit expressed)	**Day 1**	**Day 3**	**Day 7**
Hb (g/dL)	10.4	10.2	10.2
Total Count (cells/mm^3)	26,720	21,345	9300
Differential Leucocyte Count	$N_{71}L_{11}E_{13}M_5B_0$	$N_{68}L_{16}E_{11}M_5B_0$	$N_{65}L_{12}E_1M_3B_0$
Absolute Eosinophil Count (AEC) (cells/mm^3)	3030	1810	195
Liver Function Test			
• Bilirubin	Total=13.2 Indirect=3.2, Direct=10.0	Total=12.6 Indirect=1.8, Direct=10.8	Total=1.2 Indirect=0.1, Direct=1.1
• AST • ALT • Se-creatinine • Blood-urea • Na^+ • K^+	544 430 0.9 30.2 138 4.6	671 351 0.6 28.6 131 4.8	52 44 0.6 26.1 136 4.9

- **Urine RE:** Normal findings.

RADIOLOGICAL FINDINGS:

PAV CXR	Within normal limits
HbsAg	Non-reactive
Anti HCV	Non-reactive
Anti HAV	Non-reactive
Anti HEV	Non-reactive
Leptospira antibody	Non-reactive
Plasmodium falciparum/vivax	Negative
ECG	Normal Sinus Rhythm
USG (w/a)	• Presence of peritoneal fluid • Bowel gas shadow • Other parameters within normal range.

MANAGEMENT:-

- All psychotropic medications were stopped initially and the patient was started with intravenous Dexamethasone 16mg/day, antihistaminic Levocetrizine 10mg/day, topical steroid (Clobetasol lotion). Oxygen using nasal prongs was given to maintain the SP02 above 95% on the day of admission. The urine output was normal (urine collected in urine bag through urinary catheter) was removed on day 3.
- Tablet Lorazepam 2mg at bedtime was added on day three. The symptoms subsided gradually by 7th day of treatment. All the laboratory, radiological investigations were within normal range.
- Dexamethasone was gradually tapered off.
- At discharge, oral Risperidone 2mg/day once daily was added, patient and caregivers were explained regarding the possible ADR of the medications.

Follow-up

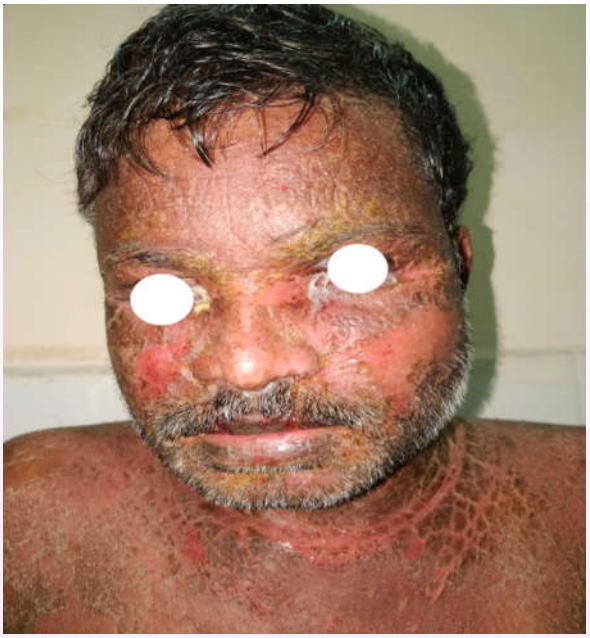
Follow up was done at 2nd and 4th weeks of discharge and the patient was found to be maintaining well with the prescribed medications. No ADR were reported by patient and the caregivers. Currently he is on oral Risperidone 2mg/day, free from psychotic symptoms and with normal biological functions.

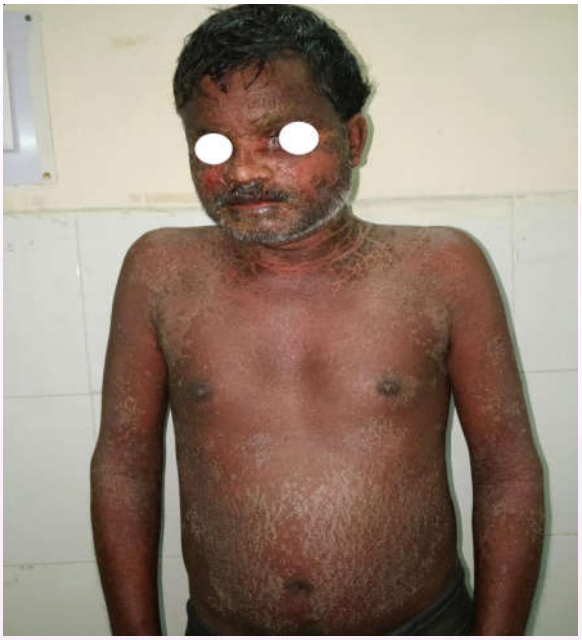
DISCUSSION:

