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ADVERSE DRUG REACTION

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ABSTRACT

Treatment decisions should be based on high-quality data, ideally obtained from randomized controlled trials. However, randomized trials are not immune from bias and other important limitations. Critical appraisal of such studies must consider both the methodological rigour of the study and the applicability of the results to routine clinical practice.Readers should work systematically through trial reports to establish the aims of the study and consider whether the methods used are able to provide an unbiased answer. Particular attention should be directed towards randomized patient allocation, ensuring that the treatment and control groups are equally balanced at the start. There should be adequate follow-up and sufficient blinding of the investigator and participants so that important outcomes are reliably recorded without any interference from preconceived notions. The trial's Results section should be reviewed to confirm that the researchers have transparently reported all data (positive or negative) relevant to the study question. Critical appraisers should also consider how closely the conduct of the trial (e.g. selection of patients, follow-up arrangements) reflects real-world medicine, and the applicability of the trial results to everyday clinical practice.

KEYWORD : *Clinical trials; critical appraisal; evidence-based medicine; intention-to-treat; MRCP; publication bias; randomization; reporting bias*

1 .INTRODUCTION

Adverse Drug Reactions (ADRs) are unintended, harmful effects that occur when a medication is administered at its normal dosage for the prevention, diagnosis, or treatment of a disease. These reactions represent a significant concern in healthcare due to their impact on patient safety, treatment outcomes, and the overall cost of medical care. ADRs can range from mild, self-limiting symptoms to severe, life-threatening conditions, making their identification and management a critical component of clinical practice.

The World Health Organization (WHO) defines an ADR as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." Unlike side effects, which can be both beneficial and harmful, ADRs are exclusively harmful and require attention to ensure patient well-being.

ADRs are influenced by various factors, including patient characteristics, drug properties, and environmental or genetic factors. Their unpredictable nature often complicates treatment regimens and necessitates a careful approach to prescribing and monitoring medications. With the increasing prevalence of polypharmacy and complex treatment protocols, ADRs have become a leading cause of morbidity, hospitalizations, and even mortality worldwide. Understanding ADRs is, therefore, essential for healthcare professionals to improve drug safety and optimize therapeutic outcomes.

2. DEFINITION OF ADRS

According to the World Health Organization (WHO), an ADR is defined as:
"A response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."

ADRs are distinct from drug side effects, as side effects can include both beneficial and harmful effects, whereas ADRs exclusively refer to harmful responses.

3. TYPES OF ADVERSE DRUG REACTIONS

1. Type A (Augmented) Reactions

These are dose-dependent and predictable based on the pharmacological properties of the drug. They are often related to the drug's therapeutic effects but occur to an exaggerated degree.

- Examples:
  - Sedation from antihistamines (e.g., diphenhydramine).
  - Hypotension from antihypertensive drugs (e.g., beta-blockers).

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- Gastrointestinal upset from nonsteroidal anti-inflammatory drugs (NSAIDs).
- Characteristics:
  - Usually related to the drug's primary or secondary pharmacological effects.
  - More common and easier to anticipate.
  - Can often be managed by adjusting the dose or discontinuing the drug.

2. Type B (Bizarre) Reactions

These are dose-independent and unpredictable. They are often immune-mediated or related to genetic factors, making them less foreseeable.

- **Examples:**
  - Anaphylaxis (severe allergic reaction) to penicillin.
  - Stevens-Johnson syndrome (skin and mucosal eruption) due to anticonvulsants or sulfonamides.
  - Hemolytic anemia caused by certain antibiotics (e.g., penicillin).
- **Characteristics:**
  - Often related to individual susceptibility, such as genetic variations or immune system responses.
  - Rare, but can be severe or fatal.
  - Requires immediate medical intervention and discontinuation of the offending drug.

3. **Type C (Chronic) Reactions**

These are related to prolonged use of a drug and occur after long-term administration. They are often related to drug accumulation or chronic toxicity.

- **Examples:**
  - **Osteoporosis** or **fractures** with long-term use of corticosteroids.
  - **Kidney damage** from long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs).
  - **Liver damage** from chronic use of alcohol or certain hepatotoxic drugs.
- **Characteristics:**
  - Develop after extended exposure to the drug.
  - Can be minimized by monitoring for side effects and adjusting dosages.

4. **Type D (Delayed) Reactions**

These reactions manifest after a long latency period, sometimes months or years after exposure to the drug. They may be related to carcinogenesis or teratogenicity.

- **Examples:**
  - Cancer due to chemotherapy agents like alkylating agents.
  - Birth defects from drugs like thalidomide or isotretinoin.
- **Characteristics:**
  - May not become apparent until after prolonged exposure or years after the drug has been discontinued.
  - Can have severe, long-lasting consequences.

5. Type E (End-of-Treatment) Reactions

These reactions occur after discontinuation of a drug, particularly if the drug was stopped abruptly.

- **Examples:**
  - Withdrawal symptoms **(**e.g., from benzodiazepines or opioids**).**
  - Rebound hypertension after stopping an antihypertensive like clonidine**.**
  - Adrenal insufficiency after abrupt cessation of corticosteroids.
- **Characteristics:**
  - Occur when the drug is withdrawn too quickly or not tapered properly.
  - Can be prevented by proper discontinuation protocols.
  -

6. Type F (Failure) Reactions

These occur when the drug **fails to produce the desired therapeutic effect**, often due to issues like drug interactions, incorrect dosing, or patient noncompliance.

