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Adverse drug reactions - the downside of conventional drugs

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Background

A major drawback to the use of most conventional drugs is the adverse drug reactions often experienced. This is especially unfortunate, as the bedrock of conventional (or orthodox medicine) is their extensive and systematic use. Anyone taking a conventional drug rightly expects the desired therapeutic effect, namely clinical relief from the offending disorder. However, there is a real possibility that the person will also experience one or more undesirable or unexpected responses; that is, adverse drug reactions (ADRs). An ADR is not just an unfortunate, but minor, side issue or complication of a drug's action. It can have major, devastating effects on a person's lifestyle and behaviour, and markedly reduce his or her quality of life. It often leads to the use of further drugs to reduce the symptoms associated with the ADR. Although most ADRs are troublesome, they are rarely severe or serious – otherwise the drug would be promptly withdrawn from general use. However, severe ADRs do occur; these are undesired responses by the patient, which are life-threatening or even fatal, or result in a child with a birth defect, or lead to hospitalisation. Persistent interference in a patient's quality of life would also be described as a severe ADR, as is any ADR which leads to long-term changes to a person's lifestyle, metabolic profile, or physical behaviour.

Conventional drug action

Virtually all conventional drugs exert their pharmacological action either by stimulating or inhibiting cell receptors[1]. These intricate structures are built into the membranes enclosing all cells and their internal structures. The receptors bind the body's natural signalling agents, and this leads to the cell reacting in its individual pre-determined response. There is a wide variety, and large number, of receptor types in the many different body tissues, and these normally respond to agents such as hormones (like insulin) and chemical transmitters (such as histamine, adrenaline and acetyl choline). Each type is programmed for its own specific physiological function, such as initiating an allergic response, or increasing the heart rate, or secreting digestive fluid.

The reason that drugs work is that they also interact with the receptors. They bind to them in a reversible and temporary way, and either stimulate them (as agonists) or inhibit them (as antagonists). Drugs, unfortunately, are not very selective, and rarely, if ever, attach just to one particular type of receptor. So if the therapeutic effect brought about by the drug is achieved by stimulating one type of receptor, an ADR may occur due to stimulation of one (or more) different type of receptor. In effect, the drug has disturbed the person's bodily inner harmony, or homeostasis, by interfering with existing physiological processes.

What is an ADR?

An ADR is an undesired or harmful effect resulting from treatment with a particular drug when given at the normal dose recommended for the particular person[2]. An ADR differs from a *side-effect*. Not all side-effects are harmful, and may even be beneficial. For example, a drug given to prevent migraine attacks may lead to a patient experiencing increased appetite, which may be regarded as desirable. Another example is the antihistamine in a cough and cold remedy, which may make the patient feel drowsy. This is often a benefit, as it leads to a good night's sleep.

The more people take a particular drug, then the greater the chance of an ADR. If there are large numbers of people taking a popular drug (such as an oral contraceptive, anti-inflammatory agent or hypnotic), even a very low incidence of an ADR will represent a sizable number of people affected.

In the early 2000s, ADRs accounted for 1 in 16 (> 6%) of all UK hospital admissions, at a cost of approx R5 billion.

ADRs can occur even after a single dose, or after multiple doses taken over a long time. Drugs can occasionally produce an *idiosyncratic reaction*, where the patient shows an unusual, unexpected and sometimes bizarre response to the drug in standard usage. They can also occur as a result of an interaction between two or more drugs, or between a drug and food, or between a drug and a herbal medicine.

Drugs are often withdrawn from the market because the number of ADRs reported is unacceptable. However, in many cases the benefits of treatment with the drug are judged to outweigh the risks it poses. This is particularly relevant to new drugs recently launched onto the market. Sometimes a particular ADR is not detected in pre-launch clinical studies, but only appear in post-marketing surveillance studies, in which much larger numbers of patients are exposed to the drug.

