IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Factors Influencing Adverse Drug reactions (ADR's) A Comprehensive Review

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Abstract

Talk about how some factors affect the likelihood of adverse drug reactions (ADRs). Using PubMed, the Cochrane database of systematic reviews, EMBASE, and IDIS, a comprehensive review of the literature published between 1991 and 2012 was conducted. The following keywords were used: ambulatory care, primary health care, iatrogenic disease causes, adverse drug reactions, medication errors, side effects, and treatment hazards. ADRs are caused by a vari”ty of variables, some of which are associated with ”he patient, the medication, or society. For example, age has a significant influence on the incidence of adverse drug reactions (ADRs); patients of all ages are more susceptible to these responses than those of other age groups. ADRs are significantly impacted by alcohol use as well.

ADRs are caused by a variety of reasons. Healthcare practitioners can do this by being aware of these factors. 1. Select the best medication schedules 2. Give each patient tailored guidance. 3. Take into account pharmacogenomics, or genetic predispositions. When making treatment decisions, healthcare providers can lower ADRs by taking into account both modifiable (such as smoking and alcohol consumption) and non-modifiable (such as age and genetics) factors.

Introduction

➢ What are Adverse Drug Reactions (ADRs)?

ADR is defined as a noxious and unintended response to a drug, occurring at normal doses, For prophylaxis, diagnosis, therapy, or modification of physiological function [WHO, 1973]. It’s also described as an undesirable effect reasonably associated with drug use, which May occur predictably or unpredictably [Edwards and Aronson, 2000].

➢ Prevalence of ADRs

Research suggests that ADRs represent a major cause of iatrogenic morbidity and mortality In patient care. In the primary care setting, the pooled prevalence of ADRs is estimated to Be around 8.32% ². Furthermore, 22.96% of these reactions are considered preventable ².

➢ Factors contributing to ADRs

Several factors contribute to ADRs, including:

-Deficiencies in system design, organization, and operation

-Lack of quality assurance checks

-Inadequate testing for long-term safety

-Limited patient exposure during clinical trials

Factors affecting the development of advers drug reactions

Pregnancy and lactation factors:

➢ During pregnancy, various physiological changes and pregnancy-specific factors Influence Adverse Drug Reactions (ADRs). Physiological changes include increased Blood volume (40%), cardiac output (30-50%), renal function alterations, hepatic Changes, and hormonal fluctuations. These changes affect drug pharmacokinetics And pharmacodynamics.

➢ Pregnancy-specific factors include placental transfer, fetal development, and Maternal-fetal interactions. Drugs crossing the placenta can impact fetal Development, as seen with isotretinoin (Accutane), which causes fetal Abnormalities. Angiotensin-converting enzyme (ACE) inhibitors increase the risk of Fetal renal impairment.

➢ Trimester-specific factors also play a crucial role. The first trimester (0-12 weeks) Poses the highest risk of teratogenicity, as seen with lithium, which increases the Risk of cardiac malformations. The second trimester (13-26 weeks) is associated With growth restriction and respiratory issues, while the third trimester (27-40 Weeks) poses risks for neonatal/infant ADRs, such as persistent pulmonary Hypertension with SSRI use.

➢ Breastfeeding factors, including drug excretion in breast milk and infant age and Weight, also impact drug pharmacokinetics and pharmacodynamics. Codeine and Morphine can cause infant sedation and respiratory depression.

➢ Examples of pregnancy-specific ADRs include Fetal Hydantoin Syndrome (associated with phenytoin use), Neonatal Abstinence Syndrome (associated with Opioid use), and Fetal Alcohol Syndrome.

Hormonal Factor

➢ Hormonal factors significantly influence Adverse Drug Reactions (ADRs). Various Hormones, including estrogen, progesterone, testosterone, thyroid hormones (T3, T4), cortisol, insulin, and growth hormone, affect drug response.

➢ For instance, estrogen-containing oral contraceptives increase the risk of Thromboembolism with warfarin, while estrogen replacement therapy enhances Fluconazole metabolism. Progesterone increases the sedative effects of Benzodiazepines and decreases the efficacy of bronchodilators. Testosterone Replacement therapy increases the risk of erythrocytosis with erythropoietin and Affects warfarin metabolism.

