The Medicine Cabinet: Adverse Reactions

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Introduction

All medications and in fact anything taken into the body are foreign substances to the human body and thus may have wanted as well as unwanted effects. The desired effects are those with positive outcomes to the person taking them. The unwanted (adverse effects) are those that are described as side effects as per "A response to a drug which is noxious and unintended, and which occurs at doses normally used or tested in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function"[1] There are also adverse events or mishaps associated with medication use and these are occurring also at an alarming rate – amongst the general population the incidence can be as much as 1-2% of all hospital admissions costing about 1% of total health care budget[2]. Adverse drug events are defined as any injuries resulting from medication use including physical harm, mental harm or loss of function[3]. Although some of these are avoidable these are not the reactions that will be covered in this article.

When assessing a new medication, there are many phases in the evaluation process. Prior to the beginning of the 20th century, the medical profession and associates relied on observation to identify herbs and therapies that were worthy. With the advancement of science, a scientific approach was developed by the Federal Drug Administration (USA) and other regulatory bodies for the clinical trials associated with new therapies and substances for human and animal use. These started with laboratory analysis followed by clinical study.

Then, as a result of the worldwide thalidomide disaster in the 1960s and other medications, there was increased testing and surveillance of clinical trials. Medications had to have proof of safety as well as 'substantial evidence' of a drug's efficacy in the clinical trial setting[1]. For more information about the history of clinical drug trials see www.fda.gov/AboutFDA/WhatWeDo/History/Overviews

Today pharmaceutical medications go through a thorough and rigorous investigation process which includes:

1. Preclinical testing – subject to extensive chemical, toxicological, and animal testing.
2. Clinical testing phase 1 – safety and pharmacological profiles determining actions and dosing, involves small number of healthy volunteers
3. Clinical testing phase 2 – pilot efficacy studies – controlled studies
4. Clinical testing phase 3 – extensive clinical trials - clinical trials by practicing physicians to patients with the actual targeted condition
5. Clinical testing phase 4 – post marketing surveillance [2]

Adverse reaction lists are then compiled from the phase 3 and phase 4 trials and this is part of pharmacovigilance or drug safety - collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products[8] . Serious adverse events from phase 2 usually means that further investigations will be halted and going back to the drawing board. Most new drugs coming onto the market would have only approximately 1,500 patient exposures and only for a short period of time prior to the marketing of the medication ie after phase 3 trials. Phase 3 testing usually occurs in small homogenous populations and then once marketed the population experiencing the medication initially can be millions. However there are some drugs that cause very serious side effects but at very low frequencies. Phase 4 testing is usually the time when patients who would normally not fit into clinical trials ie have more than one clinical condition would use the medication. This would include the patient with intellectual disability and autistic spectrum disorders (ASD) and paediatric patients if the medication is not specifically designed to treat that condition.

Thus, it is important that adverse reactions to medications be reported as the rarer significant ones will only be picked up during post marketing surveillance. It is the responsibility of all to report the adverse drug reactions (ADRs) to help compile the list of known adverse effects. The post marketing surveillance is maintained by the Therapeutic Goods Administration (TGA) branch of the federal Department of Health through a 'blue card' system http://www.tga.gov.au/consumers/problem.htm#medicine. The pharmaceutical companies also have an obligation to report any adverse reaction reported to them to the TGA. Even if not previously reported this might be the first or not connected to the medication at all.

Identifying a causal relationship

"It is the responsibility of all to report the adverse drug reactions (ADRs) to help compile the list of known adverse effects..."

A scale was developed – Naranjo scale for determining ADRs. This is a numerical scale of 10 questions to help determine the probability of an ADR[5].