- **Examples:**
  - **Inadequate blood pressure control** with an antihypertensive due to drug resistance or noncompliance.
  - **Antibiotic treatment failure** due to bacterial resistance.
- **Characteristics**
  - Can result from incorrect drug selection, inadequate dosage, or resistance.
  - Requires a reassessment of the treatment plan.

Other Important Classifications:

- Allergic Reactions**:** Immune-mediated responses, ranging from mild rashes to severe anaphylaxis**.**
- Idiosyncratic Reactions: These are unusual responses that do not follow typical patterns of ADRs and are often unpredictable, potentially related to genetic or immune factors.
- Toxic Reactions: Result from high doses or prolonged exposure, leading to toxicity to organs like the liver or kidneys.

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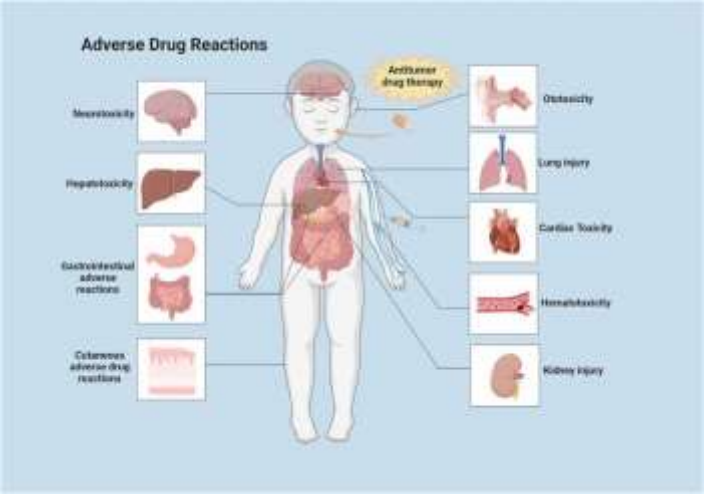


(Fig : Types of ADR)

4. CAUSES OF ADRS

Several factors contribute to the development of ADRs, including:

1. Polypharmacy: The use of multiple medications increases the risk of drug interactions and ADRs.
2. Patient Factors: Age (elderly and children are more vulnerable), genetic predispositions, comorbidities (e.g., liver or kidney disease).
3. Dosage Errors: Incorrect dosing can lead to toxicity or therapeutic failure.
4. Drug Interactions: Concurrent use of drugs that potentiate or inhibit each other's effects.
5. Allergic Reactions: Hypersensitivity to certain drugs, often unpredictable.



(Fig : Causas of ADR)

5. IMPACT OF ADRS

ADRs can have widespread implications for patients and healthcare systems:

1. On Patients

Increased morbidity and mortality.
Reduced quality of life.
Non-compliance with treatment due to fear of side effects.

2. On Healthcare Systems

Prolonged hospital stays and additional treatments.
Increased financial burden on healthcare providers and patients.

3.Effective Strategies Can Minimize The Occurrence And Impact Of Adrs:

1. Patient Education: Informing patients about potential side effects and signs of ADRs.

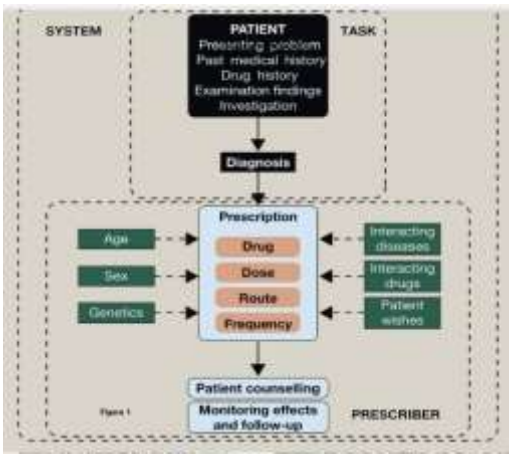
2. Monitoring and Reporting: Regular monitoring of drug levels and patient symptoms. Adverse events should be reported to pharmacovigilance centers.

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3. Personalized Medicine: Tailoring drug therapy based on genetic profiles, especially in cases of hypersensitivity or idiosyncratic reactions.
4. Dose Adjustments: Modifying doses in vulnerable populations like the elderly, children, or patients with organ impairments.
5. Avoiding Polypharmacy: Simplifying drug regimens to reduce interactions and errors.
6. Global Statistics: ADRs are among the leading causes of hospital admissions in many countries.
They account for 5-10% of hospitalizations globally and are a significant cause of mortality.

6. METHODS OF DATA ANALYSIS AND FOLLOW-UP

There are numerous reasons why patients drop out of trials, with the consequences of incomplete or missing outcome data. Some decide to withdraw after experiencing adverse effects, while others give up because they feel no better on the trial treatment.
This potentially leads to a situation where the only people who persevere with trial follow-up are the ones who are doing well, without any adverse reactions. If drop-outs are not accounted for in the statistical analysis, the trial results can be misleading because these remaining patients are not representative of those who were originally randomized to the specific interventions (Figure 1).
To get round this type of bias, 'intention-to-treat' analysis is carried out. All randomized patients are included in the analysis according to the assigned treatment group, irrespective of whether or not the treatment and follow-up were completed in the specified manner. If such analysis is not possible, the trial should report on the number who dropped out, and the reasons Why.



