Adverse Drug Reaction (ADR)

A harmful, unintended response to a drug at normal therapeutic doses (WHO definition).

· Key distinctions: ADRs differ from side effects (which may be beneficial) and overdose toxicity.

· Alternative definition addresses limitations of WHO definition regarding product contamination and herbal medicines.

ADR vs ADE

· Adverse Drug Event (ADE): Any adverse outcome following drug use, regardless of causality.

· Relationship: All ADRs are ADEs, but not vice versa. Causality is key for ADR classification.

Epidemiology & Impact

· ADRs cause 2.6%-6.5% of hospital admissions and are the 4th-6th leading cause of death in the US.

· Hospital stays are prolonged (20 vs. 8 days), increasing healthcare costs significantly.

Classification (Rawlins-Thompson)

1. Type A: Augmented pharmacological effects (predictable, dose-dependent, 80% of ADRs). Bradycardia in BB

2. Type B: Bizarre/immunological effects (unpredictable, serious, rare). Hepatotoxicity in isoniazid ,allergic reaction

3. Type C: Dose/time-related (cumulative effects). Suppression of hypothalamic pituitary adrenal axis by corticosteroid

4. Type D: Delayed effects (e.g., carcinogenesis).

5. Type E: Withdrawal effects. Opiate withdrawal syndrome

6. Type F: Therapeutic failure (often due to drug interactions). Failure of OCP by enzyme inducers

Risk Factors

1. Age: Elderly (reduced metabolism/excretion) and children (physiological differences) are more susceptible.

2. Gender: Women have higher risk for certain ADRs (e.g., torsade de pointes).

3. Comorbidities & Polypharmacy: Liver/kidney impairment and multiple medications increase risk.

4. Ethnicity: Genetic variations affect drug metabolism and response (e.g., ACEI angioedema in Africans).

5. Pharmacogenetics: Individual genetic makeup influences drug efficacy and toxicity.

6. Immunological Factors: Prior exposure can trigger allergic reactions ranging from mild to life-threatening.

Causality Assessment

· Naranjo Algorithm: An objective tool scoring the likelihood of ADR causality as doubtful, possible, probable, or highly probable.

· Regulatory actions often rely on suspicion rather than definitive proof.

Prevention Strategies

1. Review patient history for previous ADRs.

2. Avoid high-risk drugs when possible.

3. Individualize therapy based on patient-specific factors.

4. Practice rational prescribing and improve inter-provider communication.

5. Implement therapeutic drug monitoring (e.g., renal function, blood counts).

Clozapine causes risk of agranulocytosis so monitor WBC

6. Educate patients about potential risks to enable informed decision-making.

Terminology & Classification

· Serious ADE: Results in death, hospitalization, disability, or birth defects.

· Severity: Mild (no activity limitation), Moderate (some limitation), Severe (unable to perform usual activities).

· Prevalence: Very common (>10%), Common (1-10%), Uncommon (0.1-1%), Rare (<0.1%).

Drug Interactions

Introduction & Epidemiology:

Drug interactions are adverse reactions occurring when one substance alters another's effects. They are increasingly common due to polypharmacy, herbal supplement use, and food-drug interactions. Incidence ranges from 1–4% but is likely underreported.

Susceptible Populations:

High-risk groups include elderly patients, those with renal/hepatic impairment, polypharmacy users, ICU patients, and individuals with chronic diseases (e.g., epilepsy, diabetes).

Useful Interactions:

Some interactions are beneficial, such as combining drugs to enhance efficacy (e.g., antiplatelets + anticoagulants in MI) or to reduce side effects (e.g., pyridoxine with isoniazid).

Harmful Interactions:

Adverse interactions can lead to severe outcomes like bleeding, arrhythmias, stroke, unwanted pregnancy, and serotonin syndrome.

Mechanisms:

-Chemical: Incompatibility when drugs are mixed outside the body (e.g., heparin + gentamicin)(diazepam +IV fluids)

-Pharmacodynamic: Interactions at receptor/physiological levels (e.g., warfarin + aspirin → bleeding).

-Pharmacokinetic: Includes

absorption (absorption affected by pH,chelation,motility,transport proteins),

metabolism :enzyme inhibition (grape fruit+erthromycin), enzyme induction:(rifampicin)

distribution:protein binding displacement

elimination :renal,biliary,p -glycoprotein effect

Food & Herb Interactions:

Food can alter drug absorption (e.g., iron with meals). Herbs like licorice and St John's wort can cause significant interactions (e.g., hypertension, reduced drug efficacy).

Clinical Recommendations:

-Always review a patient's full medication list, including OTC drugs, herbs, and supplements.

-Monitor high-risk patients closely.

-Adjust doses or timing to avoid interactions.

-Educate patients about potential risks.

Conclusion:

Drug interactions are a major cause of preventable adverse drug reactions. Awareness, careful prescribing, and patient education are essential to minimize risks.

Therapeutic Drug Monitoring

Therapeutic Drug Monitoring is the clinical practice of measuring drug concentrations in blood to optimize dosing. It is essential because individuals respond differently to medications due to variations in pharmacokinetics (how the body handles the drug) and pharmacodynamics (how the drug affects the body). TDM helps personalize treatment, ensuring effectiveness while minimizing toxicity.

When is TDM Used?

TDM is valuable when:

· There's a direct relationship between drug concentration and effect

· Clinical effects are difficult to assess directly

· There's high variability between patients

· The drug has a narrow therapeutic index (toxic dose close to effective dose)

· Multiple drugs are used together

· Medication non-adherence is suspected

· Drugs have non-linear pharmacokinetics (like phenytoin)

TDM is NOT useful for drugs with active metabolites, irreversible actions, or when tolerance develops.

