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The Sri Lanka Prescriber

The Sri Lanka Prescriber is the only national, independent drugs and therapeutics bulletin in the country. Published quarterly by the Department of Pharmacology, Faculty of Medicine, University of Colombo, in collaboration with the State Pharmaceuticals Corporation (SPC), it has served as a source of unbiased, evidence-based information for several decades.

The Sri Lanka Prescriber evolved from the pocket size bulletins published by the Department of Pharmacology, Formulary Notes, which began publishing in 1966, continued as 'The Prescriber' from 1973. The Sri Lanka Prescriber started publication in the current format in 1993, which is also a continuation of the two previous bulletins. The Sri Lanka Prescriber continues with an updated scope and an Editorial Board from 2025.

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A Review of Combined Hormonal Contraceptives

Abstract

Hormonal contraceptives play a critical role in reproductive health, providing effective options for pregnancy prevention and managing various gynaecological conditions. Formulations can be combined oestrogen and progesterone preparations or progesterone only preparations. They can be available as oral pills, injectables or as implants. This review discusses the pharmacology of combined hormonal contraceptives, including mechanisms of action, pharmacokinetics, clinical applications, and potential adverse effects.

Keywords: oestrogen contraceptives, pharmacokinetics, pharmacodynamics, UKMEC, missed pills

Introduction

Hormonal contraceptives are widely used for birth control and offer several health benefits beyond pregnancy prevention. Oestrogen containing hormonal contraceptives primarily work through the actions of oestrogens and progestogens (also known as progestins). They can be available as oral pills, patches or as vaginal rings. Health care workers need be thorough with their mechanisms of action, pharmacokinetics and adverse effects before prescribing them. We should also use a holistic approach while considering patient wishes and choices. Patient counselling and education play a crucial role in offering contraceptive methods. Clinicians should adhere to United Kingdom Medical Eligibility Criteria (UKMEC), which was produced in line with the World Health Organization (WHO) Guidelines to provide safe care for the patients.

Combined Hormonal Contraceptives (CHCs)

- Combined Oral Contraceptive Pills (COCP)
- Vaginal rings
- Transdermal patches

1. Combined Oral Contraceptive Pills (COCP)

These contain both oestrogen and progestogens.

Oestrogen: Ethinyl oestradiol (EE) is the most commonly used oestrogen component. Dose content ranges from 20–40 µg per tablet. Some products use mestranol, oestetrol or oestradiol.

Progestogens: types vary and can be classified as generations as give below;

1. First Generation: contain progestogens like norethindrone, ethynodiol diacetate, lynestrenol and norethynodrel.
2. Second Generation: contain progestogens such as levonorgestrel (LNG) and norgestrel.
3. Third Generation: contain progestogens like desogestrel, gestodene and norgestimate.
4. Fourth Generation: contain progestogens like drospirenone.

History and evolution

The first COCP, ‘Enovid’, was approved for contraception in the USA by the Food & Drug Administration (FDA) in 1960. Since then, new formulations have been introduced. With increasing popularity of the COCPs, serious adverse effects associated with the early pills were soon reported, including thromboembolism. Over time, the dosage of both oestrogen and progestogen components of combination pills was markedly reduced and safety increased. Since 1990s, development of COCPs has progressed, with experimentation using varying type of progestogen, with introduction of the third and fourth generation COCPs.

With advancement in pharmaceutical industry, combined contraceptives have been subjected to substantial modifications, allowing for reduced dosages and expanded routes of administration (injectables, vaginal rings and dermal patches), thereby increasing safety, with multiple product choices being available.

Mechanism of action

They primarily prevent ovulation by suppressing the release of gonadotropins (FSH and LH) from the pituitary gland by inhibiting the positive feedback. Additionally, COCs thicken cervical mucus, making it difficult for sperm to enter the uterus and alter the endometrial lining to prevent implantation.

Formulations

- Monophasic preparations (fixed doses of oestrogen and progestogen in each tablet)
- Biphasic preparations (2 different doses)
- Triphasic preparations (3 different doses)

Phasic preparations try to mimic normal oestrogen and progestogen fluctuations in the menstrual cycle.

Pharmacokinetics

1. Absorption and Distribution: COCPs are taken orally, leading to absorption of the hormones from the small intestine. Hormones in the vaginal ring and transdermal patch are absorbed through vaginal mucosa and skin respectively. Hormones in COCPs, like levonorgestrel, are highly protein-bound, primarily to sex hormone-binding globulin (SHBG) and albumin.
2. Volume of Distribution: Known to vary depending on factors like Body Mass Index (BMI).
3. Metabolism: The liver plays a crucial role in metabolizing the hormones in COCPs.

   Enzyme Inhibition: Ethinyl oestradiol and progestogen inhibit steroid-metabolizing enzymes in the liver, potentially leading to increased serum levels of contraceptive steroids.

   Metabolic Pathways: Levonorgestrel undergoes conjugation, forming sulfate and glucuronide conjugates in the plasma.
4. Excretion: The metabolites of COCP hormones are excreted through the kidneys and the bile.
5. Drug Interactions: Certain drugs, like anticonvulsants (phenytoin, carbamazepine, oxcarbamazepine, topiramate etc), antibiotics (rifampicin), griseofulvin, st john's wort, and some antiretrovirals, can induce liver enzymes and potentially reduce the effectiveness of COCPs by accelerating the metabolism of the hormones.
6. Factors Influencing Pharmacokinetics: Obesity can affect the pharmacokinetics of COCPs, potentially leading to lower peak circulating levels of hormones.

There can be significant inter-individual variability in the pharmacokinetics of COCPs, influenced by factors like genetics, liver function, and other physiological variables.

Prescription and initiation

Preparations have 21 active pills. Some preparations have 7 inactive pills. Pills should be taken daily at around the same time of the day, continuously for 21 days. Then a Pill Free Interval (PFI) of 7 days is allowed during which the woman has withdrawal bleeding. Following that, the next pack should be taken. If vomiting occurs within 2 hours of taking the pill, another pill should be taken as soon as possible.

