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Behavioural Toxicity of Medicinal Drugs

Practical Consequences, Incidence, Management and Avoidance

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Contents

Summary

Behavioural toxicity is relatively common among medicinal drug users and evidence shows that drugs frequently produce adverse effects that prevent their users from performing everyday operations in a normal manner. Epidemiological research generally indicates that the use of sedative drugs is associated with an increased risk of becoming involved in injurious accidents. Empirical studies have also demonstrated adverse effects of sedative drugs on the performance of healthy volunteers and patients in laboratory tests designed to measure psychomotor and cognitive function, and in real life-tests measuring on-the-road driving performance. Empirical studies also indicate that behavioural toxicity can vary widely between individual drugs depending on differences in dose, dosing regimen, duration of treatment, pharmacokinetics or mechanisms of actions.

Besides sedation, other CNS adverse effects such as aggression, paranoia, social withdrawal or lack of motivation may disrupt or prevent the initiation of normal performance, thus imposing a burden on the ability of the patients to function in a normal manner. Emotional disturbances are rare as indicated by the small number of case reports that mention their existence. Yet theses disturbances sometimes involve severe reactions that are more debilitating than sedation.

Behavioural toxicity can be minimised by avoidance of pharmacodynamic and

pharmacokinetic drug interactions, adjustment of dosage regimens to a patient's individual response to a drug, nocturnal administration of drugs that are expected to produce sedation and patient education on the potential risks of the drugs they receive. Much of this information can be gained from experimental literature comparing the effect of individual drugs on performance. Unfortunately this is presently incomplete, since most research on behavioural toxicity has been confined to psychiatric drugs. Yet, in the interest of the patient, it should be the responsibility of drug manufacturers and regulators to always identify problematic drugs.

Many drugs possess a mechanism of action, additional to their major mode of efficacy, that can disrupt behaviour. Sedation is probably the most frequently occurring CNS adverse effect. It is produced by a wide range of drugs that act via a variety of mechanisms. This effect may differ quantitatively and qualitatively between different drugs and different dosages of the same drug, but feelings of drowsiness, lethargy and inability to concentrate are common to them all.

Sedation may impair neuropsychological processes controlling behaviour and consequently place a patient at increased risk of becoming involved in an accident leading to injury or death. If such an association between drug use and injurious accidents exists, the adverse effect of the drug can truly be called behaviourally toxic.

Other CNS adverse effects (such as memory and motor disturbance or emotional dysfunction) may either disrupt or prevent the initiation of normal performance, thus imposing a burden on the ability of the patients to function at home, work or any other social setting. Some of these effects are more debilitating than sedation and should be considered as potential sources of behavioural toxicity. This article provides epidemiological and empirical evidence for the existence of behavioural toxicity and offers some insights into its management.

1. Behavioural Toxicity: Origin and Definition

The earliest medicines were all plant products and many drugs used today have similar origins. Before the advent of modern medicine, however, most of these compounds were recognised and occasionally used by humans as poisons.

Throughout evolution, plants have had to cope with the feeding behaviour of herbivorous animals. It would seem that plants that evolved neurotoxins capable of killing or disabling herbivores increased their chances of survival. Most of these toxins are concentrated in seeds and typically cause massive neuronal discharges by selectively blocking inhibitory neurotransmitter systems at their postsynaptic receptors [e.g. picrotoxin at γ-aminobutyric acid $(GABA)_A$ sites, and strychnine at glycine sites], or by inhibiting enzymes that inactivate excitatory transmitters (e.g. physostigmine inhibiting acetylcholinesterase).

Nevertheless, plant toxins are not necessarily lethal to animals. Compounds of far lesser toxicity, which also act selectively at CNS receptors in all higher vertebrates, are synthesised by many plants. Opioids, belladonna alkaloids, mescaline and Δ^9-tetrahydrocannabinol are but a few of many possible examples. Their relatively low toxicities make it more likely that animals consuming them will experience reversible intoxication rather than death.