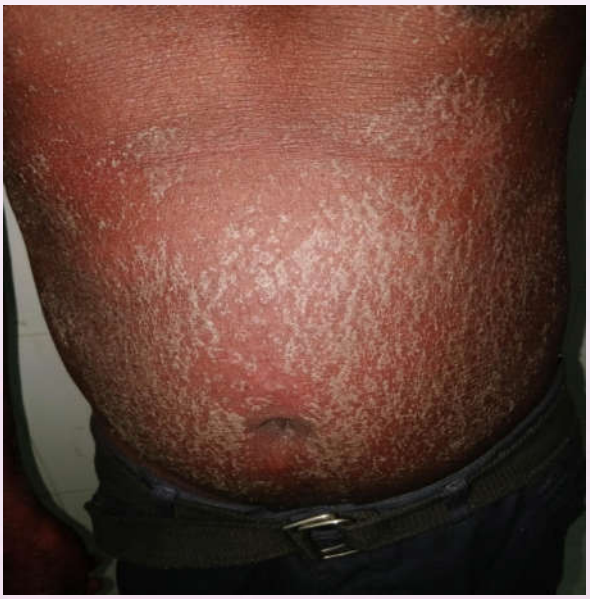
Although DRESS is a rare disease, it represents a significant and potentially devastating adverse reaction to psychotropic drugs. Psychotropic causing DRESS is scarcely reported. Extensive reporting and educating clinicians as well as patients regarding DRESS and its seriousness will lead to timely intervention and decreased mortality and morbidity.

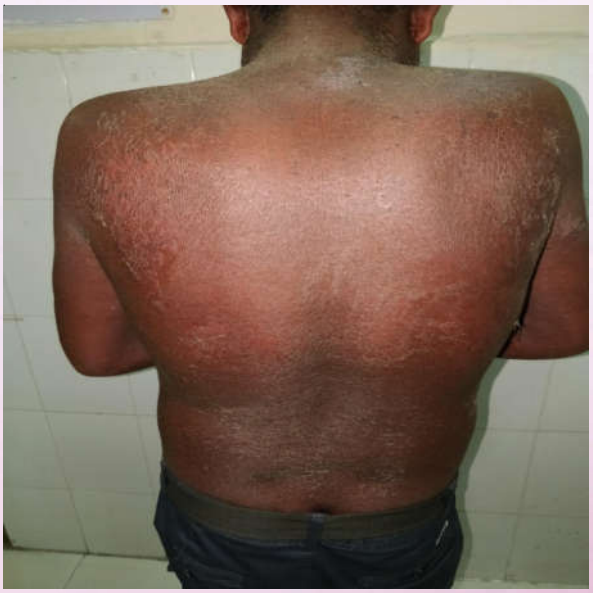
Further extensive research is required in elucidating DRESS pathogenesis so that vulnerable patient groups can be identified and prompt management could be done.

PHOTOGRAPHS OF THE PATIENT









- Rashes involving face, trunk and back

References

(1) Remajean JC,Stern RS.Severe adverse cutaneous reactions to drugs. New England Journal of Medicine 1994, Nov 10,331 (19):1272-85.

(2) Cacumb P, Musetta F, Meyer O, Remajean JC The DRESS syndrome: A literature review: The American Journal of medicine 2011, Jul 1:124 (7): 386-97.

(3) Chen YC, Cha YT, Chu CY Drug reaction with eosinophilia and systemic symptoms: A drug induced hypersensitivity syndrome with variable clinical features, Dermatologica 2013 Dec1:31(4);196-204.

(4) Bagut N, Remajean JC Drug induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic Symptoms: DRESS), in clinical medicine and surgery 1996 Dec 1 (vol15, No. 4, page 250-257).

(5) Biayat JP, Broton H, Frymann H Network of the French Pharmacovigilance centre. Variability in the clinical pattern of cutaneous side effects of drugs with systemic symptoms does a DRESS syndrome.

(6) Chimma OC, Yang LC, Mung SL, Chang VC Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: A study of 30 cases in Taiwan. Journal of the European Academy of Dermatology and verenology 2020 Sept 22; 1044-49.

