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Review Article

Adverse Drug Reactions due to Systemic Medications- A Narrative Review

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ABSTRACT

The objective of writing this review is to explore the knowledge and spread awareness among general population towards ADR (Adverse Drug Reactions) with their medical advice. By this review, people can take several precautions to keep safe themselves and others too. This also helps in minimising the morbidity and rate of mortality to control of adverse effects. Adverse drug reactions are one of the commonest medical challenges presenting to an emergency room in any hospital. Side effects are also a big public health concern and a major barrier to the development of new medicines. In the present scientist and researchers aim to find new way to treat or prevent diseases with more potent and safe drugs. The manifestations range from Stevens - Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Risk of miscarriage, seizures, increases the risk of stroke, heart attack, cause of blue skin discoloration and eye abnormalities are the common adverse drug reactions which can have severe morbidity and even mortality. Seek medical attention immediately if they experience adverse drug reactions while on treatment, should contact their health care professional, advise patients to immediately stop taking drug if they develop agitation, aggressive behaviour on the case along with supportive measures helps in salvaging most patients. An overview of adverse drugs effects with their medical attention is being reviewed in this article.

1. Introduction

Medical research aims to discover more about health and to find new ways to treat or prevent diseases[1]. The beneficial medicines can cause side effects, which is why they are monitored for safety. Safety issues arise whenever medical choices have to be made[2]. During the period of treatment, prescribed drugs produce certain effects other than the desired or expected effects. These are generally referred to as 'side effects. The unwanted effects are categorised into many types such as toxic effects, side effects, adverse reactions, and adverse drug events etc., depending upon the taxonomic classification used. Worldwide, studies have shown that it is a major cause of morbidity and mortality[3]. Adverse drug reactions (ADR) are rated as the fifth leading cause of death among all diseases. Approximately 5-8% of all hospitalisation worldwide is due to ADR[4].

Adverse drugs reactions put simply, are noxious, unintended, and undesirable effects that occur as a result of drug treatment at doses normally used for human for diagnosis, prophylaxis, and treatment. Although there are many terms indicating the harmful and undesirable effects of drug treatment, the term 'adverse drug reaction' describes them best[3].

The Institute of Medicine, in the United States (US) (2000) reported that between 44,000 and 98,000 deaths occur annually from medical errors. Of this total, an estimated 7000 deaths occur due to ADRs. Analysing 39 studies of the American pharmaceutical system over four decades found that in 1994, 106,000 people died as a result of ADRs. More than 2 million suffered serious side effects. These figures showed that there was a trend of increasing death and injury from ADRs[2]. It is important to remember that most adverse drug reactions would subside once the offending agent is discontinued or dosage reduced, however, many results in permanent damage or some drugs shows severe adverse effects which become fatal, causes death and even some drugs causes injury for whole life. Therefore, there is need to spread awareness among people about using minimal doses of the drugs, at least in the beginning of the treatment and about safety measures[3].

Pharmacogenomics can help to improve the safety (and effectiveness) of drugs on an individualized basis. Many adverse events are due to individual overdosing because of drug metabolism differences. FDA is working on several projects to better characterize these differences and reduce the frequency of such adverse events[5]. Safety is often measured by toxicity testing to determine the highest tolerable dose or the optimal

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dose of a drug needed to achieve the desired benefit. Studies that look at safety also seek to identify any potential adverse effects that may result from exposure to the drug[6].

Drug safety became a focus of public interest in the 1960s when thalidomide – a drug prescribed for morning sickness – was found to cause birth defects (Phocomelia). In 2006 drug safety again came to wider attention following a clinical trial that tested an antibody drug from the company Te Genero Immuno Therapeutics[7].

The Food and Drug Administration (FDA) is working on many fronts to expect the unexpected when it comes to medication side effects. FDA wants to strengthen researchers' ability to detect chemical or biological substances that could be life threatening, or even fatal, before products containing them hit the market. "All drugs have side effects," says FDA's Vicki Seyfert Margolis, Ph.D., senior advisor for science innovation and policy. The goal is to "predict side effects earlier and better" to help ensure that patients avoid them altogether. The safety of drugs and other medical products regulated by the FDA has always been a key focus of FDA's commitment to its mission to protect and promote the public health.

We herein describe the severe adverse drug reactions (ADR) seen in clinical practice. It is important that all medical fraternity be aware of these adverse reactions to correctly diagnose them at an early stage and prevent complications by kept in mind the safety measures and thereby minimizing the morbidity and mortality due to these conditions. List of drugs which cause adverse effects and their safety measures are given below (Table 1).