Humans have long used many of these drugs for their euphorogenic or hallucinogenic properties.[1] They are said to be 'psychotoxic' and highly detrimental to socially acceptable or self-fulfilling behaviour.[2] Although many medicinal drugs possess additional therapeutic mechanisms of action that also disturb behaviour, the effects of these are described in less pejorative terms, as 'CNS' or 'psychiatric' adverse effects.

Sedation is probably the most common CNS adverse effect. It is produced by a wide variety of drugs that, through a variety of mechanisms, reduce overall CNS arousal.[3] Although this effect differs quantitatively and to some extent qualita-

tively between different drugs and dosages, somnolence, feelings of drowsiness, inability to concentrate, diminished energy, unusual fatigue and lethargy are common to all. The recognised behavioural correlates are diminished speed and accuracy of psychomotor and cognitive performance. The diminished behavioural capacity that accompanies sedation can be highly detrimental to ambulant patients attempting to follow occupational or educational pursuits, and can even be the cause of injurious accidents. Some 'sedative' drugs and others, such as selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs), also provoke aberrant behaviour, although this is infrequent and usually occurs after prolonged use.

Finally, some drugs inhibit spontaneous behaviour without necessarily affecting the efficiency of behaviour once initiated. Any of these effects can have a pervasive influence on the way an individual functions within human society and, consequently, the manner in which society treats the individual. The affected individual would be less likely to achieve normal goals and avoid predictable sanctions than before taking the drug or while taking an equally efficacious alternative that was devoid of the adverse effect. The activity of the drug could therefore be seen as behaviourally toxic.

A broader definition focuses on the causes rather than the extreme effects of behavioural toxicity. The fundamental cause is, of course, a pharmacological activity that disrupts the neuropsychological processes controlling behaviour. However, these processes are poorly understood. More evident are the behavioural changes that frequently develop over time in patients taking certain classes of drugs. These should lead physicians to view adverse behavioural reactions as commonplace and by no means limited to toxic psychosis.

Previous attempts to define behavioural toxicity also stipulated the broad scope of human functioning that is encompassed.[4-6] However, 2 of the definitions[4,5] seem to imply that any toxic property of drugs that impairs behaviour, whether it disturbs neuropsychological processes or not, falls under the definition of behavioural toxicity. The third[6] assumes that behavioural toxicity depends on the intensity of impairment brought about by a drug; that is, 'sedation' would not be included in the term, but 'excessive sedation' would, 'mood dampening' would not be included, but 'depression-inducing' would. Without more clearly specifying the causes and effects of behavioural toxicity, such definitions do not seem particularly useful.

An alternative definition offered by this author is as follows. Behavioural toxicity is fundamentally a reversible, pharmacological, drug-induced disruption of neuropsychological processes controlling behaviour. The existence of behavioural toxicity can be inferred by certain changes in the individual's behaviour while taking the drug; or, by certain differences in his/her behaviour between periods when the individual uses that drug and a therapeutically equivalent alternative lacking the same behaviourally toxic effect. Changes and differences will imply that the behaviourally toxic drug inhibits or reduces the efficiency of normal behaviour and/or causes aberrant behaviour, in a manner reducing the individual's ability to obtain benefits and avoid sanctions within the society.

The reminder of this article offers evidence for the existence of behavioural toxicity, indicates what is known about its underlying pharmacological mechanisms and provides insights into its management. Epidemiological evidence for the existence of behavioural toxicity is confined to studies demonstrating causal relationships between medicinal drug use and injurious accidents, published over the last decade. Empirical evidence is confined to those classes of medicinal drugs that have been most frequently indicated as causing impaired, inhibited or aberrant behaviour (anxiolytics, hypnotics, antidepressants, antipsychotics and antihistamines). Other drug classes will be only briefly mentioned as possibilities for further study.

2. Epidemiological Evidence

Perhaps the strongest evidence supporting the present concept of behavioural toxicity comes from a host of epidemiological surveys. These con-

vincingly show that patients taking a variety of medicines often experience performance deficits responsible for injury or death in several common situations. This breakthrough was mainly achieved because of epidemiologists' simultaneous access to computer records of prescription and accident histories from sometimes several hundreds of thousands of patients.[7,8]

Three types of design have been used for associating injurious accidents and the use of medicines: cross-sectional, case-control and cohort designs.