7. PRESCRIBING IN HEALTHCARE

Prescribing of medicines is central to the work of trainee doctors in most developed countries. They write a large proportion of the
prescriptions (medication orders) in most hospitals, and the task is high-stakes for all concerned. For patients, medicines are a major influence on present and future health outcomes. For doctors and hospitals, prescribing represents an important source of clinical risk and cost. Prescribing is also arguably one of the most complex intellectual challenges trainee doctors face. Prescribers have to select the correct medicine, dosage, route and frequency of administration, sometimes in the face of diagnostic uncertainty, taking into account predicted individual variability in drug-handling and response as a consequence of co-morbidity, genetics and
interacting drugs (Figure 1).l Given that individual patients hav

8. PRESCRIBING ERRORS

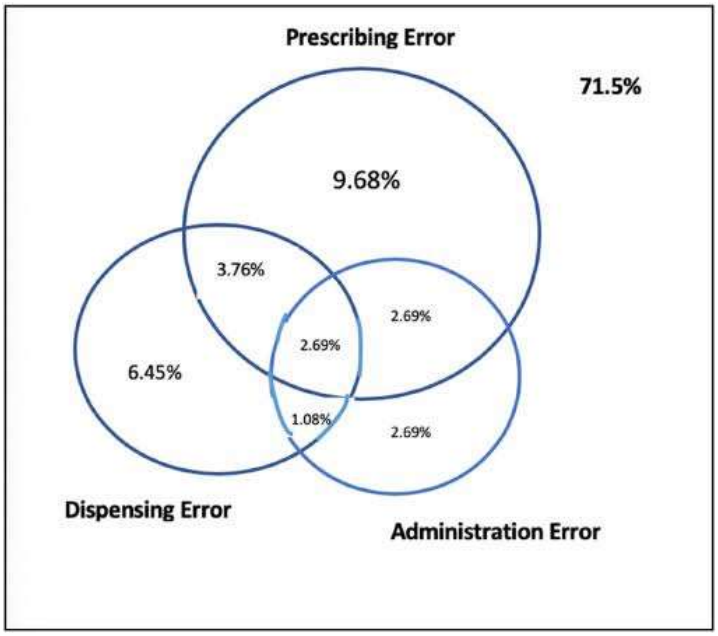
Given the complexity of the prescribing process, it is unsurprising that studies consistently find evidence of poor prescribing in all areas of healthcare. A prescription can be considered to contain an error if it results in either: (1) a significant reduction in the probability of treatment being timely and effective, or (2) a significant increase in the risk of harm, when compared with generally accepted practice. Additional failures of the prescribing process considered in some studies are underprescribing (failure to prescribe a medicine that is indicated), overprescribing (prescribing a medicine that is not indicated or with which the patient is not concordant) and failing to put in place adequate monitoring arrangements.

9. COMMON PRESCRIBING ERRORS

Type of error Frequency (%)
Medication omitted 29
Incomplete prescription 16
Incorrect dose:
C Sub-therapeutic 8
C Supra-therapeutic 5
Incorrect frequency:
C Correct total daily dose 1
C Incorrect total daily dose 7
Medication prescribed without indication 5
Duplication of therapy 5
Inappropriate abbreviation 4
Incorrect timing 3
Omission of prescriber's signature 3
Incorrect formulation 2
Illegible 2
Missing instructions for use 3
Incorrect drug 1
Significant drugedrug interaction 1

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Incorrect route 1	<1
Incorrect duration 1	Patient allergic to medication prescribed
Contraindication to medication 1	<1
Wrong patient	



(Fig : Common Prescribing Errors)

10. OTHER WAYS OF IMPROVING PRESCRIBING

Prescribers themselves play a major role in delivering safe, effective and error-free drug therapy. However, there are other important means of achieving optimal prescribing and reducing errors, based on ameliorating the factors listed in Table 2.

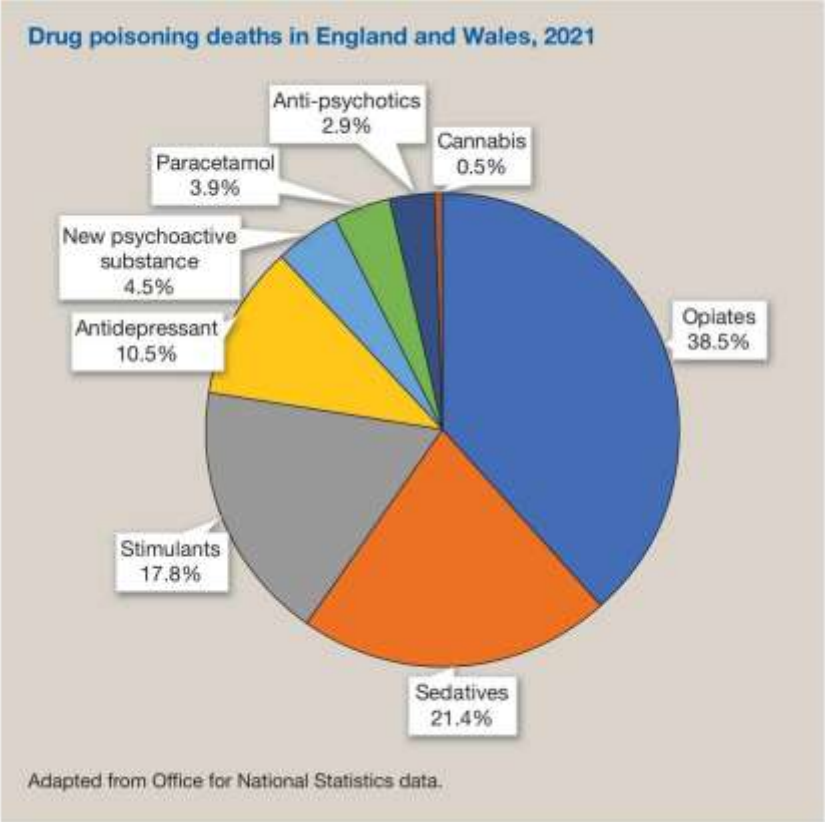
Task factors Errors are more likely when inexperienced prescribers are required to treat complex patients using medicines with which they are unfamiliar or which are associated with significant risk of adverse effects. These situations can be minimized if prescribers work in supportive environments where they care for appropriate patients, under supervision, and feel able to ask for help at any time, without prejudice.