Methods to initiate

1. First-day start: started on the day one of menstrual bleeding. It is the best method as contraceptive efficacy is faster than other methods.
2. Quick start: started on any day of the cycle. Patients should be advised to use an additional contraceptive (barrier) or abstinence from sexual intercourse in the first 7 days.
3. Miscarriage/ectopic pregnancy (1st and 2nd trimester): start within the first 7 days
4. Postpartum: Avoid COC for the first 21 days postpartum (high risk of venous thromboembolism (VTE). Avoid during the first 42 days postpartum if breastfeeding.

Regimen choices

- Shortened HFI (Hormone Free Interval): 21 days of continuous use followed by 4 days of HFI
- Extended use (tricycling): 9 weeks of continuous use followed by 4 or 7 days of HFI
- Flexible extended use: continuous use for 21 days or more, followed by 4 days of HFI when breakthrough bleeding occurs
- Continuous use: continuous Combined hormonal contraceptive use with no HFI.

Table 1: Failure rate and return to fertility of various contraceptive methods

Method	Typical use (pregnancy rate)	Perfect use (pregnancy rate)	Return to fertility
COCP	70 per 1000	3 per 1000	No delay
Combined Vaginal ring	70 per 1000	3 per 1000	No delay
Transdermal patch	70 per 1000	3 per 1000	No delay

2. VAGINAL RING

A small ring that contains and releases oestrogen and progestogens continuously over 21 days. Following that, 7 days of ring-free interval are allowed for withdrawal bleeding, and a new ring is inserted. The ring can be self-inserted and should be worn day and night.

3. TRANSDERMAL PATCH

A small adhesive patch applied onto the skin (upper outer arm, abdomen, back, buttocks) which releases oestrogen and progesterone over 7 days. After 21 days, that is after wearing 3 patches consecutively, 7 days of patch-free interval are allowed, and the next patch is applied in the next cycle. The patch change day should be the same day of the week. The patch should be worn all the time during the day and night. Skin irritation at the application site would be an added adverse effect.

Benefits of CHCs

Contraceptive benefits

Highly effective with pearl index (the number of pregnancies per 100 women-years of treatment) of 0.3 – 4.4. (Table 1).

COCPs can be used as a method of emergency contraception (EC)

eg: 0.02mg EE + 0.1mg LNG – 5 tablets at first and repeated after 12hrs

0.05mg EE + 0.25mg LNG – 2 tablets at first and repeated after 12hrs

Non-contraceptive benefits

- Overall, 12% reduction in risk of developing cancers
  - Ovarian cancer – protections begins from commencement and lasts more than 30 years after stopping.
  - 50% reduction in endometrial cancer
  - Protection from colorectal cancer
- Treatment and control of gynaecological syndromes (endometriosis, adenomyosis, polycystic ovarian syndrome (PCOS))
- Improves acne
- No reduction in bone mineral density (BMD)
- 30% reduction in rheumatoid arthritis
- Reduce pelvic inflammatory disease (PID)
- Reduces ectopic pregnancy
- Lighter menstrual blood flow
- Good menstrual cycle control

Adverse Effects of CHCs

Common adverse effects:

- Irregular vaginal bleeding: Spotting or breakthrough bleeding between cycles, resolves as the body adjusts to the hormones.
- Nausea: when starting the pill or if taken on an empty stomach.
- Breast tenderness
- Headaches
- Mood changes: Hormonal fluctuations can sometimes lead to changes in mood.
- Bloating or changes in fluid retention.
- Skin changes: Some develop darkened patches.
- Decreased libido

Less common but serious adverse effects

Venous thromboembolism: The overall absolute risk of VTE is approximately 60 per 100,000 women, compared with 30 in non-users. It varies with different types of pills, compared with levonorgestrel-containing pills.

Myocardial infarction or Stroke: Lower doses of oestrogen in COCP may have a lower risk of stroke and myocardial infarction compared to higher oestrogen dose pills (50 µg/day). However, users of low oestrogen dose COCP still have an increased risk compared to non-users. These risks are greatest particularly in women with other risk factors, such as smoking, long duration of use and being aged more than 35 years.

Increased risk of certain cancers: Breast cancer and cervical cancer has been reported to be increased with long-term use of COCP, but the overall risk remains low. Cervical cancer risk in those infected with HPV is increased. It is thought to be due to the non-usage of barrier contraception while using COCP.

Important Considerations: Not everyone experiences adverse effects. Many women take the pill without significant problems. Adverse effects often improve with time: If adverse effects are bothersome, they often subside within a few months. Combined contraceptives do not protect from sexually transmitted infections.

Overdose & toxicity

No significant effects are reported on adults or children due to overdose. An overdose might lead to severe vomiting and withdrawal bleeding. Serum electrolytes (Sodium, Potassium) should be monitored in the case of overdose with COCP

containing Drosperinone, as it is a spironolactone analogue.

Contra-indications of CHCs

The UK Medical Eligibility Criteria for Contraceptive Use (UKMEC) guide is used categorize contraceptive methods based on health conditions, with categories ranging from no restrictions to unacceptable health risks (contraindications). It is based on the best available evidence and expert consensus.

UKMEC Categories (Table 2):

- Category 1 (unrestricted use): There are no restrictions on using the contraceptive method for the specific condition.
- Category 2 (benefits generally outweigh risks): The advantages of using the method generally outweigh the potential risks. Some follow-up or monitoring may be needed.
- Category 3 (risks generally outweigh benefits): The risks of using the method generally outweigh the benefits.
- Category 4 (unacceptable health risk): The contraceptive method poses an unacceptable health risk and should not be used.

Table 2: UKMEC criteria of combined hormonal contraceptive methods.