Table 1: List of drugs showing their adverse effects and medical advice

S. No.	Drugs	Diseases/ function	Adverse effects	Medical advice
1.	Acetaminophen	Pain reliever/ fever reducer	Acetaminophen may rarely cause serious skin reactions. Symptoms may include skin reddening, rash, blisters, and the upper surface of the skin may become separated from the lower layers. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematouspustulosis (AGEP), can be fatal.	Anyone who has experienced a serious skin reaction with acetaminophen should not take the drug again and should contact their health care professional to discuss alternative pain relievers/fever reducers.
2.	Non-Steroidal Anti-Inflammatory Drugs NSAIDs (i). Include ibuprofen, diclofenac, and celecoxib (ii). Opioids include oxycodone, hydrocodone, hydromorphone, morphine, and codeine)	Pain reliever/ fever reducer	Risk of miscarriage in the first half of pregnancy. The risk of birth defects of the brain, spine, or spinal cord in babies born to women who took these products during the first trimester of pregnancy.	Avoid using nonsteroidal anti-inflammatory drugs (NSAIDs) in the third trimester of pregnancy because these drugs may cause a blood vessel in the foetus to close prematurely.
3.	Chantix (Varenicline)	Help adults quit smoking.	Risk of attention deficit hyperactivity disorder (ADHD) in children born to women who took this medicine at any time during pregnancy. Seizures have been reported in patients treated with Chantix. When uncontrolled, can increase the risk for serious complications, including blindness, nerve and kidney damage, and heart disease.	Advise patients to discontinue Chantix- a) if they develop agitation, hostility, aggressive behaviour, depressed mood, or changes in behaviour or thinking that are not typical for them, or if they develop suicidal ideation or behaviour. b) seek medical attention immediately if they experience a seizure while on treatment.
4.	Injectable diabetes medicines	Diabetes (To lower or regulate blood sugar)	Sharing pens can lead to transmission of infections such as the human immunodeficiency virus (HIV) and hepatitis viruses.	Never share your diabetes pen device with other people.
5.	Docetaxel	Used in cancers of the breast, prostate, stomach, head and neck cancers, and non-small-cell lung cancer.	Affects the central nervous system and can impair your ability to drive or use machinery for one to two hours after infusion. Cause symptoms of alcohol intoxication after treatment.	Before receiving docetaxel, tell your health care professional if you have problems with alcohol or drinking, have liver disease or other medical conditions that may be affected by alcohol intake.

6.	Testosterone products	Use in men with low testosterone levels who lack an associated medical condition.	Testosterone treatment increases the risk of stroke, heart attack, or death.	Contact your health care professional right away if you take testosterone .
7.	Sodium phosphate products	Over-the-counter sodium phosphate products to treat constipation.	Cause rare but serious harm to the kidneys and heart, and even death have occurred in adults and children who used more than the recommended dose of OTC sodium phosphate products to treat constipation. Risk of kidney injury with the use of oral sodium phosphate drug products at higher doses bowel cleansing prior to colonoscopy or other procedures.	Do not use more than one dose of these products in 24 hours. Even if you or your children do not have a bowel movement after taking a single oral or rectal dose, do not use another dose within 24 hours. Contact a health care professional for advice. Do not give these products by mouth to children 5 years and younger without first talking with a health care professional.
8.	Saxagliptin	Diabetes (To lower or regulate blood sugar)	Increased rate of hospitalization for heart failure, when the heart does not pump blood well enough, with use of saxagliptin.	Health care professionals should continue to follow the prescribing recommendations in the drug labels.
9.	Oral viscous lidocaine	Teeth pain	Not approved to treat teething pain, and use in infants and young children can cause serious harm, including death. When too much viscous lidocaine is given (Overdose) to infants and young children or they accidentally swallow too much, it can result in seizures, severe brain injury, and problems with the heart. Cases of overdose due to wrong dose or accidental ingestion have resulted in infants and children being hospitalized or dying.	Gently rub or massage the child's gums with your finger to relieve the symptoms.
10.	Potiga (ezogabine)	An anti-epileptic drug	Can cause blue skin discoloration and eye abnormalities characterized by pigment changes in the retina.	Patients should not stop taking Potiga or any anti-seizure medication without talking to their health care professional.
11.	Azithromycin	Used in asthma (antibacterial)	Can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Slightly higher risk of heart and brain adverse events.	Seek immediate care if you experience an irregular heartbeat, shortness of breath, dizziness, or fainting while taking azithromycin. Do not stop taking azithromycin without talking to your health care professional.
12.	Xolair (Omalizumab)	Used to treat asthma	Slightly higher risk of heart and brain adverse events.	Xolair is administered by a health care professional by subcutaneous injection under the skin every 2-4 weeks.
13.	Methylphenidate products	Used to treat attention deficit hyperactivity disorder (ADHD)	May rarely cause priapism – long-lasting and sometimes painful erections in males of any age. If not treated right away, priapism can lead to permanent damage to the penis.	Patients who take methylphenidate and develop erections lasting longer than four hours should seek immediate medical treatment to prevent long-term problems with the penis.
14.	Xenical/Alli (Orlistat)	Used for weightloss	Severe liver injury	If liver injury is suspected, orlistat and other suspect medications should be discontinued immediately and liver function tests and ALT and AST levels obtained.
15.	Valproate sodium	An anti-epileptic drug	Can cause decreased IQ scores in children whose mothers took them while pregnant. There is also a higher risk of birth defects if you take valproate during pregnancy.	Valproate products should not be used in pregnant women for prevention of migraine headaches. Valproate products should be used in pregnant women with epilepsy or bipolar disorder only if other treatments have failed to provide adequate symptom control or are otherwise unacceptable.
16.	Anzemet	Used to prevent	Abnormal heart rhythms associated with	Seek immediate care if you experience