Cross-sectional designs relate the patient's medication use at a particular moment in time to their history of sustained injuries. The odds ratio (OR) is used as the measure of association to estimate the likelihood of medication use among those involved in an accident compared to those who were not. However, in cross-sectional designs, the temporal sequence of the events cannot be definitely established and some medication might be used as a consequence of the accident. The predictive validity of results from this type of study is consequently rather limited.

In case-control and cohort designs, the temporal relationship between medication use and accidents is fixed. Case-control studies compare the frequency of prior medication use by individuals who sustained injuries (cases) with that in persons without adverse outcomes (controls). An increased frequency among the cases indicates a positive association and a higher OR. In cohort designs, classified groups of medication users and matched nonusers are, prospectively or in retrospect, followed over time to calculate their frequencies of accident involvement. Higher rates of accident involvement among users indicate a higher risks relative to nonusers. The drug users' frequency of involvement in injurious accidents, relative to that of the nonusers, is used as a measure of association, expressing their relative risk (RR).

Thus, case-control and cohort designs are clearly best suited to establish causal relationships between drugs and accidents. The epidemiological surveys listed in table I have generally followed either one of them. It should be noted that RRs and ORs given in this table reflect the overall risks associated with drugs, since many of them were prescribed to patients in various dosages. However, some of these surveys have demonstrated that the users' risk increases with the prescribed dosage and the numbers of different drugs concurrently received.

Understandably, relationships have been found most frequently for those psychoactive drugs that were not only most frequently used during the survey periods (usually 5 to 10 years before their publication dates), but also the ones suspected of causing accidents beforehand. Thus, the benzodiazepines (BZDs) and tricyclic antidepressants (TCAs) are commonly cited as causal factors in accidental injury. Surveys not listed in the table have also shown greater use of medical services by benzodiazepine users,[26,27] and a greater incidence of TCA and benzodiazepine use among instigators, compared with victims, of accidents.[28] This does not mean, however, that the use of some more recent, less used or less notoriously impairing drugs is not also a cause of accidents.

2.1 Falls

Besides death, hip fracture is the most serious consequence of falls in the elderly. About one-third of noninstitutionalised elderly over the age of 65 years experience one or more injurious falls and their probability of falling increases as they grow older.[29-31] The use of psychoactive medication in general has been shown to significantly contribute to their risk of falling.[29-34]

Ray et al.[9] demonstrated that the association between falls and use of psychoactive drugs was more pertinent to some drugs than to others. Elderly users of long-acting benzodiazepine hypnotics, or of anxiolytics, antipsychotics and TCAs, were found to be 1.8 to 2.0 times more likely to experience hip fractures, relative to controls. In contrast, use of short-acting hypnotics and anxiolytics was not associated with an increased risk; the latter category included drugs with an elimination half-life of 24 hours or less and predominantly consisted of chloral hydrate and the antihistamines,

Table I. Summary of epidemiological studies, according to type of study, indicating risk ratio (RR) or odds ratio (OR) of becoming involved in injurious falling, traffic and occupational accidents for drug users versus non–drug users