Factor	UKMEC 1	UKMEC 2	UKMEC 3	UKMEC 4
Age	<40yrs	>40yrs		
Hypertension (HTN)		HTN during pregnancy	SBP = 140-159mmHg DBP = 90-94mHg	SBP >160mmHg DBP >95mmHg
Migraine		<35yr, without aura	>35yrs, without aura	With aura
BMI	<29 kg/m2	30-34 kg/m2	35-39 kg/m2	>40kg/m2
Diabetes	Gestational diabetes	IDDM, NIDDM, no vascular disease	Vascular disease	
Vascular disease				Stroke, Myocardial infarction, valvular/ congenital heart disease
VTE		Family history in a <45yrs old first degree relative	Family history in a >45yrs old first degree relative	On anticoagulation or self-history
Surgery	Minor surgery / history of pelvic surgery	Major surgery without prolonged immobilization		Major surgery with prolonged immobilization
Post partum (breast feeding)	>6 months	6month – 6 weeks, partially breast feeding	6months – 6 weeks	<6 weeks
Postpartum (not breast feeding)	>6 weeks	>21 days, no risk factors	>21days, with risk factors	<21 days
Post miscarriage / ectopic	Immediately in 1st & 2nd trimester			
Breast disease	Benign/ family history	Undiagnosed mass	History of cancer / recurrence with in 5yrs / positive gene mutation	Current breast cancer

Table 3: Comparison between four generations of COCP

Factor	1st generation	2nd generation	3rd generation	4th generation
Progestogens	Norethindrone, lynestrenol, ethynodiol diacetate, norethynodrel	Levonorgestrel, norgestrel	Desogestrel, gestodene, norgestimate.	Drospirenone, dienogest, nomegestrol acetate.
Oestrogen	Mestranol	Ethinyl oestradiol	Ethinyl oestradiol	Ethinyl oestradiol, oestradiol valerate, oestradiol hemihydrate.
Characteristics	Higher oestrogen doses, more androgenic effects and fluid retention	Reduced oestrogen dose, less androgenic than 1st generation	Reduced androgenic properties compared to 2nd generation.	Drospirenone is a spironolactone analogue with a mild diuretic effect. Reduced withdrawal bleeding and androgenic effects
Availability	No longer in general use	Available and less costly	Expensive than 2nd generation	Expensive
Safety concerns	Increased side effects	"Gold standard" in relation to safety profile.	Increased risk of VTE compared to 2nd generation pills, benefits continue to outweigh the risks	May improve lipid profiles, reduce the risk of arterial thrombosis, increased risk of VTE compared to 2nd generation

MISSED PILLS/ RING/ PATCH guideline

Instructions for missed pills, rings, or patches to maintain contraceptive effectiveness and prevent pregnancy are given in Table 4.

Table 4: missed pill/ ring & patch guideline (Faculty of Sexual and Reproductive Healthcare [FSRH] guide)

Method	Time	Advice
COCP	Late start (≥ 9 days of active pill)	Restart and continue Use condoms/ abstinence for 7days Follow up urine pregnancy test
	1 pill missed ≤72hrs	Next pill soon as possible, and continue Emergency contraception not needed
	2 - 7pills missed 1st week	Restart and continue Use condoms/ abstinence for 7days Follow up urine pregnancy test Emergency contraception needed if unprotected sexual intercourse happened
	2-7 pills missed 2 / 3rd week	Restart and continue Use condoms/ abstinence for 7days In 3rd week – avoid hormone free interval
Transdermal Patch	Late start after patch free interval	New patch soon as possible If <48hrs (no need of backup methods)

		If >48rs (use backup method)
	Late change after 1st / 2nd week	If <48hrs (change immediately, no back up needed) If >48rs (begin new patch cycle, backup method)
	Patch came off and was off <48hrs	Change patch, no backup needed
	Patch came off and was off >48hrs	Change patch, use backup method If in 3rd week, avoid patch free interval
Vaginal ring	Ring out <48hrs	Put back as soon as possible, no need of backup
	Ring out, >48hrs in week 1or 2	Put back as soon as possible, use backup methods, if unprotected sexual intercourse happened use emergency contraception
	Ring out >48hrs week 3	Put back as soon as possible, use back up method Avoid ring free interval

Monitoring

All information regarding adverse effects and warning signs should be given to the patients, preferably in the form of leaflets at initiation. The patient should be followed up by a physician annually for the given adverse effects and newly developed contraindications.

Unscheduled bleeding may occur and causes include: vomiting within 2hrs, Severe Diarrhoea, Missed pills, sexually transmitted infections (STI), pregnancy, malabsorption, and phasic preparations.

The patient should be advised to take the pills continuously despite bleeding and seek urgent medical advice. If there are no specific causes as above, she can be prescribed phasic preparations or can allow for a withdrawal bleeding for 4-7 days (with barrier contraception or abstinence) and restart the new pack/ring/patch.

Availability

Though the Family Planning Association of Sri Lanka was first established in 1959, Hormonal contraceptives were first introduced in Sri Lanka in the 1960s. Government participation and legal authority were granted in 1965. However, active involvement started in 1968 after the establishment of the Family Planning Bureau, which is now known as the Family Health Bureau. UNFPA supported the national family planning programme. 'Mithuri' COCP was introduced as a non-profit marketing in 1976 through the Local MOH services and the Family Planning Association. Since then, various types of COCP have been available in the Sri Lankan market as an over-the-counter medication. However vaginal ring and transdermal patches are not available in Sri Lanka. Some 4th-generations and 3rd-generations are available to purchase from non-governmental centres, but they are expensive.

Newer preparations and future

Combined injectable contraceptives

Contains an oestrogen and a progestogen as an injectable formulation given monthly. Is injected deep into the gluteal muscle, deltoid, or anterior thigh. Examples are given below

I. Medroxy Progesterone Acetate (MPA) + oestradiol cypionate injectables

II. NET-EN (norethisterone enanthate) + oestradiol valerate injectables

Adverse effects include irregular bleeding patterns, headache, weight gain, dizziness and breast tenderness. These have equal non-contraceptive benefits as COCP. After stopping, returning to fertility may be longer than other combined hormonal methods (5 months).

III. Combination of 17β oestradiol (1.5 mg) and nomegestrol acetate or NOMAc (2.5 mg); a 19-norprogesterone derivative was recently approved in Europe. It has shown high contraceptive efficacy and good bleeding control.

IV. Another natural form of oestrogen, oestetrol (E4), which is only produced during pregnancy by the liver of the foetus under physiological conditions, has now been synthesized. Formulations with E4 have been developed in combination with potent progestogens such as levonorgestrel or etonogestrel. E4 is known to be 18 times less potent than EE and does not convert into other oestrogens in the liver. Therefore, a lower adverse effects profile is expected.

Two examples of contraceptive related cases are given below.

Scenario 1

A 23-year-old woman, who is planning to marry next month, comes for contraceptive advice. How will you address the issue?