Practical Requirements

· Timing is critical: Blood samples must be taken at specific times

· Steady-state: Measurements should be after 4-5 half-lives of regular dosing

· Peak vs. Trough levels:

  · Trough: Just before next dose (minimum concentration)

· Peak: After distribution complete (maximum concentration)

· Never use random sampling

· Expert interpretation needed: Consider clinical context and other medications

Drugs Requiring TDM with Monitoring Details

Cardiovascular Drugs

· Digoxin: For heart failure/arrhythmias. Measure trough (>8 hours post-dose). Therapeutic range: 0.5-2.0 ng/mL

Psychotropic Drugs

· Lithium: For bipolar disorder. Measure 12 hours post-dose. Range: 0.6-1.2 mEq/L

· Clozapine: For schizophrenia. Measure trough levels due to agranulocytosis risk

Antiepileptic Drugs

· Phenytoin: Trough level. Range: 10-20 mg/L. Has non-linear kinetics

· Carbamazepine: Trough level. Range: 4-12 mg/L

· Valproate: Trough level. Range: 50-100 mg/L

· Lamotrigine, Ethosuximide, Zonisamide: Trough levels

Antibiotics

· Aminoglycosides (Gentamicin, Tobramycin):

· Peak: 30-60 min post-dose (5-10 mg/L)

· Trough: Pre-dose (<2 mg/L)

· Risk: Nephrotoxicity and ototoxicity

· Vancomycin:

· Peak: 1 hour post-infusion (20-40 mg/L)

· Trough: Pre-dose (10-20 mg/L)

· Teicoplanin: Trough level

Chemotherapy & Immunosuppressants

· Methotrexate (high-dose):

· Monitor at 24h (<5 µmol/L), 48h (<0.1 µmol/L)

· Requires folinic acid rescue if levels high

· Cyclosporine: Trough or 2-hour post-dose in whole blood

· Tacrolimus, Sirolimus: Trough levels in whole blood

· Mycophenolate: Trough level or AUC

Other Drugs

· Theophylline: For asthma/COPD. Trough level. Range: 10-20 mg/L

· Various antiarrhythmics

Clinical Cases Demonstrating Importance of TDM

Case 1: Diabetic patient developed permanent hearing loss and balance problems after 5 weeks of gentamicin without proper TDM.

Case 2: Patient with multiple conditions died from methotrexate toxicity due to poor monitoring, communication failures, and inadequate documentation.

Drug Use During Pregnancy

1. Introduction and Basic Principles

· Most drugs cross the placenta by diffusion, potentially reaching harmful fetal concentrations

· Maternal albumin decreases while fetal albumin increases during pregnancy → higher free concentrations of protein-bound drugs in fetus

· Pregnant women excluded from clinical trials → safety evidence from animal studies, case reports, observational studies (limited quality, recall bias)

· Thalidomide (sedative/hypnotic) demonstrated animal-human discrepancy (safe in animals, teratogenic in humans)

2. Indications for Drug Therapy During Pregnancy

1. Pregnancy-induced conditions: Nausea/vomiting, preeclampsia/eclampsia

2. Chronic conditions: Epilepsy, asthma, diabetes mellitus, hypertension (pre-existing)

3. Acute conditions: Infections, gestational diabetes, hypertension (developing during pregnancy)

4. Fetal therapy:

· Corticosteroids (for fetal lung maturation/surfactant production in preterm birth)

· Phenobarbital (barbiturate for epilepsy/sedation) reduces neonatal jaundice by inducing fetal liver enzymes

· Zidovudine/antiretroviral combinations (HIV treatment) prevent maternal-fetal HIV transmission

3. Factors Affecting Placental Drug Transfer

Physicochemical Properties

· Lipid solubility: Lipophilic drugs cross easily (thiopental - anesthetic); ionized drugs cross slowly (tubocurarine - muscle relaxant)

· Molecular size:

  · <500 daltons: cross easily

  · 500-1000 daltons: cross with difficulty

  · 1000 daltons: cross poorly/not at all

  · Heparin (anticoagulant) and insulin (diabetes treatment) don't cross due to large size/polarity

· pH gradient: Maternal pH 7.4 vs fetal pH 7.3 → weak bases ion-trapped in fetus → higher fetal concentrations

Biological Factors

· Placental transporters: P-glycoprotein effluxes drugs back to mother (vinblastine, doxorubicin - anticancer drugs; anti-HIV drugs)

· Protein binding: Reduces transfer; fetal proteins have lower affinity; glyburide (diabetes drug) doesn't cross due to high maternal binding + fetal efflux

· Placental/fetal metabolism: Placenta metabolizes some drugs (pentobarbital); may produce toxic metabolites (ethanol, benzopyrenes)

4. Teratogenicity: Mechanisms and Examples

Mechanisms of Teratogenesis

1. Folic acid deficiency/antagonists → neural tube defects (spina bifida)

2. Neural crest disruption → multiple structural defects

  · Drugs: bosentan (pulmonary hypertension), folic acid antagonists, retinoic acid (vitamin A derivative)

3. Cell differentiation disruption → developmental abnormalities

· Drugs: isotretinoin, etretinate (acne/psoriasis treatments)

4. Endocrine disruption → hormonal/gender development issues

· Example: diethylstilbestrol (synthetic estrogen) → vaginal adenocarcinoma in daughters, genital defects in sons

5. Oxidative stress → DNA/protein/lipid damage → enzyme inactivation/cell death/gene alteration

6. Vascular disruption → hypoperfusion/hypoxia → tissue damage

7. Specific substance syndromes:

· Fetal Alcohol Syndrome (chronic high ethanol) → CNS, growth, facial defects

· Maternal smoking → cardiovascular/musculoskeletal/facial defects, preterm delivery, growth restriction, cerebral palsy, learning disabilities