System factors The systems in which prescribers work are often suboptimal,emphasizing the importance of adequate training and preparation as an important defence and source of resilience. The working environment could be improved in several ways:

Clinical pharmacy service e pharmacists improve medicines safety by advising prescribers at the point of care (e.g. on ward rounds), scrutinizing prescriptions beforeadministration and supporting medicines reconciliation on admission and discharge from hospital. They also have an important role in educating and reinforcing good prescribing habits.

Electronic prescribing e this requires prescribers to enter the details of prescriptions into a computerized system that can also offer some clinical decision support by drawing on;individual patient details from the electronic health record. Prescribers can be provided with relevant information and Priorities in the emergency treatment of poisoning When caring for the patients who are undifferentiated or have potentially time-critical pathologies, clinicians should consider the order in which management priorities are addressed. Immediately life-threatening issues should be identified and managed using standard Airway, Breathing, Circulation and Disability protocols; consideration may need to be given to using personal protective equipment. Decontamination should be considered once the patient is stabilized (or separately, while stabilization is continuing). Advice on these approaches in the UK is provided by national advisory groups, such as NHS England, the UK Health Security Agency and the Joint Emergency Services Interoperability Programme. Subsequently, additional relevant assessments can include:
electrocardiogram analysis (i.e. rhythm, QRS duration, QT interval)blood gas analysis (i.e. pH, lactate, anion gap, calculated osmolarity)blood glucose and temperature (often forgotten in disability assessment) toxidrome (toxic syndrome) identification (Table 2) specific investigations (e.g. paracetamol concentration,

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(Fig : Drug Poisoning Death in England And Wales)

The broad Categories of poisoning requiring emergency care :

The broad categories of poisoning requiring emergency care

Cause	Example
Use of illicit drugs	Heroin, benzodiazepine, cocaine or amphetamine toxicity
Self-harm ingestions	Paracetamol overdose, antidepressant overdose
Unintentional (accidental) poisoning	Cognitive impairment leading to excess anticoagulant ingestion
Body packing or stuffing	Drug smuggling. Short-notice concealment of poorly packed drugs by ingesting them or inserting them into cavities
Exploratory poisoning	Paediatric ingestion of detergent capsules
Environmental exposure	Carbon monoxide poisoning
Industrial exposure	Hydrocarbon exposure in oil and gas workers
Ocular or dermal exposure	Caustic agents
Envenomation	*Vipera berus* (adder) envenomation
Major incident or mass casualty events	Salisbury poisonings (Novichok)

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Classical toxidromes

Toxidrome	Example agent	Mechanism	Symptoms	Antidote
Anticholinergic	Tricyclic antidepressants	Block binding of acetylcholine to receptors	Confusion, agitation, flushed dry skin, dilated pupils, hypertension, tachycardia, hyperthermia, urinary retention, decreased bowel motility	Supportive care (physostigmine is not routinely recommended in the UK because of concerns of asystole; use is more common in Australia and the USA)
Cholinergic	Organophosphorus compounds	Inhibition of cholinesterases	Variable, depending on level of nicotinic/muscarinic activation. Sweating, lacrimation, bronchorrhoea/spasm, pupillary constriction, decreased consciousness, vomiting, defecation, urination, respiratory failure	Atropine (and pralidoxime for organophosphorus insecticides or nerve agents)
Opioid	Heroin	μ-Opioid receptor activation	Reduced respiratory rate, decreased consciousness, pupillary constriction	Naloxone
Sedative-hypnotic	Benzodiazepine	Enhanced GABA receptor binding (sedative-hypnotic is a broad category with many alternative mechanisms)	Decreased level of consciousness, ataxia, dysarthria	Supportive care (flumazenil is not routinely recommended because of concern of refractory seizures, but it may have a role in selected patients)
Sympathomimetic	Cocaine	Adrenoreceptor activation	Hypertension, tachycardia, agitation, tremor, seizures, dilated pupils, hyperthermia, sweating	Sedative, typically benzodiazepines

GABA, γ-aminobutyric acid.

(Fig : Classical Toxidromes)

11. DEALING WITH UNCERTAINTY IN EMERGENCY CARE

Emergency care of undifferentiated patients is a careful balance of being guided by pre-test probability while avoiding anchoring bias.

Clinicians can obtain information about emerging drug trends (thusimproving their pre-test probability) from a variety of sources. Multi-agency drug alerts are often circulated to emergency department staff, and the Royal College of Emergency Medicine (RCEM) issues ‘safety FLASH’ alerts nationally that aim to identify emerging trends for recreational drugs and unintentional poisoning. When better informed, clinicians must avoid anchoring bias,and recognize when new information means a prior diagnosis becomes unlikely. For example, clinicians are often witnessed to give naloxone to patients with a decreased level of consciousness, even in the absence of bradypnoea or pupillary constriction to support a diagnosis of opioid toxicity. When unsure, the good clinician seeks guidance.