Study	Number of cases[a]	Number of controls[b]	Age (y)	Accident/injury	Drugs implicated	RR/OR (95% CI)
Case-control						
Ray et al.[9]	1021	5606	>65	Hip fracture	BZDs (long acting)	1.8 (1.3-2.4)
					TCAs	1.9 (1.3-2.8)
					Antipsychotics	2.0 (1.6-2.6)
Granek et al.[10]c	184	184	>65	Falls	Antidepressants	2.6 (1.1-6.0)
					Hypnotics	2.6 (1.2-6.5)
					NSAIDs	2.4 (0.9-6.5)
					Vasodilators	2.1 (1.1-4.1)
					Tranquilizers	1.8 (0.8-3.9)
Ray et al.[11]	4501	24 041	>65	Hip fracture	TCAs	1.6 (1.3-1.9)
Ryynänen et al.[12]d	380	342	>65	Falls	BZDs	2.2 (1.2-4.2)
					Antidepressants	2.2 (1.2-3.9)
					Antipsychotics	4.4 (1.6-11.9)
Lichtenstein et al.[13]	129	324	>65	Hip fracture	Antidepressants	2.7 (1.0-7.4)
					BZDs	2.1 (1.1-3.8)
Cumming and Klineberg[14]	209	207	>65	Hip fracture	BZDs	1.6 (1.0-2.5)
					Temazepam	3.8 (1.6-8.9)
Shorr et al.[15]	4500	24 041	>65	Hip fracture	Opioid analgesics	1.6 (1.4-1.9)
Leveille et al.[16]	234	447	>65	Traffic accidents	TCAs	2.3 (1.1-4.8)
					Opioid analgesics	1.8 (1.0-3.4)
Koepsell et al.[17]	234	446	>65	Traffic accidents	Insulin	5.8 (1.2-28.7)
					Oral hypoglycaemics	3.1 (0.9-11.0)
Gilmore et al.[18]	3394	6788	>18	Occupational injuries	Antihistamines	1.5 (1.1-1.9)
					Antibacterials	1.2 (1.0-1.5)
Cross-sectional						
Cumming et al.[19]	108	1250	>65	Multiple falls	Diazepam	3.7 (1.5-9.3)
Govaarts et al.[20]	130	2665	>18	Occupational injuries	BZDs	2.6 (-)
Prospective cohort						
Malmivaara et al.[21]	2164	17 354	>20	Falls	Anxiolytics	1.7 (1.4-2.6)
					Antipsychotics	2.0 (1.4-3.0)
Lord et al.[22]	76	338	>65	Multiple falls	BZDs (long-acting)	2.0 (1.5-2.6)
					TCAs	2.8 (2.0-3.6)
Ruthazer and Lewis[23]	228	407	>70	Falls	TCAs + SSRIs	1.8 (0.9-3.7)
Neutel et al.[8]d	225 796	98 000	>20	Falls	Flurazepam	4.2 (2.4-5.1)
					Triazolam	3.5 (2.6-6.7)
					Oxazepam	3.0 (1.7-5.2)
					Diazepam	3.0 (1.6-5.6)
					Lorazepam	2.7 (2.0-4.4)
Maxwell et al.[24]	223 868	97 554	>20	Falls	BZD anxiolytics	2.0 (1.5-2.6)
					TCAs/hypnotics	2.8 (2.0-3.6)
Retrospective cohort						
Ray et al.[25]	5418	33 283[e]	>65	Traffic accidents	BZDs	1.5 (1.1-2.0)
					TCAs	2.2 (1.3-3.5)
Neutel[7]	226 000	98 000	>20	Traffic accidents	BZD anxiolytics	3.9 (1.9-8.3)
					BZD hypnotics	2.5 (1.2-5.2)

a Refers to drug users in cohort designed studies, and to individuals involved in accidents in other types of study design.

b Refers to non-users of drugs in cohort designed studies, and to individuals who were not involved in accidents in other types of study design.

c Confidence interval calculated from available data in the manuscript.

d RR and CI calculated from available data in these manuscripts.

e Expressed as person-years (person-days/365) of follow-up; the total cohort comprised 16 262 elderly drivers.

Abbreviations: BZD = benzodiazepine; CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

diphenhydramine and hydroxyzine. The use of short-acting benzodiazepines was still too infrequent for evaluation at the time of this survey.

Subsequent epidemiological studies generally confirmed the higher fall frequency among users of benzodiazepines, antipsychotics or TCAs.[10-13,21] Others differentiated between effects of short and long acting benzodiazepines. Lord et al.[22] found higher falling rates among 13 users of long acting benzodiazepines, but not among 23 users of shorter acting oxazepam or temazepam, compared with nonusers. In contrast, another study showed that use of temazepam was more frequent among 29 patients with hip fracture, compared with controls.[14] Clearly the numbers of participants in these studies were too low to calculate reliable risk estimates for these individual drugs.

