

Pharmacological iatrogenesis

Since 1994, a substantial number of papers have been published in major refereed journals on Adverse Drug Reactions (ADRs). The ballpark estimate is that each year 2.2 million Americans are hospitalised for ADRs and over 100,000 die from them. These are simply adverse reactions to drugs, which are often but not always, unpredictable, and appear only in the fine print of prescribing information.

The first papers were greeted with disbelief but were found to be scientifically sound and follow up data confirms these findings. This causes concern at every level but it might be the case that the will to take appropriate action is somewhat influenced by the huge donations made to political parties on both sides of the aisle by the pharmaceutical companies.

Studies in Australia reveal that the same problems occur at a similar rate. The adverse event reporting system in Australia, which is voluntary, is routinely ignored and one wonders what the value of such a random reporting system is or if it might be counterproductive, although costly, by lulling the population into a false sense of security.

These statistics make adverse drug reactions rate as the fourth highest cause of death in the United States after heart disease, cancer and strokes. Improperly prescribed or improperly used medication causes another 80,000 deaths in the USA, making Adverse Drug Reactions the third rating cause of death in the United States

The risk of suffering an adverse drug event increases with admission to hospital where polypharmacy is a regular event.

Psychiatric drugs have hardly rated a mention, as psychiatric side effects in psychiatric patients have been routinely missed or dismissed by the pharmaceutical companies with 'It's the disease, not the drug, doctor.'

This was the case until the 2003 Healy Whittaker analysis of the clinical trials presented to the US Food and Drug Administration, (FDA) to get the SSRI antidepressants and later, the atypical antipsychotics licensed. David Healy's analysis of the very incomplete data put out by the Eli Lilly about Zyprexa in Schizophrenia and Janssen about Risperdal in schizophrenia studies makes it almost impossible to gain informed consent to use these two most suicidogenic drugs in clinical trial history. See lillytrials.com. Suicide is not mentioned as a side effect in prescribing information but it shows up, along with sudden death in the clinical trials presented to the FDA.

David Healy's analysis of SSRI suicides presented to get 9 antidepressants licensed, sparked Congressional hearings into the FDA whose licensing processes had deteriorated to the point that 16 drugs had to be withdrawn for lethal side effects that had been known to the FDA and to the manufacturers and had not been previously disclosed.

On March 22, the FDA issued public health advisories about the use of SSRIs but these have been blocked from publication by the Australian Therapeutic Goods Administration (TGA) and Dr Bill Lyndon, Chairman of the Committee for Psychotropic Drugs and Other Physical Treatments of the Royal Australian and New Zealand College of Psychiatrists says "We are not convinced." But the relative risk of suicide alone, let alone the myriad of other psychiatric disturbance that lead to suicide are barely in the awareness of the general, specialist or hospital practitioner who uses these medicines so freely in Australia.

These deaths are measurable tip of an iceberg of sub lethal but serious adverse events, which might have led to death in more vulnerable persons. They place massive costs on any Health Care system.

So psychiatry is not alone. Psychotropic drugs have psychiatric side effects, which were late in coming to notice, and are now well established. Companies settle thousands of lawsuits when they are sued, and still find it profitable to sell these drugs with minimal warnings.

Half of these events are thought to have been preventable, if certain procedures had been observed. The best way we have of identifying the individual at risk is by asking about their previous responses to other medications which may be similarly metabolised, warning and watching and considering the state of their livers, which may be already affected by alcohol, smoking nicotine or cannabis or other drugs, medical, naturopathic or illicit.

Physician errors account for only 5% of those deaths. The odds of adverse reactions increase with hospital admission.

When used alone, some drugs might be successful, but when more than one drug is used a same time, another set of problems emerges, due to interactions and competition for the pathways of metabolism. .

Drug interactions are not the subject of black box warnings nor of medical education. They are discovered by reading the small print of prescribing manuals and combining the known effects. There is a shortcut: Google on the Internet will disclose most of them, in a fraction of a second. Some understanding metabolic pathways, which deal with these drugs in the body, is needed.

With the drugs used in psychiatry, (and this is very general) many, are metabolised in the liver by an enzyme system called cytochrome P 450 (and other cytochrome systems).

There are genetic, biological differences between individuals, some of whom do not produce certain cytochromes at all. In practice this means that somewhere between 12 and 20% of Caucasians cannot metabolise certain drugs, for example, SSRIs, at all or they do it slowly. Others are fast metabolisers. It is likely that biology accounts for massive drop out rates in clinical trials for both SSRIs and atypicals (up to 50% do not complete the trials and other have Valium co-prescribed and the public is not told.) Statistics about those who could not tolerate drugs do not appear on prescribing information.

Their levels shoot up. Some people do not get nausea, a useful early warning, but develop akathisia and psychosis.

Such people might reject their medication at home but, in hospital, one finds nurses and doctors who urge patients to keep taking medicines, which, they should realize, are making patients sick

These cytochromes can be induced by many 'toxins' that is more of them are produced, or induced, but it does not happen overnight. Their availability or lack of metabolising enzymes produces a logjam at the liver.

This is why, when prescribing an SSRI or one of the many other drugs, which are similarly metabolised, you 'start low - go slow'. Then 'tolerance' has a chance to develop and the drug is better tolerated, and it might more useful, used with impunity. Toxins slowly 'induce' the enzymes that metabolize them and in time, the liver is able to deal with higher doses.

There is now literature that suggests that higher than minimal doses of SSRIs are of no therapeutic benefit and some suggests that minimal doses of Prozac twice a week, but I do not need to get into that unless - as in one case) the patient was on dialysis. (That was not Albury but St. Vincent's, Caritas).