A person can experience an ADR *systemically,* that is, one which affects the body as a whole. Examples of a systemic ADR are *fatigue* (from beta blockers, older antihistamines and some anti-depressants, for example); *low blood pressure* (from some diuretics, drugs for erectile dysfunction and ACE inhibitors); an *allergic reaction* (from penicillin, some anti-inflammatory drugs and local anaesthetics) and *tremor* (from corticosteroids, caffeine and SSRI antidepressants). They may manifest *locally,* that is, at a particular site on the body. Typical localised ADRs are *headache* (from analgesics, opioids and triptans, for example); *blurred vision* (from anticholinergics, anti-malarials and antihistamines); and *rash* (from statins, anti-HIV medications and some antibiotics).

An ADR resulting from medical treatment is termed* iatrogenic*. In the USA, several thousand hospital deaths yearly are allegedly due to ADRs.

Types of ADRs

There are six categories of ADR, based on the time they appear, their severity, and their impact upon the person[3].

Type A. *The patient over-reacts to the drug*. The desired effect is much more than reasonably expected. For instance, if an *anti-hypertensive agent* is given to a patient with high blood pressure, an excessive fall in the blood pressure may occur, so that the symptoms of *hypotension* (such as dizziness) appear. These side effects are often predictable, and are usually dependent on the dose of the drug employed.
Drug intolerance is included here. Several drugs used to treat cancer (chemotherapeutic agents) are notorious for poor tolerance by the cancer sufferer. Nausea and vomiting are typical ADRs with these potent drugs.

Type B. *The patient has an idiosyncratic reaction.* Sometimes termed *bizarre effects,* these tend to be totally unpredictable, and not related to the dose of drug given. Examples are the development of Reyes syndrome in children following aspirin treatment, and the allergic reaction shown by many to penicillin.

Type C. *The patient shows* a *deteriorating drug response*. When a drug is given for a long time for a chronic disorder (such as arthritis), the desired effect gradually wears off. This means the drug dosage has to be adjusted upwards, but intolerance may develop. Usually an alternative drug has to be substituted. Opioid analgesics like morphine provide a good example of this ADR. Certain anti-hypertensive agents are also prone to this effect, as are the benzodiazepine sleep-inducers.

Tachyphylaxis *refers to the falling off in the effect of a drug which is given long term. Drugs acting on the nervous system are often prone to this ADR.*

Type D. *The ADR only occurs in the patient after long term drug use*. The development of antibiotic resistance by pathogenic bacteria falls into this category. Many of the ADRs linked to long-term corticosteroid usage (such as skin thinning and osteoporosis) also belong here.

Type E. *These occur after drug treatment has been discontinued*. Here we include certain corticosteroids which are often used to treat bronchial asthma or arthritis. When they are stopped, the body takes some time before it resumes endogenous corticosteroid synthesis, so the body becomes vulnerable to infection and ADRs such as osteoporosis and red skin syndrome.

Type F. *The patient does not respond to the drug.* Treatment failure occurs – the drug fails to deliver the expected therapeutic effect, even after frequent dose increases. For example, in the treatment of depression with fluoxetine, the recommended dose is ineffective in some people. Up to four times this dose may be needed for any effect.

Table I (*below*) summarises the main types of ADR, with examples from specific drug groups.
[*Note: Not all drugs in each class actually cause the ADRs listed. These are just reported examples for illustration purposes*.]

Type of ADR / Drug	Type A (excessive)	Type B (idiosyncratic)	Type C (chronic)	Type D (delayed)	Type E (subsequent)
Anti-ulcer drugs [*Proton pump inhibitors*]	Diarrhoea Abdominal pain	Headache Fatigue B_{12} deficiency	Bacterial infection	High blood magnesium levels	Dependency on further dosage
Anti-retrovirals [*Protease inhibitors*]	Abdominal pain Diarrhoea Flatulence	Insomnia Headache Mood swings	Hepatitis Anaemia Skin rash	Raised cholesterol Ingrown nails Gynaecomastia	Liver failure
Anti-hypertensives [*ACE inhibitors*]	Hypotension	Headache Dizziness Fatigue		Hyperkalaemia Renal impairment	Persistent cough Congenital abnormalities
Anti-asthma drugs [*Bronchodilators*]	Tachycardia	Effects on the heart			Deterioration of lung function
Anti-inflammatories [*Corticosteroids*]	Hypertension	Eye damage Depression Anxiety	Peptic ulceration Hypogonadism Hypothyroidism	Osteoporosis	Osteoporosis Skin damage