- Review her past medical history. Exclude all contraindications and cautions to start hormonal contraception according to UKMEC criteria
- Go through her concerns. E.g.: duration she wishes to have contraceptives, wishes for pills or devices, ability to keep pace with the compliance
- Prescribe suitable contraception with advice on missed pills, withdrawal bleeding and follow-up.

Scenario 2

35-years-old woman who is on COCP for contraception is seeking your advice on the 16th day of the cycle. She has missed taking pills on the previous 2 days as she went on a tour and forgot to carry her pills. She has had unprotected sexual intercourse a couple of times during the tour. How will you advise her?

- Ensure that she has taken the pills correctly in the previous 13 days since starting the pack.
- If so, she should restart the current pack immediately.
- She does not need emergency contraception as she has taken the pills properly in the previous 7 consecutive days, which means she is unlikely to have a mature follicle when she had unprotected sexual intercourse.
- She should avoid the hormone free interval in the next cycle and start the next pack immediately after.
- She should follow abstinence or use condoms in the next 7days.

Summary

Table 5 summarizes the benefits and adverse effects of CHC.

Table 5: Summary of benefits and adverse effects of CHCs

Topic	Key points
Key benefits	• Overall, 12% reduction in risk of developing cancers (ovarian cancer, endometrial cancer, colorectal cancer) • Treatment and control of gynaecological syndromes (endometriosis, adenomyosis, polycystic ovarian syndrome) • Improve acne • No reduction in bone mineral density • 30% reduction in rheumatoid arthritis • Reduce pelvic inflammatory disease • Reduce ectopic pregnancy • Good menstrual cycle control
Important adverse effects	• Irregular vaginal bleeding: Spotting/ breakthrough bleeding • Nausea, bloating, breast tenderness, headaches • Mood changes • Decreased libido • Venous thromboembolism • Myocardial infarction/ Stroke
Cancer risks	May increase breast and cervical cancer risk slightly

Conclusion

Understanding the pharmacology of hormonal contraceptives is essential for healthcare providers to optimize patient care. These medications not only effectively prevent pregnancy but also offer significant benefits for various gynaecological conditions. Continued research and patient education are vital for maximizing their use and minimizing risks.

Further Reading

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Self-assessment questions - A Review of Combined Hormonal Contraceptives

1. What is the drug that should be avoided if the woman is on COCP?
   A. Sodium Valproate
   B. Co-amoxiclav
   C. Aspirin
   D. Metformin
   E. Carbamazepine

2. Which of the following is a fourth generation COCP?
   A. COCP containing Norethesterone
   B. COCP containing desogestrel
   C. COCP containing Drosperinone
   D. COCP containing levonorgestrel
   E. COCP containing gestodene

3. A 28-year-old woman attends a family planning clinic for contraception advice. She has tested positive for the BRCA1 gene. She has blood pressure (BP) of 140/92 mmHg at her last visit with her GP. What is the incorrect statement out of the following, regarding contraceptive use for her?
   A. She can be advised that there may be an additional risk of breast cancer with COC use
   B. She can be advised that there is a reduction in the risk of colorectal cancer with COC use
   C. She being a BRCA1 gene carrier, her risk of ovarian cancer increases by 30% with COC use
   D. She can be advised that COC use provides a protective effect against endometrial cancer that continues for 15 years or more after stopping COC
   E. Hypertension may increase the risk of stroke and myocardial infarction (MI) in those using COC

Answers

1. E = Carbamazepine is a liver enzyme inducing drug. All others are either enzyme inhibitors or they do not affect the metabolism of COCP
2. C = COCP containing Drosperinone
3. C - For women who are at high risk of developing ovarian cancer (such as those who are BRCA1 and BRCA2 gene carriers), studies suggest that this risk can be reduced by 60% by using COC pills

The Growing Influence of Artificial Intelligence in Pharmacology: A 360° Insight

Like many other fields, Pharmacology, is undergoing a major transformation as artificial intelligence (AI) becomes more deeply integrated into the field. AI techniques are no longer confined to the areas of computer science but are increasingly being employed across various scientific disciplines, including Pharmacology, to tackle complex challenges and drive progress. This evolution is particularly evident in pharmacology research, where AI is demonstrating its potential to enhance efficiency, reduce costs, and improve the safety and precision of pharmaceutical processes. The substantial attention garnered by AI for its transformative capabilities in drug discovery and development underscores its growing importance as a pivotal tool in the pharmaceutical industry. Indeed, AI techniques are fuelling remarkable advancements in research, effectively addressing the intricate challenges inherent in drug development with unprecedented momentum. The present article aims to explore the multifaceted advancements and profound implications of AI within pharmacology, focusing on key areas such as drug discovery, clinical decision support, personalised medicine, and other pertinent applications, thereby providing a framework for understanding this rapidly evolving landscape.

1. AI in Drug Discovery and Development

The traditional process of drug discovery and development is often characterised by its lengthy duration, substantial financial investment and a high rate of failure. Artificial intelligence offers promising solutions to these inherent challenges, presenting opportunities by accelerating the identification of potential drug candidates and optimising their pharmacological properties with greater accuracy and efficiency, as highlighted below.

A) Accelerating Target Identification and Validation

A crucial initial step in drug discovery involves the identification and validation of appropriate biological targets. AI algorithms excel at analysing vast and complex datasets, including genomic, proteomic, and other biological information, to pinpoint potential drug targets and gain a deeper understanding of disease mechanisms. This includes the ability of AI to predict the intricate 3D structures of proteins and RNA molecules, which is fundamental to identifying potential targets for therapeutic intervention. Machine learning techniques enable the rapid scanning and comparison of numerous molecular structures, facilitating the identification of the most promising models for specific health problems. Furthermore, AI can effectively analyse extensive public databases, such as ChEMBL and PubChem, which contain information on millions of molecules and their interactions with various disease targets, thereby uncovering novel therapeutic avenues. This capability to process and interpret large biological datasets allows AI to uncover novel targets that might remain elusive through traditional research methods, potentially expanding the scope of treatable diseases.

