



## The Need to Establish a Common Base Line for the Characteristics of Safety Withdrawal of Prescription Drugs from Worldwide Pharmaceutical Markets

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So often at conferences or in introductions to papers certain facts are stated that headline the dangers of pharmaceutical agents and why certain areas of work should be prioritised. Such statements are useful, but only if they are well researched and their validity as can be established. If not they become under-researched dogma, which unfortunately gains status simply by its repetition. This editorial is a plea to toxicologists, clinical pharmacologists and drug metabolism scientists to try to establish a documented link to primary literature material. Similarly when research is conducted in these areas certain controls and conditions are applied.

Typically hepatotoxicity is spoken of as the major cause of drug withdrawal without further qualification and with little reference to other causes. This is often the opening remark to an experimental *in vitro* test for hepatic effects. The most cited reference is that of Fung et al (1) dealing with the period 1960-1999. Periods are important, as the availability of several drugs (e.g. non selective, and selective cyclo-oxygenase inhibitors) in a class allow comparisons concerning safety, often leading to withdrawal of the one(s) or more with the worst benefit-risk. This statement leads the reader in two ways highlighted in italics.

(i) *If hepatotoxicity is the major cause, all others are minor.* Since 1980 to date, 24 drugs have been withdrawn from the US market with 6 drugs (25%) due to hepatotoxicity (2). In contrast 5 drugs have been withdrawn due to effects of their primary target pharmacology and 8 drugs due to off target pharmacology against recognised receptors or enzymes. Interactions with the IKr channel account for 4 (50%) of this subclass. Perhaps the headline statement should be “of the reasons for the safety failure of pharmaceutical agents hepatotoxicity is the area we have made the smallest impact numerically and scientifically”.

(ii) *Hepatotoxicity is a black or white characteristic of a drug. Screens and other in vitro experiments can therefore compare a series of drugs and look for signals from the hepatotoxic ones. Exceeding the physiological concentrations by many orders of magnitude is permissible, if the output discriminates good from bad.*

In fact almost all drugs can be linked to some degree of hepatic toxicity. A recent review cites over 1000 hepatotoxic drugs (3). The incidence of hepatotoxicity correlates to some degree with the number of patients prescribed the drugs, somewhat confounding simple analysis. Moreover, studies of individual drugs or classes of drugs show a high variation due to the low incidence of, toxicity. For instance, controlled-cohort studies (4) have shown Ibuprofen (44.6/100,000 patient years) to have a higher incidence of liver disease (defined as  $>2XULN$  in liver clinical chemistry) than diclofenac (22.7/100,000 patient years). This is contrary to the widely perceived view and contrary to other reports. For actual withdrawn drugs, those withdrawn tend to show a higher incidence than comparable agents, but others in the class are usually not devoid of toxicity. Because of their relatively rare nature, the random generation of a series of findings relatively close together can be influential in the withdrawal of a drug and explain inter-country differences. As an example, most antidepressants are not normally judged as hepatotoxic, nevertheless cases are reported at 1.28 to 4.00 cases per 100,000 patient years.

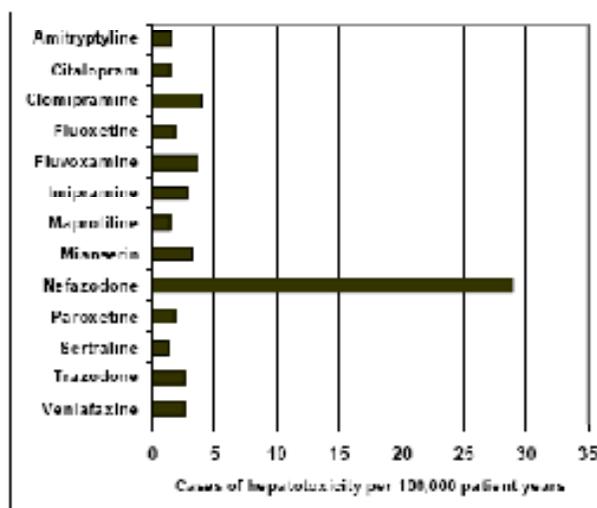


Figure 1. Relative incidence of hepatotoxicity across antidepressants.