Arguably the most serious ADR that can occur is a *congenital abnormality*. This happens when the drug interferes with the mother's reproductive processes, especially in the first trimester of pregnancy. If the body's protective mechanisms fail to deal with the drug, which is essentially an alien and unfamiliar chemical, then malformation of the foetus may occur. The new-born child may be born with a serious, perhaps life-threatening disorder, or a physical or mental abnormality. The classic example of this type of abnormality is provided by *thalidomide*. This was extensively promoted in the 1950s for the prevention of morning sickness in pregnant women, but tragically led to children being born with *phocomelia*, or abnormally shortened limbs. More recently, *isotretinoin*, which is given to treat intractable acne, has also been linked to birth abnormalities.

ADR effects in practice

If an ADR develops, the patient usually complains of unusual, unexpected or troublesome changes in his or her physical activity or mental behaviour.

- *Physical symptoms.* Common examples are nausea, vomiting, gastric upsets and headaches. Loss of normal function may be reported, as with diarrhoea, indigestion, constipation and blurred vision.
- *Mental symptoms*. Common ones are insomnia, depression, confusion and drowsiness.

There may be a number of *signs* picked up by the practitioner on examination:

- *Physical signs.* Typical ones are evident rapid weight loss or gain, pallor or rash, and abnormal blood pressure.
- *Mental signs.* Included are reduced attention span, agitation, incoherence and aggression.

- *Pathological changes.* Common ones detected either in the laboratory or in the practice include raised plasma cholesterol or blood uric acid, and the presence of protein or sugar in the urine. Changes in blood composition elements may also surface – a fall in red blood cell or leucocyte count.

Features of drugs leading to an ADR

Two basic mechanisms are involved in the occurrence of most ADRs. The first is related to the drug's intrinsic *pharmacokinetic* behaviour. That is, how it is absorbed, distributed, metabolised and eliminated by the person's body.
The second is how the drug interacts with other factors. These are (a) other drugs the person maybe taking (*drug/drug interaction*); herbal products the person may be ingesting (*drug/herb interaction*); and what the person may be consuming (*drug/food interaction*).

***Pharmacokinetics*.** Several factors affect the patient's response to the drug being administered. The main ones are: (a) the disease being treated, and (b) co-existing clinical disorders. For instance, if the patient's liver is inflamed, as in hepatitis, drug metabolism and elimination may be markedly reduced. Accumulation of the drug, and/or toxic metabolites, occurs insidiously. Also, if a person has longstanding hypertension, kidney function may be abnormally low. Giving an anti-hypertensive agent may lead to a build-up of drug and/or active metabolites. In both cases an ADR is likely to occur due to abnormally high drug levels.

ADME is shorthand for: Absorption, Distribution, Metabolism and Elimination of conventional drugs.

A less frequent situation is: (c) the patient may be *genetically incapable* of effectively eliminating the drugs (which are essentially alien or 'new-to-nature' substances). There are numerous genetic differences between individuals, which may influence the metabolism of drugs[4]. A similar scenario, where there is a decrease in the efficiency of a person's excretory mechanisms, leads to an accumulation of the drug and any toxic metabolites. An ADR invariably follows.

The incidence of ADRs invariably increases when several drugs are used simultaneously. This may occur when the drugs are taken deliberately, as with *polypharmacy* (*see below*); or unknown, as when OTC or illegal drugs are involved. One drug may interfere or compete *metabolically* with another, especially if they possess similar chemical or structural features. They may impede one another at the kidney tubule's excretory mechanism, or compete with each other at metabolic enzyme active sites. They may also contest for binding sites on *plasma proteins* such as albumin, so that more of the drug is left in free-form (rather than protein-bound), and are therefore more active metabolically. The result of both phenomena is an accumulation of the active drug or active metabolites, leading ultimately to an ADR. Obviously the larger the number of drugs administered simultaneously, the greater the probability of biochemical competition or interaction.