➢ Thyroid hormones also impact drug response. Hypothyroidism decreases warfarin Metabolism, whereas hyperthyroidism increases theophylline clearance.Corticosteroids increase the risk of hypokalemia with diuretics and enhance Warfarin metabolism. Insulin affects oral hypoglycemic agent efficacy and increases The risk of hypoglycemia with beta-blockers. Growth hormone replacement therapy Affects insulin sensitivity and increases the risk of fluid retention with Corticosteroids.

➢ Hormonal changes, such as those experienced during the menstrual cycle, Pregnancy, and menopause, also influence drug pharmacokinetics. Drugs can, in Turn, affect hormone levels, as seen with oral contraceptives (estrogen and Progesterone), steroids (cortisol), and thyroid supplements (T3 and T4).

➢ Healthcare providers must consider these hormonal factors when prescribing Medications, especially for patients with hormonal imbalances or fluctuations, to Minimize ADR risks and optimize treatment outcomes.

Breastfeeding Factor

➢ Drugs can enter breast milk through lipid solubility, molecular weight, protein Binding, maternal plasma concentration, and breast milk pH.

➢ Lipophilic drugs (e.g., anesthetics, sedatives), low-molecular-weight drugs (e.g., Antibiotics, antihypertensives), and weak bases (e.g., codeine, morphine) can Transfer into breast milk. Examples include:

➢ Analgesics: codeine (1-3% of maternal dose), morphine (0.5-2% of maternal dose), And acetaminophen (0.1-1.3% of maternal dose)

➢ Antibiotics: penicillins (0.1-1.5% of maternal dose), cephalosporins (0.2-2% of Maternal dose), and macrolides (1-5% of maternal dose)

➢ Antidepressants: fluoxetine (1-3% of maternal dose), sertraline (0.5-2% of maternal Dose), and paroxetine (1-4% of maternal dose)

➢ Anxiolytics/Sedatives: diazepam (1-5% of maternal dose) and alprazolam (0.5-2% of Maternal dose)

➢ Infants may experience adverse effects, including sedation, respiratory depression, Hypotension, hyperbilirubinemia, and allergic reactions.

To minimize risks, healthcare providers should:

Monitor infants for adverse effects

Use the lowest effective dose

Choose drugs with low milk transfer

Avoid drugs with high potential for toxicity

Consider temporary cessation of breastfeeding

Resources include

World Health Organization (WHO) – Breastfeeding and Maternal Medication

American Academy of Pediatrics (AAP) – Breastfeeding and Medication

LactMed – Database of drugs and breastfeeding

Lifestyle Factor

 Diet and nutrition, such as grapefruit juice interacting with statins and calcium Channel blockers, and vitamin K-rich foods affecting warfarin, play a crucial role. Smoking induces CYP1A2 enzyme, affecting metabolism of theophylline and Warfarin, and increases cardiovascular disease risk. Alcohol consumption interactsWith sedatives, antidepressants, and antihypertensives, and increases bleeding risk With anticoagulants.

 Caffeine intake interacts with antidepressants, stimulants, and certain antibiotics, And affects cardiovascular medications. Exercise and physical activity impact drug Absorption, distribution, and renal function. Sleep patterns affect drug metabolism, Clearance, and medication adherence.

 Stress and mental health influence drug metabolism, response, and medication Adherence. Environmental exposures, such as pollutants and UV radiation, interact With medications and increase ADR risk. Travel and altitude affect drug Pharmacokinetics and pharmacodynamics.

 Lastly, social and cultural factors, including medication adherence, health literacy, And cultural beliefs, significantly impact medication use.

 Healthcare providers must consider these lifestyle factors when prescribing Medications to minimize ADR risk and optimize treatment outcomes.

 Newly Approved Drugs (2020-2024)

 The latest market drugs from 2020 to 2024 have potential adverse drug reactions (ADRs) associated with pregnancy, lifestyle, hormonal, and breastfeeding factors.

 Pregnancy-related ADRs include Invokana (canagliflozin) and Mounjaro (tirzepatide), Which pose fetal cardiovascular and growth restriction risks, respectively. Myfembree (relugolix) and Livmarli (maralixibat) also pose fetal harm and liver Damage risks. Zavzpret (zavegepant) has been linked to fetal cardiovascular risk.