When managing patients with an unclear diagnosis, it is important to anticipate the potential risks and benefits of treatment. Used injudiciously, naloxone can precipitate opiate withdrawal, activated charcoal can cause aspiration (rare), and sodium bicarbonate can cause hypernatraemia. Supportive care is often the mainstay of care even in severe toxicity, because innate detoxification mechanisms often succeed given sufficient time Planning in emergency care It is easier to ensure satisfactory outcomes if issues have been anticipated and addressed. The NPIS and RCEM produce guidelines on antidote stocking for emergency departments. The antidotes shown in Table 3 are those it is felt should be immediately available in any emergency department. Unfortunately, compliance with these guidelines is frequently poor. Some presentations require extremely high doses of antidote tocking. For example, glucagon antidote therapy (often trialled in severe b-adrenoceptor blocker and calcium channel blocker toxicities) can require 10 mg of glucagon every hour, which can easily exhaust hospital stocks. Similarly, organophosphorus poisoning can easily deplete a hospital’s entire stock of atropine. Large stocks of some antidotes are held by ambulance services (e.g. atropine) and in regional centres (e.g. pralidoxime). Major incident plans should address how these stocks can be accessed when needed, and all hospitals should ensure that their antidote quantities are stocked in line with recommendations. The future of the emergency treatment of poisoning Clinical knowledge in toxicology is always increasing, and the speed of knowledge translation to direct clinical care is being reduced by online medical education resources and podcasts.

While this undoubtedly makes a difference to patients on a caseby-case basis, clinicians caring for individuals with poisoning would benefit from an increased understanding of the specific reasons for poisoning attendances. Current primary prevention in toxicology is limited, and these insights would allow for both continued lobbying for regulatory change when clear issues are identified, and local solutions to emerging problems

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Toxicology care is now largely protocolized. While this has significant benefits (supporting clinicians caring for rare presentations, reducing variability in quality of care), the future islikely to see an increased focus on identifying patients who would benefit from variations in standard care, including, for example, antidote administration earlier than normal or in different doses. Finally, toxicology is currently largely focused on the prevention of injury through supportive care and antidote therapy. When antidotes do not work, and significant injury occurs (e.g.hepatotoxicity after paracetamol overdose), there are limited options. Future research in toxicology may identify routes by which to reverse injury when patients with established injury present to emergency departments; awareness of these therapies and how to use them will be critical.

12. ADVERSE EFFECTS AND LIMITATIONS

Adverse Drug Reactions (ADRs)

ADRs are unintended, harmful reactions to a drug administered at normal doses for prevention, diagnosis, or treatment. They are a significant concern in clinical practice and can range from mild symptoms like nausea to severe effects such as organ failure or death.

Adverse Drug Effects (ADEs)

ADEs encompass any injury resulting from drug use, including ADRs, medication errors, or improper usage. While ADRs occur despite appropriate use, ADEs can result from both proper and improper drug administration.

Common Adverse Drug Reactions

1. Gastrointestinal effects: Nausea, vomiting, diarrhea.
2.Allergic reactions: Rash, itching, anaphylaxis.
3. Central nervous system effects: Drowsiness, dizziness, confusion.
4. Cardiovascular effects: Hypotension, arrhythmias.
5. Hepatotoxicity: Liver damage.
6. Nephrotoxicity: Kidney damage.Nephrotoxicity: Kidney damage.
7. Blood dyscrasias: Anemia, leukopenia, thrombocytopenia.

Limitations of ADR Reporting

1. Underreporting: Many ADRs go unreported, especially mild ones.
2. Subjectivity: Variability in perception and reporting by healthcare professionals and patients.
3. Delayed effects: Some ADRs manifest long after drug exposure, complicating detection.
4. Complexity: ADRs may be mistaken for symptoms of underlying conditions.
5. Bias: Reporting may focus on severe or well-known ADRs, ignoring subtle or less common effects.
6. Limited population diversity: Clinical trials often exclude certain demographics (e.g., pregnant women, elderly), making ADR data less generalizable.
7. Insufficient monitoring systems: Inadequate post-marketing surveillance limits ADR detection.

13.MANAGING ADRS

Prevention: Use patient history, avoid polypharmacy, and adjust dosages for specific populations (e.g., elderly, renal impairment).
Monitoring: Regular follow-ups and blood tests for at-risk drugs (e.g., hepatotoxic or nephrotoxic drugs).
Education: Inform patients about possible ADRs and the importance of reporting symptoms.
Pharmacovigilance: Strong reporting systems (e.g., WHO's VigiBase) are crucial for early detection of ADRs.
Would you like a deeper discussion on ADR management or pharmacovigilav Managing ADRs:
Prevention: Use patient history, avoid polypharmacy, and adjust dosages for specific populations (e.g., elderly, renal impairment).
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Pharmacovigilance: Strong reporting systems (e.g., WHO's VigiBase) are crucial for early detection of ADRs.
Would you like a deeper discussion on ADR management or pharmacovigila system

14 . THERE ARE TWO GROUPS OF INTRABODY

Endoplasmic reticulum intrabodies produced as singlechain fragment variables. These small single polypeptides contain the variable light chain and variable heavy chain of an antibody connected by a flexible linker peptide.