Defining Characteristics of Teratogens

1. Cause characteristic malformations (specific target organs)

2. Act during specific developmental windows (organogenesis of target organs)

3. Show dose-dependent incidence

4. Effects include: malformations, growth retardation, miscarriage, stillbirth, neurocognitive delay

5. Critical Developmental Periods

· Blastogenesis (days 1-8): Exposure may kill embryo; no malformations produced

· Embryogenesis (weeks 2-8): Highest vulnerability (organogenesis) → major malformations or death

· Fetogenesis (week 8 to term): Affects external genitalia differentiation, CNS histogenesis → genital defects, behavioral/mental impairment

6. Specific Drug Teratogens and Effects

Known Human Teratogens

· Thalidomide (sedative/hypnotic): Phocomelia (limb defects), heart defects, gut atresia (weeks 4-7)

· Warfarin (anticoagulant): Saddle nose, growth retardation, limb/eye/CNS defects

· Phenytoin (anticonvulsant): Cleft lip/palate, microcephaly, mental retardation

· Valproate (anticonvulsant/mood stabilizer): Neural tube defects (spina bifida)

· Carbamazepine (anticonvulsant): Fetal head growth retardation

· Lithium (bipolar disorder): Cardiac defects (Ebstein's anomaly)

· Retinoids (isotretinoin - acne; etretinate - psoriasis): Hydrocephalus, CNS/heart defects

· ACE inhibitors (hypertension): Oligohydramnios, renal failure (2nd/3rd trimester)

· Methotrexate (cancer/autoimmune): Hydrocephalus, cleft palate, neural tube defects

· Cyclophosphamide (cancer): Multiple congenital anomalies

· Sex hormones (androgens, estrogens, progestins): Masculinization of females, testicular atrophy in males

Drugs with Late Pregnancy Effects

· Salicylates (aspirin - pain/anti-inflammatory): Bleeding, delayed labor, low birth weight

· NSAIDs (ibuprofen, naproxen - pain/anti-inflammatory): Premature ductus arteriosus closure, renal impairment

· Tetracycline (antibiotic): Tooth/bone staining, enamel hypoplasia, impaired bone growth

· Aminoglycosides (gentamicin - antibiotic): Deafness

· Opioids (morphine, codeine - pain relief): Fetal dependence, neonatal withdrawal, respiratory depression

7. Pregnancy Risk Categories

· Category A: Controlled studies show no risk (safe)

· Category B: Animal studies show no risk/human studies inadequate, OR animal studies show risk but human studies show no risk

· Category C: Animal studies show risk/human studies inadequate, OR no studies available

· Category D: Positive evidence of human fetal risk (benefits may outweigh risks in serious situations)

· Category X: Contraindicated in pregnancy (risks outweigh benefits)

8. General Prescribing Principles

1. Prefer older, well-studied drugs over newer alternatives with less pregnancy data

2. Use lowest effective dose for shortest necessary duration

3. Avoid polypharmacy and eliminate nonessential medications

4. Discourage self-medication with OTC drugs, supplements, herbs

5. Consider timing: Avoid known teratogens during organogenesis (weeks 2-8)

6. Monitor carefully: Adjust doses based on pharmacokinetic changes in pregnancy

7. Balance risks: Consider risks of untreated maternal condition vs. drug risks

8. Provide preconception counseling: Optimize medications before pregnancy

9. Special Considerations

· Chronic conditions: Continue essential treatments (epilepsy, asthma, diabetes, hypertension) with safest options

· Mental health: Untreated depression/anxiety may harm fetus more than medications (SSRIs often continued)

· Infections: Treat appropriately (untreated infections often more dangerous than antibiotics)

· Pain management: Use acetaminophen preferentially over NSAIDs/opioids when possible

· Vitamin supplementation: Folic acid (preconception through first trimester) reduces neural tube defects

10. Key Monitoring Points

· First trimester: Avoid known teratogens during organogenesis

· Second/third trimesters: Monitor for drugs affecting fetal growth/development

· Near delivery: Avoid drugs causing neonatal depression/sedation/withdrawal

· Postpartum: Consider drug transfer through breast milk

Conclusion

Drug therapy during pregnancy requires careful risk-benefit analysis, with consideration of:

1. Drug properties affecting placental transfer
2. Developmental timing of exposure
3. Dose and duration of therapy
4. Maternal health status and risks of untreated conditions
5. Available safety data (though limited for most drugs)

Drug Use in the Elderly

1. Physiological Changes in the Elderly

· Decreased body water (53% vs 61% in young adults)

· Increased body fat (Women: 38-45% vs 26-33%)

· Decreased serum albumin (3.8 vs 4.7 g/dL)

· Decreased hepatic blood flow (55-60% of young adults)

· Decreased kidney function (reduced GFR)

· Impaired homeostatic mechanisms: orthostatic hypotension, thermoregulation problems

2. Age-Related Pharmacokinetic Changes

Absorption

· Drugs with increased bioavailability: Propranolol BB (for hypertension/arrhythmias), Labetalol BB (for hypertension), Chlorpromazine (antipsychotic), Diazepam (anxiety/sedation), Morphine (pain relief), Midazolam (sedation), Verapamil (hypertension/arrhythmias)

· Drugs with impaired active transport absorption: Vitamin B12 (anemia treatment), Calcium (bone health), Iron (anemia treatment), Magnesium (supplementation)