(Dolasetronmesylate)	nausea and vomiting associated with chemotherapy and surgery.	use of Anzemet.	an abnormal heart rate or rhythm, or symptoms such as a racing heart beat, shortness of breath, dizziness, or fainting while taking Anzemet.

The main difference between the SJS and TEN is the extent of skin detachment: 10% for SJS and 30% for TEN[8].

Table 2: List of Drugs causing TEN

S. No.	Group	Drugs
1.	Antibacterials	Sulphonamides, penicillins, cephalosporins, quinolones, vancomycin
2.	Anticonvulsants	Phenytoin, carbamazepine, phenobarbitone,valproate, lamotrigine
3.	NSAIDs	Phenylbutazone, piroxicam, aspirin, diclofenac
4.	ART drugs	Nevirapine, protease inhibitors, abacavir
5.	ATT drugs	Isoniazid, ethambutol
6.	Anti-gout drug	Allopurinol
7.	Anti-malarials	Chloroquine

2.1 Drugs with high risk to induce SJS/TEN

Allopurinol, carbamazepine, phenytoin, Co-trimoxazole, lamotsigine,phenobarbitone, NSAIDS (Oxicam& Meloxicam)

Drugs with moderate (significant but substantially lower) risk for SJS/TEN

Cephalosporin, Macrolides, Tetracyclines, NSAIDS (acetic acid & diclofenac)

Drugs with no increased risk for SJS/TEN

ß blocker: Ca^{+} channel blocker

ACE inhibitors: Insulin

Thiazide diuretic: Sulfonylurea anti diabetic drug

Patients with skin loss of more than 30% have a high risk of complications and should be treated in highly specialized skin centres. If these are not available, burn units or intensive care facilities with daily dermatologic consultation may be the excellent option.

Patients with SJS/ TEN – must follow these therapies:

a) Should be given fluid replacement with electrolyte solution (0.7 ml/kg/% affected area).
b) Albumin solution (5% human albumin, 1 ml/kg/% affected area).
c) Burn units are helpful for the treatment of TEN.
d) Aseptic handling, sterile field creation, initiation of oral nutrition by nasogastric tube, anticoagulation, prevention of stress ulcer, and medication administration for pain and anxiety control are all important.

Table 2.2: Supportive therapy in TEN

S. No.	Factor	Supportive measures
1.	Prevent trauma to skin	Air fluidised beds prevents bed sores
2.	Prevent hypothermia	Maintain ambient temperature (30-32^{0}C)
3.	Provide pain relief	Adequate analgesia, morphine, diazepam
4.	Prevent infection	Repeated cultures from lesions and sites of catheters Topical antibiotics and antibiotic dressings Prophylactic antibiotics not indicated
5.	Nutrition	1500 calories over first 24 h and increased gradually by 500 calories to about 3500-4000 calories/day.