 Lifestyle-related ADRs are associated with drugs interacting with factors like Smoking and obesity. Wegovy (semaglutide) and Apretude (cabotegravir) have beenLinked to pancreatitis, thyroid cancer risk, and liver damage. Pfizer's COVID-19 Vaccine has been associated with myocarditis and pericarditis.

 Hormonal-related ADRs occur when drugs affect hormone regulation, leading to Imbalances. Nexletol (bempedoic acid) and Tlando (testosterone undecanoate) Have been linked to hyperuricemia and hypogonadism. Nexterone (amiodarone) and Verquvo (sacubitril/valsartan) have been associated with thyroid disorders and Angioedema.

 Breastfeeding-related ADRs occur when drugs are excreted in breast milk, Potentially harming infants. Cabenuva (cabotegravir/rilpivirine) and Bylvay (odevixibat) have been linked to infant HIV-1 transmission and liver damage.

 Regulatory agencies, including the FDA, EMA, WHO, Health Canada, and TGA (Australia), closely monitor these ADRs. Healthcare professionals should carefully Select patients, adjust doses, monitor regularly, educate patients, and consider Alternative treatments to minimize ADR risks.

 By understanding these factors, healthcare professionals can ensure safe and Effective treatment. Close monitoring and reporting of ADRs to regulatory agencies Are crucial for maintaining patient safety.

 Latest Banned and Restricted Medications: Protecting Public Health (2020-2024)

 In 2020, Zantac (ranitidine) was banned due to carcinogenic potential from N-Nitrosodimethylamine impurities. Metformin ER, Fosamax (alendronate), Invokana (canagliflozin), and Jardiance (empagliflozin) were restricted due to fetal and infant Risks.

 In 2021, Belviq (lorcaserin) was withdrawn due to cancer risk. Qualaquin (quinine), Lipitor (atorvastatin), Astramorph (morphine sulfate), and Reclast (zoledronic acid) Were restricted due to fetal and infant risks.

 In 2023, Venclexta (venetoclax), Calquence (acalabrutinib), Kisqali (ribociclib), Verzenio (abemaciclib), and Ibrance (palbociclib) were restricted due to fetal risks.

 In 2024, Opdivo (nivolumab), Keytruda (pembrolizumab), Tecentriq (atezolizumab), Bavencio (avelumab), and Lynparza (olaparib) were restricted due to fetal and infant Risks.

 These bans and restrictions were implemented by regulatory agencies, including the FDA, EMA, WHO, Health Canada, and TGA (Australia), due to reasons such as Carcinogenic potential, fetal risk, infant risk, pregnancy complications, and Breastfeeding concerns.

 Healthcare professionals should be aware of these restrictions and monitor Patients closely to minimize potential risks. Patients should also be educated on the Potential risks associated with these medications.

Key Takeaways

2020: Zantac, Metformin ER, Fosamax, Invokana, Jardiance

2021: Belviq, Qualaquin, Lipitor, Astramorph, Reclast

2023: Venclexta, Calquence, Kisqali, Verzenio, Ibrance

2024: Opdivo, Keytruda, Tecentriq, Bavencio, Lynparza

Regulatory Agencies

FDA (US Food and Drug Administration)

EMA (European Medicines Agency)

WHO (World Health Organization)

Health Canada

Therapeutic Goods Administration (TGA, Australia)

Conclusion

Adverse drug reactions (ADRs) are a complex phenomenon influenced by multiple factors. This review highlights the significant impact of patient-specific factors, such as age, sex, genetics, and comorbidities, which significantly influence ADR risk. Additionally, drug-related factors like dose, duration, and interactions contribute to ADR development. Environmental factors, including lifestyle, diet, and concomitant diseases, also play a crucial role.Considering these factors, healthcare professionals must take patient-specific factors into account when prescribing medications. Personalized medicine approaches can mitigate ADR risk, and enhanced pharmacovigilance is crucial for detecting and preventing ADRs. Future research should focus on developing predictive models for ADR risk stratification, investigating novel biomarkers for ADR detection, and fostering international collaboration for harmonized pharmacovigilance standards. By acknowledging the complex interplay of factors influencing ADRs, healthcare professionals can provide safer, more effective care, ultimately reducing the burden of adverse drug reactions.

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