One drug may augment the physiological effect of another, so leading to a dose-related ADR of Type A. An example of this sy*nergistic action* is when two anti-hypertensive drugs administered together may depress elevated blood pressure to a degree which is more than the combined effect of both if

given individually. Another example is the synergy between MAO inhibitor anti-depressants and both antihistamines and anticholinergic drugs. ADRs can emerge from these interactions.

Table II. ADRs associated with their target clinical disorders

Drug administered	Target disorder	ADR reported
Analgesics/antipyretics *[Paracetamol]*	Pain relief; fever	*Liver necrosis*
Anti-diabetic agents	Type 2 diabetes	*Hypoglycaemia*
Anti-hypertensives	Hypertension	*Rebound hypertension*
Antibiotics *[Fluoroquinolones]*	Bacterial infection	*Peripheral neuropathy* *Spontaneous tendon rupture*
Anti-cholesterol drugs *[Statins]*	Raised cholesterol levels	*Skeletal muscle disorders* *Rhabdomyolysis*
Anti-depressants *[SSRIs]*	Depression	*Erectile dysfunction* *Increase in suicidal tendencies*
Anti-inflammatory agents *[COX-2 Inhibitors]*	Inflammation, arthritis	*Cardiovascular disorders* *Increased mortality*
Antihistamines *[Histamine-1 antagonists]*	Allergic conditions, seasonal rhinitis, eczema	*Drowsiness* *Increase in appetite*
Anti-psychotic agents *[Dopamine antagonists]*	Schizophrenia	*Diabetes*
Chemotherapeutic agents	Cancer, leukaemia	*Hair loss, anaemia, nausea*
Anaesthesics *[Propofol]*	Induction of anaesthesia	*Excessive sedation, possibly leading to death*

Why do ADRs occur?

There are several reasons why a particular person will experience an ADR after taking a conventional drug. They may be *drug-related* (dosage factors, 'spiking', or drug-drug interactions), or *patient related* (overdose, ADME variability, drug/food, or drug/herb interactions.

Dosage factors. *The most common cause of an ADR arises from dosage problems*. The dosage recommended for adults is usually a fixed amount, at fixed dosage intervals. Unfortunately, people are different; a ballet dancer does not need the same drug dose as a wrestler for the same disorder. For the same drug dose, a Type A overdose could occur in the dancer; a Type F therapeutic failure in the wrestler.

Spiking. If the drug level in the bloodstream passes a certain threshold, an ADR of Type A may occur. This usually happens because the person absorbs the drug too rapidly, so the blood level rises faster and higher than expected. This often happens because the drug passes through the stomach

too quickly, and is then absorbed rapidly from the intestine. If a drug is taken on an empty stomach, or with a fizzy drink, spiking can occur.

Drug/drug interactions. This describes the effect that one drug (say, *drug X*) has upon another's (say, *drug Y*) activity within the body. Whatever effect drug Y normally has is either reduced or increased by drug X. Another possibility is that the drugs X and Y have a combined effect which differs from that of either (*synergistic effect*).

Avoiding drug/drug interactions is not always possible, or advisable. Many conventional drug regimens, especially for chronic disorders like HIV/Aids, hypertension and asthma, and over-the-counter cold and flu preparations practise *polypharmacy*, where two or more drugs are given simultaneously. This is done to deal with a number of symptoms affecting the sufferer from both acute and chronic disorders.

> Some drug interactions are beneficial, and this phenomenon is often capitalised upon. Originally, penicillin was available in limited amounts, and had to be used sparingly. One practical tactic to avoid this problem was to administer *probenicid*, an anti-gout drug, which inhibited penicillin excretion. The net effect was a beneficial rise in blood levels of penicillin.

Mechanisms of drug/drug interactions. Most drug interactions usually occur by (a) drug X interfering with the ADME of drug X; or (b) drug X counteracting the therapeutic effect of drug Y. The effect of one or other drug may be increased (*potentiated*) or decreased (*inhibited*).

Drug X may interfere with absorption or bioavailability of drug Y. A good example is the reduced absorption of antibiotics by antacids. Drug X may also affect the breakdown of drug Y by the liver or other metabolic sites. It could induce enzyme formation in these (*enzyme induction*), so that drug Y is more rapidly metabolised and de-activated. This would lead to diminished levels of drug Y, so leading to an ADR of Type F (therapeutic failure). Alternatively, drug X could suppress the liver enzymes which metabolise drug Y (*enzyme inhibition*), so leading to a build-up of the active drug. This could lead to overdose, and so an ADR of Type A.