2.3 Supportive care

1. Management of fluid and electrolyte required.
2. I.V fluid must be given to maintain urine output 50-80 ml per hour with 0.5% NaCl supplemented + 20 mEq of KCL
3. Non- adhesive wound dressing are used where required & topical sulpha containing medications should be avoided. (cutaneous)

No treatment is available for Stevens Johnson syndrome. Care is supportive. Genetic counselling is indicated, further consultations of Clinical geneticist, Developmental paediatrician, Neurologist, Cardiologist, Ophthalmologist, Dentist, Orthopaedist , Psychologist, Physical and occupational therapist, Speech language pathologist and Audiologist may be required time to time. Family members of people with Stevens Johnson syndrome will also need help in coping with the stresses of the disease.

NSAIDs in case of pregnancy

Pregnant women should always consult with their health care professional before taking any prescription or OTC medicine.

Women taking pain medicines who are considering becoming pregnant should also consult with their health care professionals to discuss the risks and benefits of pain medicine use. Avoid using non- steroidal anti-inflammatory drugs (NSAIDs) in the third trimester of pregnancy because these drugs may cause a blood vessel in the foetus to close prematurely**[9]**.

(a). Be aware that abbreviations such as APAP, AC, Acetaminophen, Acetaminoph, Acetaminop, Acetamin, or Acetam may be written on the label in place of the word acetaminophen.
(b). Take acetaminophen exactly as directed on the prescription or package label. Do not take more acetaminophen or take it more often than directed, even if you still have fever or pain.
(c). Be aware that you should not take more than 4000 mg of acetaminophen per day. If you need to take more than one product that contains acetaminophen, it may be difficult for you to calculate the total amount of acetaminophen you are taking.

Chantix (Varenicline)

Patients who have a seizure while taking Chantix should stop the medicine and seek medical attention immediately[10]. Before you take Chantix, tell your health care professional if you drink alcohol, have a history of seizures, or have ever had depression or other mental health problems. If you develop nervousness or agitation, hostility, aggressive behaviour, depression, thoughts of suicide, or have other changes in your behaviour or thinking that are not typical for you, stop taking Chantix and contact your health care professional right away.

Note: Interactions between alcohol and Chantix (varenicline) have resulted in some patients experiencing increased intoxicating effects of alcohol, sometimes associated with aggressive behavior and/or amnesia.

Advise patients to reduce the amount of alcohol they consume while taking Chantix until they know whether the drug affects their tolerance for alcohol.

Given details to your doctor and pharmacist what other prescription and non-prescription medications, vitamins, nutritional supplements, and herbal products you are taking or plan to take. Be sure to mention any of the following: anticoagulants ("blood thinners") such as warfarin (Coumadin); insulin; other medications to help you stop smoking such as bupropion (Wellbutrin, Zyban) and nicotine gum, inhaler, lozenges, nasal spray, or skin patches; and theophylline. Your doctor may need to change the doses of some of your medications once you stop smoking.

Injectable diabetes medicines

To reduce the chances of medication errors in hospitals and other health care facilities, pens should be clearly labelled with each patient's name or other identifying information**[11]**. Be sure the identifying patient information does not obstruct the dosing window or other product information such as the product name, strength, and the warning statement "For single patient use only."

If you are accidently stuck by another person's used needle or other sharp:

Immediately wash the exposed area right away with water and soap or use a skin disinfectant (antiseptic) such as rubbing alcohol or hand sanitizer.

Seek immediate medical attention by calling your physician.

To promote safe use, we are requiring that pens and packaging containing multiple doses of insulin and other injectable diabetes medicines display a warning label stating "For single patient use.

Sodium phosphate products

Always read and follow the directions on the Drug Facts labels included on over-the-counter sodium phosphate oral solutions and rectal enemas to find out the correct dose and dosing frequency**[12]**. Changes in blood electrolyte levels, cause serious harm to the kidneys and heart and, sometimes lead to death have occurred in adults and children who used more than the recommended dose of OTC sodium phosphate products to treat constipation.

If you or your child facing symptoms of kidney injury, then seek medical attention immediately and do not take another dose of the product. Symptoms of kidney injury include drowsiness, sluggishness, decreased amount of urine, or swelling of the ankles, feet, and legs.

Lidocaine

Health care professionals should not prescribe or recommend this product for teething pain **[13]**. Parents and caregivers should follow the American Academy of Pediatrics' recommendations for treating teething pain. We advise following the American Academy of Pediatrics' recommendations listed above to help lessen teething pain.

a. Use a teething ring chilled in the refrigerator (not frozen).
b. Gently rub the child's gums to relieve the symptoms.