Single-domain antibodies are small molecules (about 15 kDa) composed of a variable domain of the heavy chain but completely devoid of the light chain; they retain the ability to bind antigens with high specificity and affinity.Intrabodies have several potential applications in canc

15. HOW CAN DRUG THERAPY BE MONITORED?

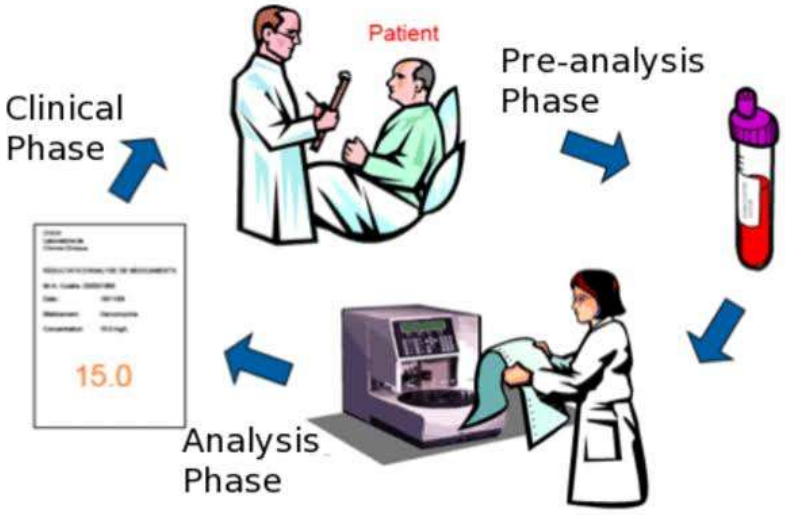
Monitoring using clinical and surrogate endpoints

In general, monitoring parameters are most informative if theyare closely related to the clinical outcome that the treatment is intended to produce (Figure 1). Indeed, wherever possible, it is best to monitor the clinical endpoint itself. A clinical endpoint is a ‘characteristic or variable that reflects how a patient feels,functions, or survives’.1 For example, when a benzodiazepine is administered to allow an interventional procedure to be performed, the clinical endpoint e sedation e is usually readily apparent. The drug dosage can be titrated to achieve the required level of sedation.

Often, however, measuring the effect of the drug on the clinical endpoint is impractical or cannot readily be used to guide therapy. This could be because the clinical endpoint is an event that cannot be detected until it is inevitable or irreversible, as in preventive therapy (e.g. anticoagulation to reduce the risk of stroke in atrial fibrillation). Alternatively, it could be because theclinical endpoint is a delayed event, which cannot be measured until after treatment has finished. For example, the clinical endpoint in the treatment of pneumonia e cure of the

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infection,most reliably confirmed by the complete resolution of symptomse may not be measurable until weeks after the treatment course has ended. In these situations, a surrogate endpoint may be required.



(Fig : . How Can Drug Therapy Be Monitored)

16 THE PRACTICALITIES OF DRUG CONCENTRATION MEASUREMENT

When is measurement of Drug Concentration Indicated?

Sampling can be indicated if:3there is (or, in the case of a preventive therapy, could be) an inadequate clinical response, which might be attributable to sub-therapeutic concentrations or incomplete adherence it is difficult to determine clinically whether an adverse event is the result of drug toxicity or a feature of the underlying condition (e.g. renal impairment in a person with sepsis can be a manifestation either of the disease or of aminoglycoside toxicity) there is a change in circumstances that can alter theplasma drug concentration. For example, if a patient taking lithium requires antihypertensive therapy with a thiazide diuretic or angiotensin-converting enzyme inhibitor, one should be alert to the risk of a drugedrug interaction leading to lithium accumulation. Monitoring lithium concentrations is essential in this context. Similarly, clearance of gentamicin depends on renal function; if this is fluctuating, more frequent monitoring can be required.

When should samples be taken?

Timing in relation to doses: the concentration of a drug rises and then falls during the dosage interval. The interpretation of measurements made during the initial absorption and distribution phases is complex and usually uninformative. It is therefore generally best to take samples during the elimination phase, such as at the end of the dosage interval (a 'trough' or 'pre-dose'concentration). Whatever time is selected, it is essential that it is accurately recorded with the measurement request, otherwise interpretation is impossible.

Timing in relation to the start of the treatment regimen: after the introduction of a medicine, the drug accumulates in the body. At some point, provided the situation remains stable, a state of equilibrium is reached at which the amount of drug administered in a given period is equal to the amount of drug eliminated during that period. This is termed steady state. The time taken to reach steady state depends on the half-life (t½) of the drug. A good rule of thumb is that steady state is achieved five half-lives after the introducing the drug or changing the dosage regimen. For example, the antibiotic vancomycin has a half-life of approximately 6 hours. After starting treatment, it takes approximately 30 hours (5 6 hours) for steady state to be achieved (Figure 3a). Only at this point can the plasma concentration associated with that dosage regimen be reliably assessed.

Likewise, if the dosage is changed, it takes another 30 hours before a new steady state is reached. There are, however, circumstances in which it can be useful to measure concentrations before steady state is reache

17. HOW DO THE RESULTS GUIDE TREATMENT?

Interpreting the target range: the target range is derived from population studies. Natural interindividual variation dictates that

some people do not derive therapeutic benefit within the population target range, and others experience toxicity below the population toxicity range.

Other variables can also influence the target range. For example, phenytoin is heavily protein bound, but only the unbound drug exerts an effect. If the measured concentration includes both the unbound and protein-bound fractions (i.e. it is a'total' concentration), a low total concentration could be associated with a therapeutic or toxic concentration of unbound drug in the presence of hypoalbuminaemia.4 It is therefore more informative to measure only the unbound (free) fraction. If this facility is unavailable, a mathematical correction can be

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applied to allow the total concentration to be assessed against the standard target range (Table 1).
The concept of diminishing returns: as discussed in 'Pharmacodynamics and pharmacokinetics for the prescriber' (pp. 1e10 of this issue).