· Drugs requiring acidic environment (reduced absorption with low stomach acid): Ketoconazole/Itraconazole (antifungals), Iron (anemia), Aspirin (pain/antiplatelet), Penicillins (antibiotics), Phenytoin (anticonvulsant)

Distribution

· Water-soluble drugs (decreased volume of distribution): Gentamicin (antibiotic), Ethanol

· Lipophilic drugs (increased Vd): Benzodiazepines (anxiety/sedation), Metronidazole (antibiotic), Rifampin (TB treatment)

· Increased brain exposure to drugs and toxins

Metabolism

· High extraction drugs (significantly decreased metabolism): Propranolol, Amitriptyline (antidepressant), Diltiazem (hypertension), Lidocaine (local anesthetic/arrhythmia), Metoprolol (hypertension), Morphine, Verapamil

Elimination (Renal)

· Avoid if CLcr <30 mL/min: Colchicine (gout), Co-trimoxazole (antibiotic), Glyburide (diabetes), Nitrofurantoin (UTI antibiotic), Probenecid (gout), Spironolactone (diuretic), Triamterene (diuretic)

· Require dose reduction in renal impairment: Acyclovir (antiviral), Amantadine (Parkinson's/flu), Ciprofloxacin (antibiotic), Gabapentin (neuropathic pain), Ranitidine (antacid), Aminoglycosides (antibiotics), Vancomycin (antibiotic)

3. Age-Related Pharmacodynamic Changes

· Increased sensitivity to CNS drugs: Benzodiazepines, Opioids, Antipsychotics, Anticholinergics, Lithium (bipolar disorder)

· Increased orthostatic hypotension from antihypertensives

· Increased bleeding risk with Warfarin (anticoagulant)

· Increased hypotensive/bradycardic effects of Calcium channel blockers

· Decreased response to β-blockers

· Reduced effectiveness of diuretics

4. Potentially Inappropriate Medications in Elderly (Beers Criteria)

Drugs to AVOID

1. Anticholinergics: Diphenhydramine (antihistamine), Hydroxyzine (antihistamine/anxiolytic) → confusion, dry mouth

2. Nitrofurantoin (UTI antibiotic) → pulmonary toxicity, neuropathy

3. α-blockers (e.g., Doxazosin, Terazosin for hypertension/BPH) → orthostatic hypotension

4. Immediate-release Nifedipine (hypertension) → hypotension, myocardial ischemia

5. Amiodarone (arrhythmia) → thyroid/lung/liver toxicity

6. Tricyclic antidepressants (e.g., Amitriptyline) → anticholinergic effects, sedation

7. Antipsychotics (e.g., Haloperidol) → cognitive decline, stroke risk

8. Benzodiazepines (e.g., Lorazepam) → falls, fractures, dependence

9. Long-acting sulfonylureas (e.g., Glibenclamide for diabetes) → hypoglycemia

10. Insulin sliding scale (diabetes) → hypoglycemia

11. Metoclopramide بعملParkinsonism (nausea/GI motility) → extrapyramidal symptoms

12. Proton pump inhibitors (e.g., Omeprazole for acid reflux) → C. difficile infection عدوى تصيب القولون عند الكبارclostridium difficule

13. Meperidine (pain relief) → neurotoxicity, delirium

14. NSAIDs (e.g., Ibuprofen for pain/inflammation) → ulcers, renal failure

15. Muscle relaxants (e.g., Cyclobenzaprine) → anticholinergic effects, falls

5. Common Drug-Disease Interactions to Avoid

· Anticholinergics in patients with BPH or dementia

· Antipsychotics in patients with history of falls or Parkinson's disease

· Aspirin/NSAIDs in patients with peptic ulcer disease

· Calcium channel blockers in patients with heart failure

· Metoclopramide in patients with Parkinson's disease

· NSAIDs in patients with heart failure or renal failure

6. Monitoring Requirements for Specific Drugs

· Antiepileptics (Phenytoin, Carbamazepine, Valproate) → drug levels

· ACEi/ARBs ادوية ضغط و قلب و سكري (Enalapril, Losartan) → serum K+, renal function

· Diuretics (Furosemide) → serum K+, renal function

· Hypoglycemics (Insulin, Glyburide) → glucose, HbA1c

· Lithium (bipolar) → serum levels, thyroid/renal function

· Warfarin (anticoagulant) → PT/INR

· Amiodarone (arrhythmia) → hepatic, thyroid, pulmonary function

· Antipsychotics → extrapyramidal symptoms, metabolic parameters

7. Key Management Principles

· Start low, go slow: Begin with lowest effective dose

· Regular medication review: Eliminate unnecessary drugs

· Monitor renal/hepatic function: Adjust doses accordingly

· Simplify regimens: Improve adherence

· Avoid polypharmacy: Limit to <5 medications when possible

· Team-based approach: Involve pharmacists, caregivers

· Patient education: Clear instructions on benefits/risks

· Use creatinine clearance (not serum creatinine) for renal dosing

8. Clinical Pearls

· Serum creatinine is unreliable in elderly (due to decreased muscle mass)

· First-pass metabolism is decreased → higher bioavailability of many drugs

· Brain exposure to drugs is increased → more CNS side effects

· Therapeutic goals should be age-appropriate (different for 80 vs 40-year-old)

· Non-adherence is common due to cost, complexity, side effects, dementia

· Therapeutic failure in elderly may be due to underdosing rather than drug ineffectiveness

Drug Use During Lactation

1. Benefits of Breastfeeding

· Optimal infant nutrition: Exclusive for 6 months, continue to at least 12 months

· Infant benefits: Infection protection (gastric, respiratory, urinary), reduced obesity/type 1 diabetes/atopic diseases, long-term lower BP/cholesterol