B) Enhancing Lead Optimization and Prediction of Pharmacokinetic Properties

Once potential drug candidates, known as leads, are identified, the subsequent stage involves optimising their properties to enhance efficacy, safety, and pharmacokinetic characteristics – how the drug is absorbed, distributed, metabolised, and excreted by the body. AI plays a crucial role in this process by predicting how modifications to a molecule's structure will impact these critical properties, enabling researchers to rapidly screen and prioritise lead compounds with the most desirable attributes. Molecular docking, a technique used to predict the binding affinity between a drug and its target, is significantly enhanced by AI algorithms. These algorithms can accurately predict drug-protein interactions, which is vital for understanding a drug's therapeutic effectiveness and potential for repurposing. While initial optimism surrounded the application of deep learning methods for protein-ligand docking, ongoing validation and rigorous benchmarking are essential to ensure the reliability of AI-driven predictions in this area. Moreover, AI is instrumental in predicting the potential toxicity of drug candidates and in screening large libraries of compounds to identify those with the most favourable safety profiles.

C) Streamlining Pre-clinical Testing through in-silico Models

Preclinical testing, which traditionally involves extensive and time-consuming *in-vitro* (laboratory) and *in-vivo* (animal) studies, can be significantly streamlined through the application of AI. AI contributes to this phase by predicting the potential toxicity and efficacy of drug candidates in-silico, using sophisticated computer simulations. Deep learning techniques hold the potential to even reduce the costs associated with clinical trials by predicting their outcomes before they commence. The involvement of AI can be envisioned across the entire spectrum of pharmaceutical development, from the initial research at the bench to the eventual application at the bedside, aiding in rational drug design and informed decision-making. Furthermore, AI algorithms can analyse the vast amounts of data generated during preclinical studies, providing valuable insights into a drug's mechanism of action and its potential for success in subsequent clinical trials. The use of computer-simulated trials, facilitated by AI, can predict drug efficacy and safety, thereby minimising the necessity for extensive physical trials.

D) Drug Repurposing for Novel Therapeutic Applications

Beyond the de novo discovery of new drugs, AI is also revolutionizing the process of drug repurposing, which involves identifying novel therapeutic applications for existing, often already approved, drugs. AI algorithms can analyse large datasets of chemical and biological information to uncover previously unknown molecular targets for existing drugs and identify patient populations that might benefit from these repurposed treatments. The advantages of drug repurposing are numerous, including a faster route to clinical application, a lower development cost, and a greater likelihood of safety due to the established profiles of the drugs. For instance, the TxGNN model, an AI tool specifically developed for rare diseases, has identified potential drug candidates from existing medicines for over 17,000 diseases, many of which currently lack any effective treatments. AI can also predict potential adverse effects and contra-indications in the context of drug repurposing, further enhancing its value in this area. This ability to efficiently identify new uses for existing drugs, particularly for rare and neglected diseases, highlights AI's potential to address unmet medical needs more rapidly.

2. AI in Therapeutic Decision Support

The integration of AI into clinical decision support (CDS) systems aims to assist healthcare professionals in making more informed and effective decisions regarding patient care. By leveraging the power of AI, clinicians can potentially improve diagnostic accuracy, optimize treatment selection, and enhance medication management, ultimately leading to better patient outcomes as highlighted below.

A) Improving Diagnostic Accuracy and Efficiency

AI algorithms possess the capability to analyse vast amounts of patient data, including medical records, laboratory results, and medical imaging, to identify complex patterns and assist in the diagnostic process. For example, AI-powered projects like Google Deep Mind's health initiative can efficiently analyse medical records to facilitate faster and more accurate diagnoses. AI can also assist in repetitive yet crucial tasks, such as the examination of X-ray images and electrocardiograms (ECGs), for the detection and identification of diseases or disorders. The capacity of AI to process and analyse large volumes of diverse patient data can lead to more accurate and timelier diagnoses, which is particularly beneficial in complex medical cases or for the early detection of diseases.

B) Guiding Treatment Selection Based on Patient Data and Predictive Models

AI plays a significant role in guiding treatment selection by analysing a patient's medical history, physical examination results, and diagnostic test data to suggest optimal treatment plans.

AI-powered systems can consider a multitude of factors and provide evidence-based recommendations to help clinicians choose the most appropriate therapies. Predictive models, driven by AI algorithms, can analyse patient data to provide insights into potential treatment responses and outcomes, enabling a more personalized approach to care. For instance, in oncology, AI tools can analyse patient data to predict the likelihood of cancer recurrence following surgery, allowing for tailored surveillance and preventive measures. This ability to personalise treatment selection based on individual patient characteristics

has the potential to improve the effectiveness of therapies and minimize adverse events.

C) Optimising Medication Management and Reducing Medication Errors

Effective medication management is crucial for patient safety and treatment success, and AI offers several tools to optimize this process. AI can assist in identifying potential drug-drug interactions, assessing the safety and efficacy of prescribed medications, and improving patient adherence to treatment regimens. AI-powered virtual nurses and smartphone applications can provide patients with medication reminders and support for managing chronic conditions. By analysing complex medication regimens and patient profiles, AI systems can flag potential conflicts and alert healthcare providers, thereby reducing the risk of medication errors and adverse drug events.

3. AI for Personalised Medicine

Personalised medicine, which aims to tailor medical treatments to the individual characteristics of each patient, is significantly advanced by the capabilities of AI. AI's ability to analyse vast amounts of data, including genetic information, medical history, and lifestyle factors, makes it an invaluable tool for developing individualized treatment strategies as described below.

A) Tailoring Therapies Based on Individual Patient Profiles and Pharmacogenomic Data

AI algorithms can analyse a patient's unique genetic makeup, known as pharmacogenomic data, to predict how they will respond to specific drugs. This is particularly valuable in fields like neurology, where AI can predict the effectiveness of certain drugs for individual patients with Alzheimer's or Parkinson disease by analysing their genetic data. By considering a patient's genetic profile alongside their clinical history and biomarkers, AI helps in developing highly personalized treatment strategies, potentially slowing the progression of diseases and improving patient outcomes. Furthermore, AI can optimize the formulation and delivery of drugs, such as through the design of personalized 3D-printed dosage forms tailored to individual patient needs. The integration of AI with pharmacogenomics allows for a deeper understanding of how individual genetic variations influence drug response, leading to more precise and effective therapies.