18. THE IDEALIZED TIME-CONCENTRATION RELATION FOR ADSORPTION (ADR)

typically describes how the concentration of a solute or adsorbate decreases in solution over time due to adsorption onto a solid adsorbent. This relationship is commonly modeled using different adsorption kinetics, depending on the system's physical and chemical conditions.

Here are the most common models

1. Lagergren's Pseudo-First-Order Model

This model assumes that the rate of adsorption is proportional to the difference between the equilibrium adsorption capacity and the amount adsorbed at time .

\frac{dq_t}{dt} = k_1 (q_e - q_t)

The integrated form is:

\ln(q_e - q_t) = \ln(q_e) - k_1 t

Where:

: Adsorption capacity at time (mg/g or mol/g)

: Adsorption capacity at equilibrium

: Pseudo-first-order rate constant

2. Pseudo-Second-Order Model

This model assumes the adsorption rate is proportional to the square of the difference between and .

\frac{dq_t}{dt} = k_2 (q_e - q_t)^2

The integrated form is:

\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{t}{q_e}

Where:

: Pseudo-second-order rate constant

3. Intraparticle Diffusion Model

This model considers diffusion within the pores of the adsorbent as the rate-limiting step:

q_t = k_i t^{0.5} + C

Where:
: Intraparticle diffusion rate constant
: Constant related to the boundary layer effect

4. Elovich Model

Often used for chemisorption, this model assumes a logarithmic decrease in the adsorption rate over time:

\frac{dq_t}{dt} = \alpha e^{-\beta q_t}

The integrated form is:

q_t = \frac{1}{\beta} \ln(\alpha \beta) + \frac{1}{\beta} \ln(t)

Where:

: Initial adsorption rate

: Desorption constant

5. Langmuir Adsorption Dynamics

For systems where adsorption follows Langmuir isotherm behavior:

C_t = C_0 e^{-k_a t}

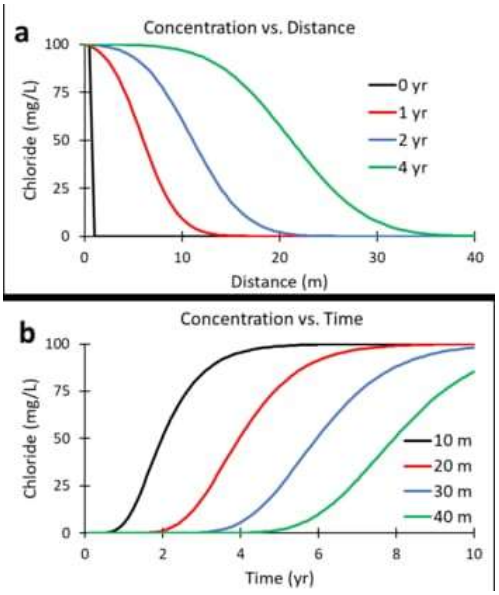
Where:
: Solute concentration in the solution at time

: Initial solute concentration

: Adsorption rate constant

The choice of the model depends on experimental conditions, the type of adsorption process, and the nature of the adsorbent and adsorbate.

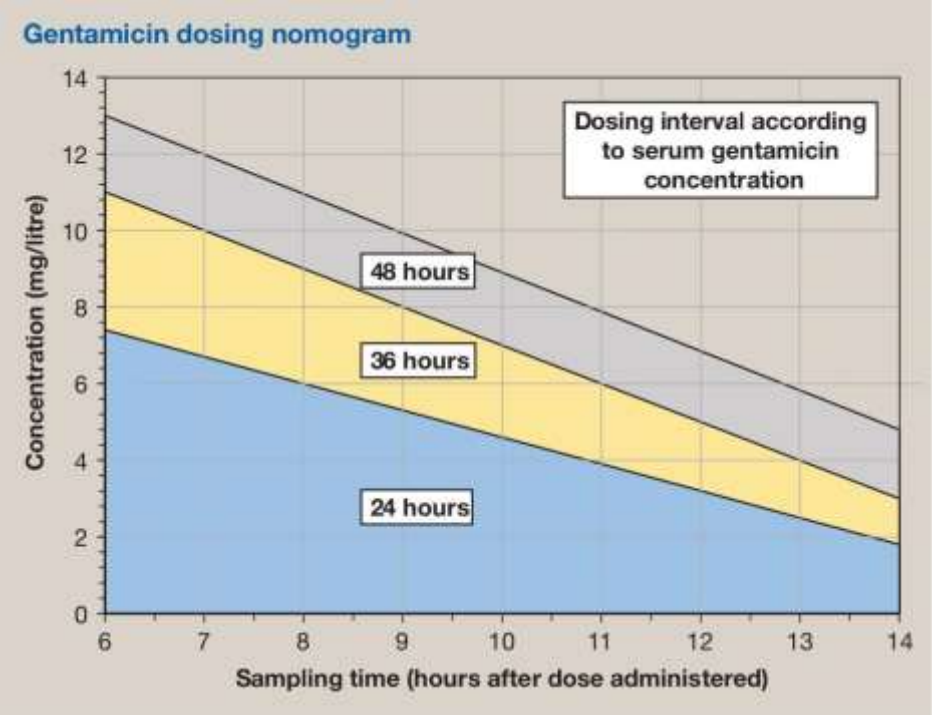
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(Fig : The idealized time-concentration relation for adsorption (ADR))