· Maternal benefits: Reduced pre-menopausal breast cancer risk, strengthened mother-infant bond

2. Drug Transfer into Breast Milk

General Principles

· Most drugs pass to milk to some extent; breastfeeding usually can continue

· Transfer via passive diffusion of un-ionized, protein-unbound forms

· Milk characteristics: pH 6.8-7.0 (vs plasma 7.4), higher fat, less buffering

Drug Properties Affecting Transfer

1. pKa:

· Basic drugs (Erythromycin - antibiotic): Ionize in acidic milk → trapped in milk

· Acidic drugs (Penicillin - antibiotic): Ionize in basic plasma → trapped in plasma

2. Protein binding: High binding (Warfarin - anticoagulant) → retained in plasma

3. Lipophilicity: Lipid-soluble drugs cross easier (CNS drugs); water-soluble cross poorly

4. Molecular weight:

· <200 daltons: Cross easily

· 500-1000 daltons: Cross with difficulty

· 6000 daltons: Virtually excluded (proteins)

Special Considerations

· First postpartum week: Gaps between alveolar cells → increased drug passage

· Colostrum اللبأ (first 2 days): Higher drug concentration but low infant intake volume

· Active transport: Some drugs pumped into milk (Iodides - thyroid/antiseptic)

Transfer Patterns

· Minimal transfer: Acidic, high protein binding, low lipophilicity (Most NSAIDs - pain/anti-inflammatory)

· Significant transfer: Basic, low protein binding, high lipophilicity (Sotalol - arrhythmia)

3. Risk Assessment for Breastfed Infants

Factors Increasing Risk

1. Drug toxicity: Antineoplastics (cancer drugs), radionuclides, iodine compounds

2. Multiple drugs with similar effects: Anticonvulsants (epilepsy), psychotropics

3. Active metabolites: Benzodiazepines (anxiety/sedation) → prolonged exposure

4. Long half-lives: Fluoxetine (antidepressant) → accumulation risk

5. Premature infants: Lower clearance capacity

6. Maternal regimen: Chronic or multiple drugs is better than single or short duration

Special Populations

· Neonates/premature infants: Higher risk due to prolonged gastric emptying, decreased protein binding, higher total body water, limited renal function, deficient conjugation (Oxazepam - anxiety)

· G6PD deficiency: Avoid breastfeeding with oxidative drugs → hemolysis risk

4. Risk Reduction Strategies

1. Select infant-safe medications

2. Time dosing: After feeding to avoid peak milk concentrations

3. Hazardous single doses (Radiopharmaceuticals - imaging): Avoid breastfeeding for 5 half-lives

4. Once-daily drugs: Dose before infant's longest sleep period

5. Avoid self-medication

6. Use lowest effective dose for shortest duration

7. Simplify maternal regimen

8. Prefer older drugs with safety data over new alternatives

9. Monitor infants for adverse effects

10. Prefer drugs with: Short half-lives, high protein binding

11. Multiple daily doses: Administer immediately after breastfeeding

12. Short-term incompatible drugs: Pump and discard milk

5. Recreational Substances

· Avoid: Cannabis (marijuana), LSD (hallucinogen), Cocaine (stimulant)

· Alcohol: Chronic/heavy use contraindicated → decreases milk let-down, infant sedation, fluid retention, hormone imbalances

· Nicotine (smoking): Decreases prolactin → reduced milk production

· Caffeine: >10 cups coffee/day → infant fussiness, jitteriness, poor sleep; preterm/newborns at higher risk (slow metabolism)

6. Drug Effects on Lactation

Drugs Decreasing Milk Production

· Dopamine agonists: Cabergoline (Parkinson's/hyperprolactinemia), Ropinirole (Parkinson's), Selegiline (Parkinson's), Rotigotine (Parkinson's)

· Antiestrogens: Danazol (endometriosis), Leuprolide (prostate/endometriosis), Anastrozole (breast cancer)

· Decongestants: Pseudoephedrine (nasal congestion), Phenylephrine (nasal congestion)

· Ergot derivatives: Ergotamine (migraine), Dihydroergotamine (migraine), Bromocriptine (Parkinson's/hyperprolactinemia)

· Others: Ethanol, Nicotine, Tamoxifen (breast cancer), Raloxifene (osteoporosis), Estrogens, Oral contraceptives

Drugs Increasing Milk Production (Galactagogues)

· Pharmacological:

· Domperidone (nausea/GI motility): Dopamine antagonist → increases prolactin

· Metoclopramide (nausea/GI motility): 10mg 3×/day for 7-14 days → prolactin stimulation

· Botanical: Fenugreekحلبة, Blessed thistle, Fennel شومر, Anise ينسون, Milk thistle خرفي, Barleyشعير, Malunggay

7. Contraindicated Drugs During Lactation

Drugs Hazardous to Infant

1. Antiarrhythmics: Amiodarone (arrhythmia) - pulmonary toxicity

2. Anticholinergics: Dicyclomine (IBS) - apnea in infants <6 months

3. Anti-infectives:

· Dapsone (leprosy) - hemolytic anemia

· Rifabutin (TB) - rash, leukopenia

· Flucytosine (fungal) - bone marrow suppression

· Foscarnet (viral) - renal toxicity, seizures

4. CNS stimulants: Dextroamphetamine, Amphetamine (ADHD), Methylphenidate (ADHD) - monitor infant

5. Cytotoxic agents: Antimetabolites, Alkylating agents (cancer) - immunosuppression, toxicity

6. Illicit substances: Cocaine (stimulant), Heroin (opioid), Marijuana - significant toxicity

7. Immunosuppressants: Cyclosporine, Tacrolimus, Everolimus, Sirolimus, Mycophenolate (transplant/cancer) - monitor infant