Note: Lidocaine viscous may cause side effects. If you are facing any of the following symptoms that given in the IMPORTANT WARNING section, stop using lidocaine viscous and call your doctor immediately or get emergency medical treatment:

Rash, itching, hives, shallow breathing, difficulty breathing or swallowing, drowsiness, blurred or double vision, shakiness.

Potiga (ezogabine)

If you are taking Potiga and develop any changes in your vision or any discoloration of your skin, including your lips and nail beds, contact your health care professional[14].

Do not stop taking Potiga without talking to your health care professional. Stopping such treatment suddenly can cause serious life-threatening medical problems such as recurrence of seizures.

Valproate products

Warnings about use during pregnancy will be added to the drug labels, and valproate's pregnancy category for migraine use will be changed from "D" (the potential benefit of the drug in pregnant women may be acceptable despite its potential risks) to "X" (the risk of use in pregnant women clearly outweighs any possible benefit of the drug).

Valproate products should not be used in pregnant women for prevention of migraine headaches.

Valproate products should be used in pregnant women with epilepsy or bipolar disorder[15] only if other treatments have failed to provide adequate symptom control or are otherwise unacceptable.

Continue to counsel women of childbearing age taking valproate about the increased risk of other major structural and functional birth defects, particularly neural tube defects, when valproate is used during pregnancy.

Anzemet (Dolasetron mesylate)

The U.S. Food and Drug Administration (FDA) is informing patients and healthcare professionals that the injection form of Anzemet (dolasetron mesylate) should no longer be used to prevent nausea and vomiting associated with cancer chemotherapy (CINV) in pediatric and adult patients[16].

Anzemet injection may still be used for the prevention and treatment of postoperative nausea and vomiting (PONV) because the lower doses used for PONV are less affect the electrical activity of the heart and result in abnormal heart rhythms.

Stronger Warnings

That both the tablet and injection form of Anzemet affect the electrical activity of the heart and cause abnormal heart rhythms have been added to the drug labels. Anzemet should not be used in patients with congenital long QT syndrome.

Xenical/Alli (Orlistat)

The people having signs and symptoms of liver injury and the need to see a physician promptly should they occur. The agency is also working with the manufacturer of Alli to ensure that consumers can understand this new warning[17].

Contact your healthcare professional if you develop itching, yellow eyes or skin, dark urine, loss of appetite, or light colored stools. These may be signs of liver injury.

Be aware that post marketing cases of severe liver injury with hepatocellular necrosis or acute hepatic failure have been reported rarely in people using Xenical and Alli. Some of these cases resulted in liver transplant or death.

Methylphenidate

Seek immediate medical care if priapism or any erection lasting longer than four hours occurs with or without sexual stimulation[18].

Xolair (Omalizumab)

It is not used to treat allergic conditions, other forms of urticaria, acute bronchospasm, or status asthmaticus **[19].** Uncontrolled asthma can cause serious breathing problems, so it is important to take all the medicines your health care professionals prescribe exactly as they tell you. Do not change or stop taking Xolair or any of your other asthma medicines unless your health care professional tells you to do so.

Docetaxel

Patients should be aware that docetaxel may cause them to become intoxicated from the alcohol it contains**[20].** Docetaxel contains alcohol, which affects the central nervous system and can impair your ability to drive or use machinery for one to two hours after infusion.

Some medications, such as pain relievers may interact with the alcohol in the docetaxel infusion and worsen the intoxicating effects.

Avoid driving, operating machinery or doing other activities that are dangerous or require skill one to two hours after you receive treatment with docetaxel.

3. Conclusion

Adverse drug reactions have been creating headlines over the last forty years. ADRs have proved a significant problem in healthcare for decades – their occurrence is influenced by many factors, and their severity and outcomes vary. This review has provided a discussion of challenges present in the communication of adverse drug reaction warnings and medical advice to the patients. Understanding the severe effects of ADRs enables healthcare professionals to choose the most appropriate medication for that particular patient. It also helps the healthcare professionals to give the best advice to patients. There is a need to develop better preventive measures that inevitably will have to be multi-functional ranging from better

education and communication to utilising specialist pharmacists to undertake medication reviews, to intelligent use of new technologies including information and bio-technologies. Therefore, in this review, we add some drugs having severe adverse effects So, people can keep their safety by using minimal dosing and take precautions at least in the beginning of the treatment and about safety measures. The objective to study these adverse effects of drugs and safety measures to have good information that allows the prescriber to assess the benefit-harm ratio of drugs, and thereby individualise medicines regimens through better choice of dose and/or drug, and through this maximise benefits and minimise harms.

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