A layman's understanding of pharmacokinetics and respect for cautions about so called 'rare' side effects. But when 6.5 million prescriptions for SSRIs are issued in Australia, the costs in lives and morbidity are substantial and they show up in Department of Health suicide, parasuicide and admission statistics. They constitute 30% of admissions in one rural psychiatric unit.

A rare side effect is one that occurs in one case in a hundred. One in 500, which is the suicide rate the suicide rate on SSRI, is not 'rare', by that definition. 1 in 500 provides a relative risk of 2.2 against sugar pills, one suicide in 208 for Zyprexa and 1 in 250 for Risperdal, provide a relative risk of up to 6 against placebo treated schizophrenics but these suicides do not rate a mention in drug companies' prescribing information.

Rare side effects can become a problem if the drug is given to large populations, (such as the 'not schizophrenic' population or, in the case of antidepressants, to anxious as well as to depressed people) and Bayesian analysis will show that the number of lives lost might be greater than lives saved by the dispensing of medicines the potentially lethal side effects for non lethal conditions.

The cytochrome P450 system is also involved in the metabolism of alcohol, cannabis, nicotine and amphetamines. The concurrent use of these substances causes problems in some people, as the metabolising system is 'stressed' or fully utilised already. Drugs build up in the blood stream, so that blood levels of prescribed drugs are reached in some people, which, in normal or fast metabolisers, might have been reached only by the ingestion of much larger doses. Further complications arise because some break down into psychoactive active metabolites, and these need several, passes through the liver to be destroyed.

Imagine a five-lane highway where road works cause narrowing to a single lane, there will be a back up of traffic. Or imagine a child pouring sugar through a small funnel; it will spill over if there is too much. The P450 metabolic pathway represents just such a bottleneck in the liver.

The following drugs are only a few of the scores that use the cytochrome P450 system for their metabolism: alcohol, nicotine, cannabis, amphetamines, Amitriptyline, Celebrex, Cipramil, Lexapro, Codeine, Valium, Warfarin, Dilantin, Efexor, Feldene, Brufen, grapefruit, Luvox, Aropax, Prednisone, Prozac, Serzone, Risperdal, Tegretol, Voltaren, Zoloft and Zyprexa.

Cannabis is an inhibitor, as well as being metabolised by this system.

As I understand it, there are some 50 genes, which determine a similar number of cytochromes, and so a person's genetic makeup will determine if and how such drugs are metabolised. Not all people have all of them and the missing ones are as yet not identifiable but this is a subject of research.

So SSRIs and Atypicals should be used with caution, both on single doses but more so in combination. One way to exert caution is to take a history of previous responses to these medicines; another is to warn of side effects.

Drugs used in Mental Health all affect neurotransmitters, so all of the have psychiatric side effects as they have multiple, 'scattergun', actions on multiple receptor and transmitter sites.

They are activating, and this activation needs to be watched and controlled. Activation is promoted as a benefit over older drugs but it has a down side risk as well, inducing side effects of, akathisia, agitation, anger, restlessness, depression, anxiety, paranoia, psychosis, hallucinations, violence towards self or others, suicidal and homicidal ideation and acts.

The problem is both an idiosyncratic response to a drug, but it is also dose-related. Anyone can have problems if too high a dose is used to start and if too many drugs using the same metabolic pathways used together. The patient should be involved in a decision whether to take a drug knowing the potential side effect is addiction or that it could induce suicide and be lethal, when the condition for which it is prescribed is not.

Getting informed consent is a useful exercise as it forces a doctor to read prescribing information to inform herself as well.

Given that all the above disturbances are well-reported side effects of all serotonin boosters (Prozac, Luvox, Zoloft, Efexor, Aropax, Zyban, Avanza) then it makes little sense to add another substance that makes demands on the P450 system, such as Zyprexa or Risperdal to counteract the side effects of SSRIs. It makes no sense to treat a toxic condition with another toxin. It always makes it worse. This is what I have been repeatedly reporting and warning about. And the drug companies also warn about it.

The atypicals, Zyprexa and Risperidone have been approved in Australia for schizophrenia. Zyprexa has recently been approved from 1st February for bipolar and I fear the adverse consequences of that. It has not been trialed in combination with any thing else and in some of the bipolar trials against placebo alone.

This means that giving these drugs to a person whose illness does not meet the criteria for schizophrenia represents 'off indication' use is (off label in the United States. It is illegal to lie about a diagnosis to get them on the Pharmaceutical Benefits Scheme. Lying about a patient's diagnosis carries a penalty of two years in Jail or a \$5,000 fine, and this is a matter for the HCCC.

Using atypical antipsychotics for substance-induced or SSRI-induced 'psychosis' is using them for a condition where they have never been tested. The diagnosis of schizophrenia demands a six-month history for diagnosis and it cannot be diagnosed during the use of use of other substances, which might themselves produce symptoms of psychosis.

Not one case that I reported had there been a six-month history of psychosis, nor had here ever been a period without medication that caused the hallucinosis.

All this is in Prescriber or Product information, put out by drug companies. Drug companies rarely name other medicines (as opposed to groups, like SSRIs, metabolised by the P450 cytochrome system' so you have to actually know the Prescriber Information for all the drugs you are using and add it all up.

Because these drugs 'induce' the enzymes (cytochromes) that metabolize them, it is possible for someone on SSRI who wants have a drink, to introduce alcohol in small doses, gradually as 'tolerance' caused by induction of enzymes develops gradually.

If they are introduced slowly and carefully, co-prescribing might be possible. The first sign of liver overloads is nausea, which is still the most sensitive indication that the liver is 'stressed.'

Res ipse loquitur