8. Leprostatic: Thalidomide (leprosy/myeloma) - multiple toxicities

9. Mood stabilizer: Lithium (bipolar) - therapeutic levels in infant

10. MAOIs: Isocarboxazid, Phenelzine, Tranylcypromine (depression) - limited data

11. Radioactive substances: I^{131} (thyroid) - thyroid destruction

12. Muscle relaxant: Tizanidine (spasticity) - sedation, hypotension

13. Tetracyclines: Tetracycline, Doxycycline, Minocycline (antibiotics) - tooth staining/bone changes if >3 weeks

14. Tricyclic antidepressant: Doxepin (depression) - sedation, respiratory depression

15. Vitamin A derivatives: Etretinate, Isotretinoin (acne) - liver damage, death

6. Professional consultation: Utilize lactation resources (pharmacists, lactation consultants)

7. Patient education: Inform mothers about safe practices, warning signs, alternatives

8. When Breastfeeding Must Be Avoided

· Maternal use of: Cytotoxic chemotherapy, radioactive substances, illicit drugs

· Infant with: G6PD deficiency (with oxidative drugs), severe adverse reaction to drug in milk

· Drugs causing: Life-threatening infant toxicity (Lithium, Cyclosporine at high levels)

· Temporary interruption: For short-term hazardous drugs with pumping/discarding

10. Conclusion

Breastfeeding provides significant benefits for both infant and mother. Most medications are compatible with breastfeeding when used appropriately. Key considerations include:

· Understanding drug transfer principles (pKa, protein binding, lipophilicity)

· Selecting drugs with favorable pharmacokinetic profiles

· Optimizing dosing timing

· Monitoring infant for adverse effects

· Avoiding absolutely contraindicated drugs

· Utilizing available resources for lactation safety information

Pharmacokinetic Changes in Pregnancy:

· Increased plasma volume, cardiac output, GFR, fat stores, and hepatic perfusion alter drug absorption, distribution, metabolism, and excretion.

· Decreased albumin increases free drug fraction.

· Dosage adjustments and monitoring are often necessary.

2. Common Pregnancy-Induced Conditions:

· Constipation: Manage with lifestyle, fiber, safe laxatives (bulk-forming, osmotic). Avoid castor oil and mineral oil.

· GERD: Lifestyle/diet first, then antacids, H2 blockers (rantadine), or PPIs(omeprazole)

Avoid sodium bicarbonate,magnesium trisiclate

· Nausea/Vomiting: First-line: dietary changes, ginger, pyridoxine(vitamin b6) doxylamine(antihistamine). Avoid ondansetron(serotonin 5HT3receptor antagonist)in first trimester(oral cleft).

· Gestational Diabetesduring 2 and 3rd trimesters: First-line: diet/exercise. Human insulin is drug of choice.

GDM risks:fetalis loss,macrosomia,congenital malformation

· Hypertensive Disorders>140\90: Includes gestational HTN(after 20 weeks of gestation), preeclampsia, chronic HTNbefore 20 weeks of gestation or pre-existing). Manage with methyldopa, labetalol, hydralazine. Low-dose aspirin(60-

81) for preeclampsia prevention. MgSO4 (magnesium sulfate)for seizure prevention/treatment in eclampsia.

The only cure of preeclampsia : delivary

Venous Thromboembolism: LMWH is treatment and prophylaxis of choice during pregnancy +6 weeks after delivary. Avoid warfarin (nasal hypoplasia,stippled epiphysis,limb hypoplasia, eye abnormalities)) and oral DOACs.

Ca supplement decrease risk of hypertension and preeclampsia in patients with low intake of ca

3rd line :Fondaparinux/synthetic pentasacchaide)

Injectable direct thrombin inhibitors(lepirudin,bivalirudin) +oral (dabigatrin)not recommended

Women with prosthetc heart valves:LMWH twice daily or UF H every 12hours

High risk with prosthetic valves:low dose aspirin75-100 mg /day

3. Acute Infections in Pregnancy:

· UTIs:most common cause E. coli ,GBS (7-14 days)

Treat asymptomatic and symptomatic infections to prevent pyelonephritis. Use β-lactams(amoxicillin,cephalosporin),nitrofurantoin (avoid >37). Avoid sulfa drugs(newborn kernicture), trimethoprim(cardiovascular malformation), fluoroquinolones(impaired cartilage), tetracyclines(tooth discolouration) at specific times.

Pyelonephritis:admission +IV antibiotics (cefuroxime,ceftriaxone),ampicillin +gentamicin, ampicillin-sulbactam then after 48hours switch to oral (10-14 days),avoid nitrofurantoin

· STDs: Use pregnancy-safe regimens (e.g., metronidazole for bacterial vaginosis , azithromycin for chlamydia, acyclovir for herpes, ceftriaxone for gonorrhea, metronidazole for trichomoniasis).

4. Management of Chronic Illnesses:

· Allergic Rhinitis: Intranasal corticosteroids, cromolyn, 1st-gen antihistamines(chlorpheniramine,diphenhydramine) are safe.

Topical decongestant(oxymetazoline) is preferable to oral

· Asthma☹preterm labour,premature birth,low birth weight,preeclampsia Control is critical. Use SABA (albuterol)+ inhaled corticosteroids (budesonide). Add LABA (salmeterol)if needed.

· Diabetes: Optimize control before pregnancy. Use human insulin.