19.GENTAMICIN DOSING NOMOGRAM

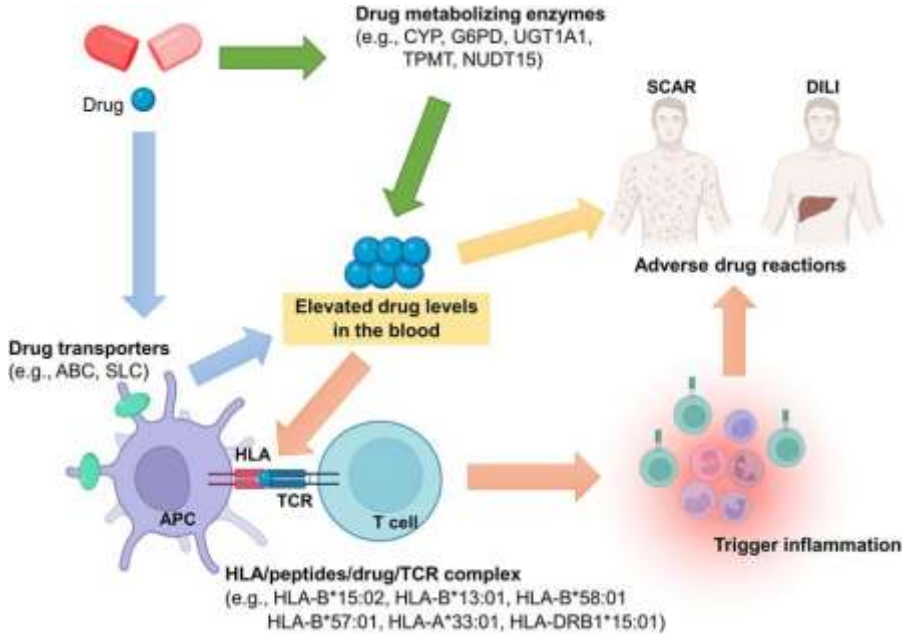
Gentamicin is monitored using the Hartford nomogram which relates observed concentration to the time post dose within a given concentration range. The dose is calculated as detailed below and repeated at 24 hour intervals or longer. interpretation of measured level The Gentamicin level is evaluated via the Hartford nomogram. interval will be recommended as 24, 36 or 48 hours respectively. If the level falls on the line, the longer dosing interval will be recommended.



20. ABNORMAL DRUG METABOLISM

Changes that alter the rate of metabolism of a drug also alter the amount present at the site of action, and thereby the extent and duration of the beneficial and adverse effects. The most important enzymes responsible for drug metabolism are the hepatic microsomal oxidases (cytochrome P450 system), of which CYP2D6 and CYP3A4 are especially relevant

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(Fig Abnormal Drug Metabolism)

21 .DETECTION AND DIAGNOSIS

When harm occurs during or after drug treatment, it may have been caused the drug but could also be a manifestation of the disease for which the drug was being taken, or it may haven another cause. In the simplest case, the reaction is identified by its close relationship in time to drug, exposure, its resolution when the drug is stopped (de-challenge) and sometimes, its emergence when the drug is restarted (re-challenge).

However,this clear relationship seldom occurs in practice. Some reactions (e.g. teratogenesis and neurodevelopmental disorders in offspring from in utero drug exposure) only become evident long after exposure. Some (including fatal reactions) are irreversible,and some occur only when several factors coincide and do not recur at re-challenge.

22.PREVENTING ADVERSE DRUG REACTIONS

While some ADRs are unpredictable e such as anaphylaxis in a patient after their first exposure to a penicillin-containing antibiotic e many are preventable with adequate foresight and monitoring. Interventions that reduce the probability of an ADR occurring are important to reduce the risk of patient harm.

There are two basic steps that can be followed to reduce risk: identify the subgroup of patients who are likely to be susceptible to the adverse effect and modify the treatment choice accordingly ensure that the treatment plan mitigates any possible adverse effects.

23. CONCLUSION

As medication experts, pharmacists are a vital part of the treatment team, especially when an ADR occurs. Treating an ADR consists mainly of supportive therapy with symptom management. Furthermore, additional steps should be taken to determine the cause of the patient's symptoms and whether they can be attributed to the use of a drug.

Begin by evaluating the nature of the event. Thoroughly review the medical history available in the patient's chart. Identify and document the clinical reaction, including the patient's subjective report of symptoms. Review the patient's medication list, and then use references such as product inserts, MedWatch reports, and published literature to evaluate whether the reaction is known to occur with any of the drugs the patient has taken. Classify the severity of the reaction. A severe reaction is fatal or life threatening; the drug should be discontinued and not rechallenged. A moderate reaction requires an antidote, a medical procedure, or hospitalization. In many cases, this may mean discontinuing the drug. Mild reactions have symptoms that often require thereapy discontinuation. It is possible that the therapy can be reinitiated with an adjustment in dosage if management of the disease state warrants continuation. Incidental reactions have mild symptoms; patients can choose whether to discontinue treatment, depending on their tolerability of the ADR. After the reaction is evaluated, the cause of the reaction should be established, if possible. Tools such as the Naranjo algorithm or the Liverpool ADR causality assessment tool can be used to assist in determining causality. Check to make sure the ADR is not caused by a medication error; this could influence whether a treatment is continued or discontinued. If the reaction can be attributed to a drug, a suggestion is to update the patient's allergy profile with the name of the drug and a brief description of the reaction.

Finally, take corrective action and follow up. Prescribers should be educated on the ADR. If necessary, a formulary review should be done to determine whether an alternative

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