Nefazodone appears to be associated with an increased risk of hepatotoxicity as shown in figure 1 but all the drugs show some incidence.

This association across most drugs means that the selection of standards for an in vitro test becomes a critical event. There are probably no negative control drugs *per se* and positive standards are a matter of judgement particularly when the toxicity is of the idiosyncratic type. With such a “noisy” test set what sorts of results would be expected. With high concentration screens, potentially not mimicking the actual toxic events, the data probably reflects the agents chosen and not the quality of the screen. Curation of an Internationally recognised set of hepatotoxicity standards by incidence, dose, concentration, pathology and known protein/gene interactions etc, used to provide an appropriate test set seems a worthy task that should be sponsored. A recent publication (5) used a test set of 243 drugs with an attempt to classify their degree of hepatotoxicity, plus using concentrations set at 30 X maximum human plasma total drug concentration or 100  $\mu$ M. In this example a high concordance was noted for the assay due to the excellence of the assay or the selection of the compound set and other intrinsic properties such as compound physicochemistry buried within. Does the test set represent and the concentrations used form a basis for discussion or are their other starting points to achieve some unity. Why we need to do this is to protect our area of science. Many of the drugs selected as hepatotoxic are actually “safe” in 99.99% or more of the population, so what signal should be given in our test. Moreover, is there any evidence that exists, showing the incidence of idiosyncratic toxicity, representing a dose response relationship we are justified in using very high concentrations in which the compounds become pharmacologically non-selective potentially making the test indiscriminate, therefore, of chemical structure (but not physicochemical properties, which correlate to many membrane effects).

Reference is often made to drug adverse events being the 5th to 7th leading cause of death in the United States and that the leading cause of Hospital Deaths is drug related. Such statements often are a prelude to a talk on CYP450 or transporter drug-drug interactions. The inference is often that the only solution is broad based screening, without which the problem is uncontrollable. At the extreme, and the one usually quoted, indicates 106,000 deaths in the US in 1994 might have been due to adverse drug reactions (6). This makes drug side effects the sixth leading cause of death in the US (4.6% of all deaths). This estimate was based on admission rates in 1994 and ADRs before 1981. Other studies that used death certificates and/or the US Med Watch data, report that only between 0.1% and 0.3% of deaths are due to adverse drug reactions. Adverse drug reactions cover a huge potential spectrum, but a retrospective analysis of Hospitals in Liverpool (7) gives a detailed analysis and offers a valuable

insight into where the problems lie. This showed 28 drug deaths out of 18,820 admissions, with 1225 admissions due to drug adverse reactions. Almost all of these adverse reactions stemmed from the primary pharmacology of the drugs or interactions of the primary pharmacology of the conmeds. The “most dangerous drug” was aspirin which was the sole medicine or in combination (particularly with other NSAIDs and warfarin) and a factor in 17 of the 28 deaths. Uncontrollable haemorrhage by these agents is the cause of death. A major study in Helsinki University Central Hospital (8) showed similar finding, with 75 of the 1511 death cases (5.0% of all deaths) probably drug-related. This corresponds to about 0.05% of all hospital admissions. The most common adverse reactions were neutropenia caused by antineoplastic agents and again gastrointestinal or intracranial haemorrhage due to anticoagulants or nonsteroidal anti-inflammatory drugs (NSAIDs). The incidence of drug-related deaths is 0.5% when based on the International Classification of Diseases (ICD) codes in death certificates which could help to explain some of the discrepancies in the various reporting systems. Another agent, paracetamol (acetaminophen), contributes greatly to hospital deaths. Paracetamol (acetaminophen) is the most common drug taken in overdose (9) in the UK, accounting for 48% of poisoning admissions to hospital and being involved in an estimated 100-200 deaths per year due to liver failure. This tragic figure makes up the major proportion of other drug related deaths in hospitals. From the above it can be seen that relatively few drugs with specific toxicities make up the bulk of the statistics, and the solution is actually not more advanced drug interaction screening but safer prescribing and the discovery of safer pain relieving and anticoagulant agents with different pharmacologies. Safer prescribing and consuming (patients do not take the drug as directed) would actually achieve an enormous impact on the adverse use of drugs and some of the grimmer statistics outlined above, but then we wouldn't have anything to introduce our pet topic with.

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