(7) Remajean JC, Victoria CC. Hypersensitivity syndrome: Archieve of Internal medicine 1995 Nov 27; 155(21): 2285-2290.

(8) Kanna T. Et al Association between anticonvulsant hypersensitivity syndrome and human herpes virus 6 reactivation and hypogammaglobulinemia.Archieve of dermatology 2004 feb1: 140 (2); 183-186.

(9) Sahuda P, Liss Y, Chu CY, Creamer D, Sideroff A, RegiSCAR Study group. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from perspective Kegi SCAR study: British Journal of Dermatology, 2013 Nov, 169 (5): 1071-80.

(10) Hashimoto K, Ellima M. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral infections. The British Journal of dermatology 2007 Mar 23; 156 (5); 1003-4.

District Residency Program Posting at Gomati District Hospital: Reflections on Scope, Learning Objectives, and Challenges Faced by an MD Pharmacology Resident

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INTRODUCTION

The District Residency Program (DRP) was introduced to ensure that postgraduate residents understand the realities of healthcare delivery at the district level. For a pharmacology trainee, the DRP is designed not only to strengthen clinical exposure but also to develop competencies in drug utilization research, pharmacovigilance, essential drug list planning, and pharmacy operations. My three-month posting at Gomati District Hospital provided significant exposure to emergency care and acute patient management, but also revealed limitations in aligning duty allocations with pharmacology-specific learning objectives. This paper documents my experience and critically evaluates the scope and challenges of the DRP.

INTENDED LEARNING OBJECTIVES OF DRP POSTING

The prescribed objectives for MD Pharmacology residents during the DRP include:

1. Conducting Drug Utilization Studies with special focus on antibiotic usage in OPD and IPD.
2. Estimating Antibiotic Consumption using hospital pharmacy store records.
3. Collecting and Reporting Adverse Drug Reactions (ADRs) to the AMC coordinator.
4. Performing Prescription Audits in both OPD and IPD settings.
5. Identifying Medication Errors and communicating findings for corrective action.
6. Preparing an Essential Drug List (EDL) tailored to the district hospital's needs.
7. Conducting Point-Prevalence Surveys to understand drug use patterns and disease burden.

EXPERIENCE AND SCOPE OF THE POSTING

1. EXTENSIVE EXPOSURE TO EMERGENCY AND TRAUMA CARE

Although my objectives emphasized research-oriented and ward-based pharmacology activities, I spent most of my posting in:

1. Trauma bay.
2. Emergency stabilisation area.
3. Poisoning and acute medical emergencies.

This exposure provided hands-on learning in:

- Emergency drug protocols.
- Use of life-saving medications.
- Management of poisoning cases.
- Triage-based pharmacotherapy.
- Rapid decision-making with limited diagnostics.

2. REAL-WORLD APPLICATION OF PHARMACOLOGY

The emergency setting allowed direct observation of:

- Rational and irrational prescribing patterns.
- High dependence on empiric therapy.

- Antibiotic escalation due to lack of diagnostics.
- Constraints in drug availability and stock-outs.
- This helped me understand how pharmacology principles meet practical limitations at the district level.

3. SCOPE FOR PUBLIC HEALTH INSIGHTS

I gained indirect exposure to:

- National health program drug supplies.
- Maternal-child health drug protocols.
- Vaccine storage and cold chain challenges.
- Seasonal disease trends (diarrheal outbreaks, Acute Respiratory Infection peaks).

4. ESTIMATING ANTIBIOTIC CONSUMPTION FROM PHARMACY STORE RECORDS.

I was able to visit the pharmacy store and review antibiotic stock. Understood general trends of high-use antibiotics such as:

- Third-generation cephalosporins
- Metronidazole
- IV amoxicillin-clavulanate

Noted practical issues such as stock-outs, emergency substitutions, and delayed procurement cycles.

5. COLLECTING ADRS AND REPORTING TO THE AMC COORDINATOR

Emergency postings allowed me to witness multiple potential ADRs, especially:

- Drug-induced gastritis.
- Antibiotic-related rashes.
- Reactions to anti-snake venom.
- Dizziness due to anti-hypertensives.

6. PRESCRIPTION AUDIT IN OPD

Formal prescription auditing in OPD/IPD was hard to perform due to limited posting time in wards.

Identified common issues like writing brand names instead of generics, and lack of documentation of indications.

CHALLENGES IN ACHIEVING LEARNING OBJECTIVES

1. LIMITED WARD EXPOSURE

Most pharmacology objectives—such as prescription audits, point-prevalence surveys, ADR reporting, and drug utilization studies require:

- Access to inpatient case records.
- Regular interaction with ward teams.
- Time for data collection and documentation.