B) Advancing Precision Medicine through AI-Driven Analysis of Multi-Omics Data

Precision medicine is further enhanced by AI's ability to integrate and analyse various types of biological data, including genomics, proteomics, and metabolomics, collectively known as multi-omics data. This comprehensive analysis provides a more holistic understanding of disease mechanisms and treatment responses at an individual level. AI algorithms can identify intricate relationships and patterns within these complex, high-dimensional datasets, leading to a more nuanced understanding of disease and individual patient variations. This advanced level of analysis can facilitate the identification of novel biomarkers for disease diagnosis and prognosis, as well as the development of highly targeted therapeutic interventions tailored to the specific molecular profile of a patient's disease.

Real-World Applications of AI in Pharmacology

The transformative potential of AI in pharmacology is best illustrated through real-world applications that have already begun reshaping the field. For example, Insilico Medicine utilized AI-driven deep learning platforms to identify a novel preclinical candidate (a fibrosis treatment), dramatically reducing the discovery timeline from the typical 4–6 years to just under 18 months (Zhavoronkov et al., 2019). In clinical decision support, IBM Watson for Oncology has been deployed across hospitals in India and Thailand to assist oncologists by analysing patient records and recommending evidence-based treatment plans, leading to increased diagnostic confidence and standardization (Somashekhar et al., 2018). Similarly, in pharmacovigilance, Bayer Pharmaceuticals has implemented natural language processing algorithms to scan global adverse event reports and social media, enhancing the early detection of safety signals (Trifirò et al., 2019). These examples underscore how AI is not merely a theoretical promise but an active driver of innovation across the pharmaceutical continuum.

Table 1: Summary of Key AI Applications in Pharmacology: provides a snapshot of AI's expanding footprint in pharmacology, underscoring its role as a transformative tool from the research laboratory to the patient bedside.

Domain	Key Applications	Example / Note
Drug Discovery & Development	Target identification, lead optimization, molecular docking	Insilico Medicine's AI-designed fibrosis candidate
Clinical Decision Support (CDS)	Diagnosis assistance, treatment planning	IBM Watson for Oncology in India & Thailand hospitals
Pharmacovigilance	Adverse event detection, safety signal monitoring	Bayer's NLP systems scanning global safety data
Personalized Medicine	Pharmacogenomics-guided therapy, multi-omics integration	AI models tailoring treatments for Alzheimer's patients
Pharmaceutical Manufacturing	Predictive maintenance, quality control via computer vision	AI ensuring batch consistency, reducing downtime

Emerging Applications and Considerations

The application of AI in pharmacology extends beyond drug discovery and clinical decision support, with emerging roles in areas such as pharmacovigilance and pharmaceutical manufacturing.

The Role of AI in Pharmacovigilance for Enhanced Drug Safety Monitoring

Pharmacovigilance, the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem, is being significantly enhanced by AI technologies. AI can automate many routine tasks in the pharmacovigilance process, such as data entry, the identification of adverse events from various sources (including unstructured data like social media and electronic health records), and the detection of potential safety signals. AI algorithms can analyse vast amounts of data much more rapidly and comprehensively than traditional methods, leading to earlier detection of potential drug safety issues. In personalised medicine, AI can also predict adverse drug reactions with greater accuracy by analysing individual patient data, including genetic profiles. This improved ability to monitor and predict drug safety contributes to better patient protection and more informed regulatory actions.

AI in Pharmaceutical Manufacturing for Quality Control and Process Optimization

Pharmaceutical manufacturing processes are also benefiting from the integration of AI, which can improve quality control, predict equipment failures, optimize production schedules, and reduce downtime. AI-powered computer vision systems can conduct real-time inspections of pharmaceutical products to detect even minor deviations and defects, ensuring higher consistency in product quality.

By analysing real-time data from manufacturing equipment, AI can predict potential failures, allowing for proactive maintenance scheduling and minimizing disruptions to production. Furthermore, AI's predictive analytics capabilities can optimize supply chain management, forecast demand, and manage inventory more efficiently, leading to significant cost savings and enhanced operational efficiency.

Addressing Ethical Implications, Data Privacy Concerns, and the Need for Transparency in AI Applications

As AI becomes increasingly integrated into pharmacology, it is crucial to address the associated ethical implications, data privacy concerns, and the need for transparency in AI applications. Concerns exist regarding potential biases in AI algorithms, which can arise from the data they are trained on, potentially leading to disparities in healthcare

outcomes. The opaqueness of some AI systems, often referred to as "black boxes," raises questions about the explainability of their decisions and the accountability for their outputs. Ensuring the privacy and security of sensitive patient data used to train and operate AI models is also paramount. Therefore, the development of robust regulatory frameworks and ethical guidelines is essential to govern the responsible development and use of AI in pharmacology, promoting transparency, fairness, and patient safety.