· Epilepsy: . Use monotherapy at optimized dose. Folic acid supplementation (4-5 mg/day) is essential safest drugs(carbamazepine,lamotrigine,levetiracetam.) high risk : valproate,topiramate ,phenobarbital

· Chronic Hypertension: Treat severe cases. First-line: methyldopa, labetalol. Avoid ACEis, ARBs, renin inhibitors.

Valproic acid (neural tube defect)

Avoid pregnancy:poor health,no adherence,poly therapy,resistance,uncontrolled epilepsy

· Thyroid Disorders: Treat hypothyroidism with levothyroxin .1mg /day (dose increases in pregnancy). Treat hyperthyroidism with thionamides (PTU in 1st trimester, switch to methimazole later). Avoid I-131damage to fetal thyroid.

5. Labor and Delivery Management:

· Preterm Labor20-37 weeks of gestation : Tocolytic therapy (e.g., nifedipine(hypotension), $MgSO_4$ not supported as a tocolytic but for neuroprotection causes dipolpia, mg toxicity;respiratory depression ,pulmonary edema ,cardiac arrhythmia,cardiopulmonary arrest, progesterone;Reduce cervical ripening+uterine wall contraction to delay delivery for steroid administration or transfer.

NSAID(indomethacin)Not used after 32 weeks. Due to closure of ductus arteriosus

Antenatal corticosteroid 24-34 weeks of gestation for fetal lung maturation (betamethazone 12mg/day IM for 2 doses,dexamthazone6mg IM every 12hours for 4 doses)

· GBS group b streptococcus : Prophylaxis: IV penicillin G during labor for colonized mothers

Ampicillin :alternatives

Anaphylaxis:clindamycin ,erythromycin

Resistant to clindamycin and erythromycin:vancomycin

· Cervical Ripening/Induction: Prostaglandins (dinoprostone PG E 2 intracervical , misoprostol vaginal pg E1)and oxytocin.

· Labor Analgesia:

Labor phases

1st :visceral pain due to uterine contractions

2nd: visceral and somatic due to pereneal stretching

: Options include

parenteral opioids (drowsiness,nausea ,vomiting)

epidural analgesia (most effective)(hypotension,pruritus,inability to void, prolongation labor,Caesarian section)

nitrous oxide ;laughing gas (Reduce anxiety and awareness) safe for newborn

Epilepsy Management:

· The primary goal is to achieve complete seizure freedom with minimal adverse effects, thereby improving quality of life.

· Anti-seizure drugs (ASDs) provide symptomatic control but are not curative. Treatment is typically long-term.

2. Treatment Strategy & Outcomes:

· Monotherapy First: Always initiate with a single ASD, starting at a low dose and titrating upward based on clinical response and tolerability.

· Sequential Approach: If the first ASD fails, switch to an alternative monotherapy or add a second ASD with a complementary mechanism before tapering the first.

· Drug Resistance: Defined as failure of two appropriately chosen and tolerated ASDs to achieve sustained seizure freedom. Affects ~20% of patients.

· Adherence: The most common cause of treatment failure (up to 60% of patients).

3. Pharmacokinetics, Interactions & Key Concepts:

· Crucial Interactions:

  · Enzyme Inducers (Carbamazepine, Phenytoin, Phenobarbital): Increase metabolism of other drugs (oral contraceptives, warfarin, other ASDs).

  · Enzyme Inhibitors (Valproic acid, Topiramate): Can increase levels of other drugs.

· Withdrawal: Must be gradual over weeks/months to avoid seizure recurrence or status epilepticus, especially for benzodiazepines and barbiturates.

· Therapeutic Drug Monitoring (TDM): A tool for dose individualization, assessing adherence, and managing special populations. Clinical response (seizure control & side effects) is always more important than serum levels.

4. Major Adverse Effects & Management:

· Common Class Effects: CNS depression (sedation, dizziness, ataxia), cognitive impairment.

· Bone Health: Several ASDs (Phenytoin, Phenobarbital, Carbamazepine, Oxcarbazepine, Felbamate, Valproic acid) interfere with vitamin D metabolism. Supplement with vitamin D and calcium; consider bone density testing.

· Drug-Specific Risks:

  · Valproic Acid: Hepatotoxicity (monitor LFTs), pancreatitis, teratogenicity, weight gain, PCOS, hyperammonemia. Toxic metabolite (4-ene-VPA) risk with enzyme inducers.

· Lamotrigine: Serious rash (Stevens-Johnson Syndrome). Risk increased with rapid titration or valproic acid co-administration.

· Topiramate/Zonisamide: Cognitive impairment, metabolic acidosis, kidney stones, weight loss.

· Phenytoin: Gingival hyperplasia, hirsutism, folate deficiency (supplementation may lower phenytoin levels).

· Carbamazepine: Hyponatremia, blood dyscrasias.

· Levetiracetam: Neuropsychiatric effects (irritability, depression, psychosis).

5. Special Populations:

· Elderly: More sensitive to side effects. Start low, go slow. Lamotrigine is often preferred due to better tolerability and fewer interactions.

· Women of Childbearing Potential:

· Teratogenicity is a major concern (Valproic acid has the highest risk).

· Enzyme-inducing ASDs reduce efficacy of hormonal contraceptives.

· Catamenial seizures occur in 10-70% and may improve at menopause.

· Pregnancy: Balance risks of untreated seizures against ASD teratogenicity. Monotherapy at the lowest effective dose is preferred. Avoid Valproic acid. Folic acid supplementation is critical.

· Children: Pharmacokinetics differ; dosing is often weight-based.

6. Key Drugs & Their Primary Indications:

· Focal Onset Seizures: Carbamazepine, Lamotrigine, Levetiracetam, Oxcarbazepine, Topiramate, Zonisamide.