1. Are there previous conclusive reports on this reaction? *Yes (+1) No (0) Do not know or not done (0)*
2. Did the adverse events appear after the suspected drug was given? *Yes (+2) No (-1) Do not know or not done (0)*
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? *Yes (+1) No (0) Do not know or not done (0)*
4. Did the adverse reaction appear when the drug was readministered? *Yes (+2) No (-1) Do not know or not done (0)*
5. Are there alternative causes that could have caused the reaction? *Yes (-1) No (+2) Do not know or not done (0)*
6. Did the reaction reappear when a placebo was given? *Yes (-1) No (+1) Do not know or not done (0)*
7. Was the drug detected in any body fluid in toxic concentrations? *Yes (+1) No (0) Do not know or not done (0)*
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? *Yes (+1) No (0) Do not know or not done (0)*
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? *Yes (+1) No (0) Do not know or not done (0)*
10. Was the adverse event confirmed by any objective evidence? *Yes (+1) No (0) Do not know or not done (0)*

Scoring

- ≥ 9 = definite ADR
- 5-8 = probable ADR
- 1-4 = possible ADR
- 0 = doubtful ADR

This can help in determining the probability of the reaction being medication related and thus needing to avoid the medication in future times especially if the reaction cannot be tolerated.

Once established there are many reasons why there is an adverse reaction. They can be due to the action of the medication on the body through other receptors such as the dry mouth and constipation association with amitriptyline (See Table overleaf).

As the collection of adverse reactions requires all to be vigilant and report, when using new medications or also medications that have been taken for a long period, adverse effects should be reported. More reports, with as much information as possible, the better the true picture of the incidence of adverse reactions in a given population – this is pharmacoepideminology.

By reporting to an external authority one has the opportunity to add to other evidence and possibly prevent the event happening to someone else or a more serious event happening.[8]

By reporting to the Australian database, this is then reported to Uppsala Monitoring Centre which is the WHO international Collaborative Centre for Medicine Safety and contributing information to the worldwide surveillance system.

Reporting adverse reactions can be done by consumers through the Adverse Medicines Line at National Prescribing Service on **1300 134 237** during business hours and further information http://www.nps.org.au/contact-us/adverse-medicines-events

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Further reading

1. **http://www.who-umc.org/graphics/24753.pdf** WHO newsletter Pharmacovigilance: ensuring the safe use of medicines
2. **http://www.preskorn.com/columns/0311.html** Preskorn, S.H. Relating Clinical trials to Psychiatric practice: Part II. The gap between usual patient in registration trials and in practice. *Journal of Psychiatric Practice*. 2003: 455-61

Category	Definition	Examples
Allergy	Adverse reaction occurring in a susceptible patient involving an immunological mechanism	• *Stevens- Johnson syndrome due to lamotrigine*
Side effect (predictable, dose related)	Any unintended effect of a pharmaceutical product, occurring at doses normally used and is related to the pharmacological properties of a drug	• *Nausea from selective serotonin reuptake inhibitors antidepressants (SSRIs)* • *Constipation from amitriptyline* • *Hyperprolactinemia from risperidone and haloperidol*
Drug interaction	Interaction with another medication causing variation in its metabolism or pharmacological effect. May increase or decrease a medicine's effect	• *Increased levels of aripiprazole with fluoxetine* • *Lamotrigine and valproate*
Intolerance (unpredictable)	A lower threshold to normal pharmacologic action of a drug	
Toxicity/overdose (predictable, dose-related) Only unintentional overdoses are classified as ADRs ie due to error	Always dose related and usually occurs by the same mechanism as the therapeutic effect	• *Renal failure due to lithium*
Idiosyncratic (unpredictable)	Adverse reaction occurring in susceptible patients. Mechanism usually unknown	• *Interstitial nephritis with paliperidone*
Other	Pseudo-allergic reaction (clinically resembling allergic reaction but mechanism NOT IMMUNOLOGICAL)	• *Photosensitivity with chlorpromazine*
	Long-term drug effects • Chronic use • Latent or delayed effects	• *Tardive dyskinesia for typical antipsychotics* • *Weight gain leading to metabolic syndrome from atypical antipsychotics*