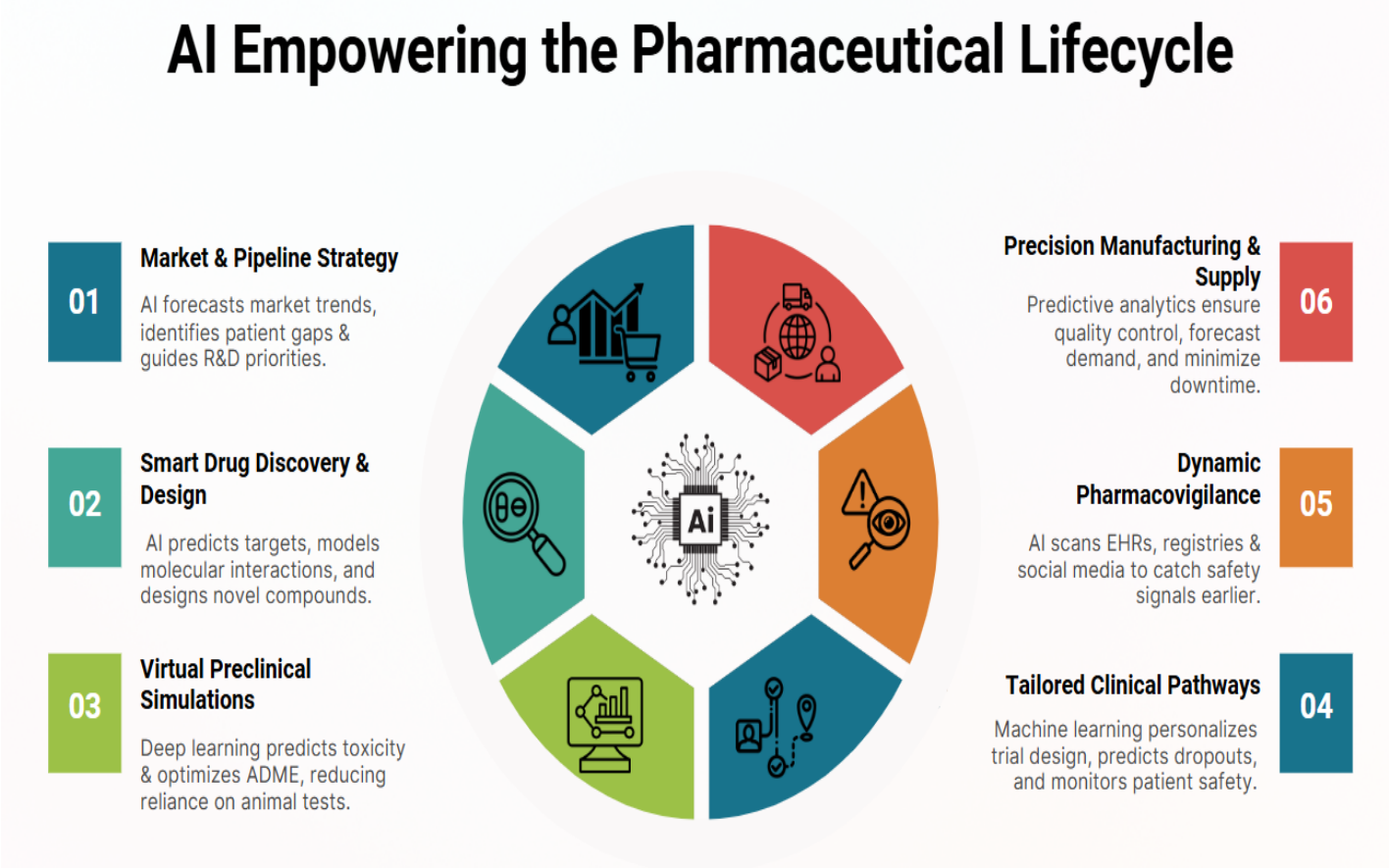

Figure 1 AI empowers the pharmaceutical lifecycle from strategic planning through discovery, clinical trials, safety monitoring, to manufacturing, ensuring data-driven innovation and patient-centric outcomes.

Conclusion

AI holds immense transformative potential for revolutionizing various facets of pharmacology, spanning from the initial stages of drug discovery to the complexities of clinical practice and the efficiencies of pharmaceutical manufacturing. The advancements discussed highlight AI's capability to accelerate the identification of novel drug candidates, enhance the precision of clinical decision-making, personalize medical treatments based on individual patient profiles, improve the monitoring of drug safety, and optimize industrial processes. However, realizing the full benefits of AI in pharmacology necessitates a careful consideration of the ethical implications, a commitment to ensuring data privacy, and a focus on promoting transparency in the development and implementation of these powerful technologies. Looking ahead, the continued collaboration between AI experts, pharmacologists, clinicians, and regulatory bodies will be crucial in navigating the evolving landscape and harnessing the full potential of AI to advance pharmacological research and ultimately improve patient health outcomes.

Further Reading

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Medication Safety Corner

Red Man Syndrome: a common and preventable adverse reaction to vancomycin

Vancomycin is a glycopeptide, which is primarily used in the treatment of infections due to Methicillin Resistant *Staphylococcus aureus* (MRSA), *Corynebacterium jeikeium* and resistant strains of *Streptococcus pneumoniae* [1, 2]. Red Man Syndrome (RMS) is a hypersensitivity reaction that occurs with vancomycin infusion. By far it is the most common hypersensitivity reaction to vancomycin, with studies reporting an incidence of 3.7% to 47% [3-5] (Table 1).

Mechanism

RMS is described as a 'non-IgE mediated reaction', caused by degranulation of mast cells and basophils resulting in the release of histamine, independent of preformed IgE or Complement [2]. This is also known as an 'anaphylactoid reaction'. Clinical studies have demonstrated no significant elevation in plasma tryptase levels with confirmed ancomycin induced anaphylactoid reactions, suggesting that they can be used to distinguish chemical reactions from immunologic reactions [6].

Table1: Types of hypersensitivity reactions to Vancomycin [2]

Reaction Type	Pathogenesis	Median Time-To-Onset	Clinical Presentation	Management Strategies
Red Man Syndromes (RMS)	non-IgE-mediated mast cell degranulation with histamine release	Can occur without prior exposure 20–45 min from the start of infusion Subsequent infusions likely to be better tolerated	Erythema, flushing, pruritus from top of head or back which can extend to chest and back, hypotension, angioedema	Antihistamine; Resolution of symptoms within an hour of vancomycin being stopped; For severe symptoms, intravenous fluids and corticosteroids
IgE-mediated Hypersensitivity (including anaphylaxis)	Type I hypersensitivity: It is immunologically mediated with drug-specific IgE antibodies. Most common with multiple prior exposures	Reaction occurs in minutes, typically during vancomycin infusion	Angioedema, pruritus, hypotension, urticaria, tachycardia, nausea and vomiting	Discontinuation of vancomycin, immediate administration of epinephrine and antihistamines, corticosteroids
Delayed hypersensitivity reaction	Type II delayed hypersensitivity: IgG- or IgM-mediated	7-14 days after vancomycin administration	Thrombocytopenia, hemolytic anemia, neutropenia	Discontinuation of vancomycin as soon as possible upon diagnosis
Linear IgA Bullous Dermatosis (LABD)	Type IV delayed-hypersensitivity: Linear disposition of IgA along basement	1-21 days after vancomycin administration	Small itchy bullae, possible eosinophil infiltrates	Discontinue vancomycin, topical corticosteroids

	membranes of the epidermis			
Drug rash with eosinophilia and systemic symptoms (DRESS)	Type IV delayed-hypersensitivity: Eosinophilic activation and inflammatory cascade	2 to 6 weeks after initial drug exposure	Skin rash, fever, atypical leukocytosis, multiple organ failure including kidneys, liver, and lungs	Discontinue vancomycin, pulsed corticosteroids with a slow taper over 4–6 weeks

Clinical features

Signs of RMS would typically emerge about 4-10 min after the initiation of the infusion or may occur shortly after the infusion is completed. This commonly presents with pruritus and a red erythematous rash affecting the face, neck and upper torso. Less commonly patient man experience hypotension and angioedema. Common complaints include widespread burning sensation, itching, general sense of discomfort which may quickly progress to dizziness, agitation, fever. chills, and in more severe instances chest pain and dyspnea [1]. Most of the reactions are said to be mild in severity [2].