Drug X may interfere with drug Y at the receptor site. If drug X is a drug agonist, and drug Y is an antagonist, then the effect of both will be

***Drug/food interactions*.** Interaction can, in theory, occur between a drug and certain foods consumed by the person. These are relatively rare, with few reported in medical literature. However, one example of a drug-food interaction is the increased absorption of *cyclosporine* (an immunosuppressant) and several other drugs by grapefruit juice. This contains a substance which inhibits a cytochrome metabolising system in the liver, so allowing an increased level of the drug to occur. Another interaction is the dramatic effect of the MAO inhibitor antidepressants on people consuming certain cheeses or red wine. The result is a large increase in the levels of biologically active amines, causing severe flushing and hypotension.

Drug/herb interactions. This interaction can have troublesome consequences. The classic interaction is between certain drugs and *St John's wort* (a herbal medicine taken to alleviate mild

depression). This increases the liver's metabolic activity via the cytochrome P_{450} oxidase enzyme, which is also involved in drug metabolism[5]. Consequently people taking the herbal medicine may experience a marked fall in blood levels of the drug. Many drugs used as chemotherapy, oral contraceptives, and protease inhibitors used to treat HIV/Aids victims are particularly affected. There are also cases of synergistic effect occurring when a herbal medicine taken to reduce raised blood pressure is combined with a conventional anti-hypertensive agent. A Type B ADR could conceivably follow.

Frequency of ADRs

A large number of interactions between drugs have been reported in the medical press[6]. Most conventional drugs are associated with numerous ADRs, but these do not preclude continued usage, as the benefits to the users are considered to outweigh the threat they pose to quality of life.

Statistics on the incidence and frequency of ADRs vary widely: from country to country, hospital to hospital, practice to practice, year to year. Overall, however, it is reckoned that between 10% and 20% of hospital patients suffer an ADR of one type or another; most relatively minor, but occasionally serious or severe[7].Up to 5% of hospital admissions are allocated to patients who have experienced ADRs, and between 0.25% and 0.5% of deaths of hospital patients are attributable to the treatment they receive, rather than the disease for which the drug was being used[8].

In the UK, it has been estimated that around 10,000 people die yearly because of ADRs. The figure for the USA is around 100,000 per year.

ADRs are more common in elderly people because their pharmacokinetic competence deteriorates substantially as they age, especially in metabolic processes. A frequency of 20% has been recorded for patients 80 years and older, which compares unfavourably with a figure of 3% for 10 to 20 year-olds[9]. Furthermore, the likelihood of ADRs occurring rises markedly as the number of drugs administered is increased, and the elderly are more likely to be consuming a number of drugs.

Clinical consequences of ADRs

The emergence of a troublesome ADR usually has a negative effect on treatment outcome. The patient may unilaterally discontinue drug therapy, especially if the original clinical disorder is regarded as mild or trivial. For example, if a person is being treated for a skin rash or blocked nose, sleep disturbances would not be tolerated. Also, if the disorder being treated does not really affect the patient's quality of life, as with hypertension or raised cholesterol, then ADRs like breathing difficulties or muscle pain would probably lead to discontinuation. However, if standard anti-diabetic therapy leads to unacceptable ADRs, then discontinuation of drug therapy could have catastrophic consequences.

ADRs may be serious, or severe, or sometimes both. A nosebleed may be serious, but not severe. A headache may be severe, but not serious. Immune system suppression is both serious and severe.

The ADR-affected patient may also fail to comply fully with medical advice. By changing the therapeutic regimen, the outcome may be compromised. If a patient is being treated for bacterial infection of the urinary tract, for example, lowering or omitting antibiotic treatment can severely compromise a successful outcome. In addition, it may cause a long-term ADR of Type F, by adversely affecting the person's immune system, so creating further potential problems. The development of bacterial resistance to the antibiotic being used is a further, most unwelcome, ADR.

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