Due to continuous emergency postings, these activities could not be performed to the desired depth.

2. CONSTRAINTS IN CONDUCTING AUDITS AND SURVEY

- The emergency and trauma posting schedule left little opportunity for structured ward visits, which are essential for collecting complete prescriptions and treatment charts.
- High patient turnover and overcrowding in the emergency department limited the time for detailed review.
- Due to shortage of staff and time constraints, healthcare teams were often unable to collect detailed history.

3. PHARMACOVIGILANCE LIMITATIONS

Although ADRs do occur frequently in emergency settings:

- Documentation is brief.
- Case load is high.
- Relatives are anxious. ADR reporting was hindered by
- Inconsistent documentation.
- Lack of access to electronic medical records or standardized reporting forms created logistical barriers to systematic ADR reporting.
- Missing drug histories and limited awareness among staff about the importance of pharmacovigilance were also acted as barriers.

LEARNING ACHIEVED DESPITE CHALLENGES

1. STRENGTHENED CLINICAL PHARMACOLOGY SKILLS IN EMERGENCY SETTINGS

I became more confident in:

- Correct dosing of emergency medications.
- Prioritizing essential drugs.
- Recognizing ADRs in acute scenarios.
- Fluid and electrolyte management principles.

2. IMPROVED COMMUNICATION AND TEAMWORK

Working closely with Emergency medical officers, Nurses & Paramedics enhanced my interpersonal and coordination skills.

3. INSIGHTS INTO HEALTHCARE SYSTEM GAPS

The posting demonstrated everyday issues in district hospitals:

- Overcrowding.
- Shortage of specialists.
- Limited pharmacy manpower.
- Inconsistencies in drug supply.

This understanding is crucial for a future pharmacologist involved in drug policy, essential drug list planning, or hospital formulary committees.

4. PRACTICAL EXPOSURE TO ANTIMICROBIAL USE

Along with formal audits, I observed:

- Frequent empiric antibiotic use.
- Challenges of antimicrobial stewardship.
- Patterns of broad-spectrum antibiotic dependence.

Such observations will guide my future research and teaching.

OVERALL REFLECTION

The DRP posting at Gomati District Hospital provided a unique mix of intense emergency exposure and limited structured pharmacology activities. While the intended objectives could not be achieved in full due to posting patterns, the experience offered invaluable insights into applied clinical pharmacology, rational drug use under constraints, and the realities of district-level healthcare. The posting highlighted the need for better alignment between learning objectives and duty allocation, especially for non-clinical residents.

CONCLUSION

The District Residency Program is a transformative policy aimed at shaping socially accountable, system-aware postgraduate doctors. For a pharmacology resident, the posting offers opportunities to translate theoretical knowledge into practice, understand drug logistics, and appreciate public health challenges. Although my experience leaned heavily toward emergency medicine, it ultimately enriched my understanding of rational pharmacotherapy and strengthened my readiness to contribute to healthcare systems in the future. Ensuring structured ward postings and facilitated access to pharmacy services would enhance the program's effectiveness for future pharmacology trainees.

REFERENCES

1. Raj A, Singh S, Rathore M. Early evidence of implementation of district residency programme: experiences and challenges of residents in Rajasthan, India. BMC Med Educ. 2024;24(1):493.
2. Khilnani AK, Pillai B, Thaddanee R. Postgraduate students' feedback on district residency program: a cross-sectional study. GAIMS J Med Sci. 2024;4(2):118–122.
3. Muthukumar A, Menon P, Mane S, Bhawalkar JS. District residency program students' perception. Med J DY Patil Vidyapeeth. 2024;17(4):927–928.

ACCOLADES

DR. PRAJNAPARMITA SAHA

Final Year Resident in the Department of Pharmacology, AGMC & GBP Hospital, Agartala, Tripura, won the 2nd prize in Paper presentation in the Resident's category during NAPTICON 2025 held at Coimbatore. Dr. Debasis Ray ,Professor & HOD of Pharmacology, Agartala Government Medical College , is her mentor and guide.

DR. NEHA THIYAM

First year Post Graduate Student of Pharmacology, Tezpur Medical College and Hospital, Tezpur, under the able mentorship of Professor & HOD of Pharmacology, Dr. Pinaki Chakravarty, won the 1st prize in the category for the Best Scientific Presentation by the Post Graduate Students, in NAPTICON 2025 held at Coimbatore.

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