Risk factors

A rapid infusion rate specially during the first dose is the most frequently identified risk factor for the development of RMS, although administering larger doses relative to body weight has also been linked to its occurrence [2]. Patients who develop a reaction during the first dose are more likely to develop reaction to subsequent doses, but the severity tends to be mild than the initial one [7]. Although available data are limited and existing studies involve small sample sizes, RMS appears to be less common in patients receiving continuous infusions and it is more frequently associated with intermittent infusion [8].

Management

If RMS occur, the vancomycin infusion should be promptly discontinued. Administration of antihistamines either intravenously or orally (diphenhydramine hydrochloride) is typically effective in alleviating most symptoms. Chlorpheniramine may be considered as an alternative when diphenhydramine cannot be used/not available but has much less direct evidence and is not routinely recommended in protocols [9]. Once the erythema and pruritus resolve, the infusion may be cautiously re-started at a reduced rate and /or lower dosage. Patients with severe symptoms who do not respond quickly to the cessation of vancomycin and an antihistamine may be given intravenous fluids and corticosteroids [10]. In more severe cases vasopressor support may be necessary [1].

Prevention

Reducing the infusion rate, premedicating with diphenhydramine or hydroxyzine has been shown to reduce the incidence [5]. Some studies have also shown that combining an H1 receptor blocker with an H2 receptor blocker such as cimetidine may help to prevent or reduce the risk [11]. Also, therapy with beta blockers prior to surgery has been found to be protective against hypotension during anesthesia caused by vancomycin infusion [12].

Vancomycin skin test has no benefit in predicting the severity of RMS [13].

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Regulatory News from the National Medicines Regulatory Authority (NMRA)

Rizatriptan

Dosage form: Tablet, 5 mg and 10 mg

Pharmacotherapeutic group: Antimigraine preparation; Selective serotonin (5HT1) receptor agonist (triptan)

ATC code: N02CC04

Pharmacodynamic properties

Rizatriptan is a selective serotonin $5HT_{1B}$ and $5HT_{1D}$ receptor agonist that causes vasoconstriction of cranial blood vessels, inhibition of neuropeptide release, and reduced transmission in trigeminal pathways. These mechanisms relieve the headache phase of migraine attacks. Rizatriptan has no significant effect on overall cerebral or coronary blood flow at therapeutic doses.

Pharmacokinetic properties

Absorption: Rapidly absorbed following oral administration, with a bioavailability of approximately 40–45%. Peak plasma concentrations are reached within about 1–1.5 hours. Delay in absorption may occur when the oral dosage form is given in the fed state.

Distribution: The volume of distribution is approximately 140 litres in males and 110 litres in females, with about 14% plasma protein binding.

Metabolism: Metabolized primarily by monoamine oxidase-A (MAO-A) to an inactive indole acetic acid metabolite.

Elimination: Eliminated predominantly by urinary excretion as metabolites. Terminal half-life is approximately 2–3 hours. In patients with renal impairment (creatinine clearance 10-60 ml/min/1.73m2), AUC levels were not significantly different from healthy subjects, however in hemodialysis patients (creatinine clearance <10ml/min/1.73m2) levels were 44% greater than healthy individuals. A significant increase in AUC (50%) was noted in moderate hepatic impairment (Child Pugh score 7).

Indication and Dosage

Acute migraine treatment (with or without aura):

- Adults: 10 mg orally, at onset of migraine. If the headache recurs, a second dose may be taken after at least 2 hours. Maximum daily dose: 20 mg.
- Some patients should receive a lower (5mg) dose – patients on propranolol (separate administration by 2 hours), patients with mild to moderate renal/hepatic impairment
- Children and Adolescents: Safety and efficacy not established; should not be used.

Rizatriptan should only be used after diagnosis of migraine has been established. Not intended for migraine prophylaxis.

Should not be administered to patients with basilar/hemiplegic migraine or to patients with atypical headaches. Clinical trials have shown that patients who do not respond to the treatment of an attack are still likely to respond to subsequent attacks.

Warnings and Precautions

- Contraindicated in patients with a history of stroke or transient ischaemic attack, ischaemic heart disease, moderately severe or severe hypertension or untreated mild hypertension, or severe hepatic or renal impairment, peripheral vascular disease.
- Should not be used concurrently with other 5HT1 agonists, ergotamine, MAO inhibitors or within 2 weeks of discontinuing MAO inhibitors.
- May cause transient increases in blood pressure.
- Should be used with caution in patients with risk factors for coronary artery disease.
- Safety during Pregnancy and breast feeding has not been established.

Interactions

- Concomitant use with propranolol increases plasma concentrations of rizatriptan; a lower dose is recommended when co-administered, separated by at least two hours from administration of propranolol.
- Risk of serotonin syndrome with other serotonergic agents such as SSRIs, SNRIs, or MAO inhibitors.
- Lower doses (5mg) are recommended for patients with mild or moderate renal insufficiency and mild or moderate hepatic insufficiency.
- Contraindicated with ergotamine and its derivatives due to additive vasoconstrictive effects.

Adverse Effects

- Common: dizziness, somnolence, asthenia, fatigue, chest discomfort, palpitations, flushing, and paresthesia.
- Rare: serious cardiac events such as myocardial infarction and arrhythmias have been reported.
- Angioedema may occur, which warrants prompt discontinuation of the drug and replacing with a drug of another class. Patient should be placed under medical supervision until the symptoms resolve.

*Prepared based on information in the Product Information Leaflet approved by the NMRA

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