· Generalized Tonic-Clonic Seizures: Valproic acid, Lamotrigine, Levetiracetam, Topiramate, Carbamazepine.

· Absence Seizures: Ethosuximide (first-line), Valproic acid, Lamotrigine.

· Myoclonic/Atonic Seizures (e.g., Lennox-Gastaut): Valproic acid, Lamotrigine, Topiramate, Levetiracetam.

· Neuropathic Pain Comorbidity: Gabapentin, Pregabalin.

Migraine Therapy

I. Pathophysiology of Migraine

Migraine is a neurovascular disorder characterized by:

· Vasodilation of intracranial extracerebral blood vessels.

· Activation of trigeminal nerves and release of vasoactive neuropeptides (CGRP, substance P, neurokinin A).

· Neurogenic inflammation and pain signaling.

II. 5-HT (Serotonin) Receptors in Migraine

· 5-HT_2B & 5-HT receptors: Activation → cerebral vasodilation → migraine onset.

· 5-HT_3 receptors: Mixed pro-nociceptive and inhibitory effects; antagonists not very effective.

· 5-HT_1B receptors: Located on cranial vessels → vasoconstriction (target of triptans).

· 5-HT_1D receptors: On trigeminal nerve endings → inhibit CGRP release and pain transmission (geptans).

· 5-HT_1F receptors: Neural inhibition of pain pathways (ditans).

III. Nonpharmacologic Management

· Rest in dark, quiet environment.

· Regular sleep, exercise, balanced diet, smoking cessation, limited caffeine.

· Trigger avoidance:

  · Food: Alcohol, caffeine, chocolate, MSG, nitrates, tyramine.

· Environmental: Light, noise, smells, weather changes.

· Hormonal: Estrogen fluctuations (menstruation, pregnancy, menopause).

· Behavioral: Stress, sleep changes, skipped meals.

· Behavioral therapies: Relaxation, biofeedback, cognitive therapy.

IV. Treatment Goals

· Acute Therapy: Rapid termination, reduced recurrence, restored function, minimal side effects.

· Preventive Therapy: Reduced frequency/severity, improved quality of life, less reliance on acute drugs, patient education.

V. Acute Pharmacologic Therapy

1. Analgesics & NSAIDs:

· First-line for mild-moderate attacks.

· Examples: Aspirin, ibuprofen, naproxen, diclofenac.

· Often combined with antiemetics (metoclopramide) to enhance absorption.

2. Ergot Alkaloids:

· Ergotamine tartrate, dihydroergotamine.

· Non-selective 5-HT_1 agonists → vasoconstriction and anti-inflammatory effects.

· Significant side effects: nausea, vomiting, ischemia, rebound headache.

· Contraindicated in cardiovascular disease, pregnancy, hepatic/renal impairment.

3. Triptans (5-$HT_1B/_1D/_1F$ agonists):

· First-line for moderate-severe migraine.

· Mechanisms: Vasoconstriction, inhibition of CGRP release, blockade of pain signaling.

· Routes: Oral, subcutaneous, intranasal.

· Examples: Sumatriptan (fast-acting), frovatriptan (long-acting).

· Side effects: Chest tightness, injection-site reactions, MOH risk.

· Contraindications: Ischemic heart disease, uncontrolled hypertension, pregnancy.

4. Ditans (Lasmiditan):

· Selective 5-HT_1F agonist → neural inhibition without vasoconstriction.

· Used when triptans are contraindicated.

· Side effects: Dizziness, sedation (avoid driving for 8 hours).

· Contraindicated with alcohol, severe liver disease.

5. Gepants (CGRP receptor antagonists):

· Acute and preventive use (e.g., rimegepant, ubrogepant, atogepant).

· No vasoconstriction; no MOH risk.

· Side effects: Nausea, fatigue, hepatic/renal monitoring required.

VI. Medication-Overuse Headache (MOH)

· Caused by frequent use of acute medications (>10 days/month).

· Features: Daily headache, reduced drug efficacy.

· Management: Drug withdrawal, detoxification (outpatient or inpatient), preventive therapy.

VII. Preventive Pharmacologic Therapy

Indications:

· Frequent attacks (>2/week).

· Significant disability despite acute therapy.

· Contraindications or side effects from acute drugs.

· Special subtypes (hemiplegic, basilar migraine).

Drug Classes:

1. Beta-blockers: Propranolol, metoprolol, timolol (reduce attack frequency by 50%).

2. Anticonvulsants: Topiramate, valproate (also useful in comorbid epilepsy, bipolar disorder).

3. Antidepressants: Amitriptyline, venlafaxine.

4. NSAIDs: Ibuprofen, naproxen (intermittent prevention).

5. Triptans: Frovatriptan, naratriptan (menstrual migraine prevention).

6. Gepants: Atogepant (daily prevention).

Principles of Preventive Therapy:

· Start low, titrate slowly.

· Allow 2–6 months for full effect.

· Continue for 6–12 months after improvement, then taper.

· Avoid overuse of acute medications during prevention.

VIII. Key Clinical Considerations

· Treatment Selection: Based on headache severity, disability, comorbidities.

· Route of Administration: Consider non-oral routes (nasal, injection) if nausea/vomiting present.

· Drug Interactions:

  · Triptans + ergots → avoid within 24 hours.

  · Triptans + SSRIs/SNRIs → risk of serotonin syndrome.

  · Eletriptan + CYP3A4 inhibitors → avoid.

· Patient Education: Self-management, trigger diaries, adherence to prevention.

IX. Conclusion

Migraine therapy is multimodal, integrating acute abortive treatments with long-term preventive strategies and nonpharmacologic interventions. Personalization based on attack profile, patient comorbidities, and response is essential for optimal outcomes.