A study conducted by Neutel et al.[7] is more definitive. It included 225 796 users of benzodiazepine medication and 98 000 controls. These investigators only included fall-related hospitalisations within 3 weeks of a first prescription in calculating the RR of benzodiazepine users compared with nonusers. It is evident from clinical trials that adverse events are generally more likely to occur shortly after a first prescription than during long term use of a drug. Nevertheless, while most epidemiological surveys have failed to consider duration of treatment as a factor determining RR, this study[7] did not. It demonstrated that the frequencies of hospitalisation for fall-related injuries among users of oxazepam and triazolam were similar to those among users of long-acting benzodiazepines and about 3 times higher than in nonusers.

SSRIs have largely replaced TCAs as the antidepressants of first choice and the former are generally less sedating than the latter. So far, only 1 survey has been undertaken to compare the separate relationships between falls and SSRI or TCA therapy.[23] Although the use of any antidepressant by patients of both genders was marginally related to the occurrence of falling accidents (RR = 1.84; $p = 0.09$), women using antidepressants had significantly higher fall rates than their controls; among them, a larger percentage of those taking the SSRIs (53%) fell, compared with those taking TCAs (14%).

Other drug classes implicated as causing hip fracture or falls include opioid analgesics,[15] nonsteroidal anti-inflammatory drugs (NSAIDs) and vasodilators.[10] The former investigators[15] indicated that their results might have been largely expected from the opioids' general sedative properties and the previously demonstrated tendency for these drugs to impair their users' balance and coordination in experimental studies. The association between NSAID use and falling accidents is more surprising. Although these drugs are known to possess CNS activity, it usually occurs with high dosages. Granek et al.[10] did not mention whether their patients received large dosages, but the frequent complaints of adverse events such as sedation, dizziness, blurred vision, confusion, vertigo and syncope suggests that many of them did. Alternatively, the possibility of confounding by indication (i.e. an over representation of persons afflicted with arthritis among those taking NSAIDs) cannot be excluded. The association involving vasodilators may be attributable to orthostatic hypotension, which is a common adverse effect of all these drugs.

With 3 exceptions, all epidemiological studies on drug-related falls have involved elderly patients. This does not necessarily mean that the problem of drug-related falls is confined to the elderly. This was clearly demonstrated by Neutel et al.[7] and Maxwell et al.[24] They observed that there is an increased in risk of falling after a first benzodiazepine prescription for all patients above the age of 20 years. Falling rates remained fairly stable up to about age 60 years and began to rise sharply beyond the age of 70 years. Likewise, Malmivaara et al.[21] observed a significant elevation in the relative frequency of drug-related falls in all adult age groups, but more so in the elderly.

2.2 Traffic Accidents

Ray et al.[25] demonstrated that benzodiazepines and TCAs, but not opioid analgesic and antihistamines, increase the risk of involvement in motor ve-

hicle crashes for elderly drivers. In a later survey, also conducted in the US, Leveille et al.[16] failed to confirm these findings in users of benzodiazepines and opioids. The conflicting results for benzodiazepine users are easily explainable. Whereas Ray et al.[25] specifically excluded patients using benzodiazepine hypnotics from their sample, preferring to concentrate on anxiolytic users instead, practically all of those included in Leveille et al.'s survey[16] were using hypnotics, particularly the short-acting agent triazolam. The conflicting results for users of opioids may be accounted for by the fact that Leveille et al.[16] included codeine-containing cough medication in their analysis, comprising 19% of the opioid prescriptions, whereas these were excluded by Ray et al.[25] because of their sporadic use in that study sample.

Both studies[16,25] obtained similar risk estimates in users of TCAs or antihistamines. However, the absence of an association with the latter is surprising in the light of experimental data showing that the older 'sedating' antihistamines can severely impair driving performance.[35] Ray et al.[25] did not mention which antihistamines were used in their study sample. The possibility thus exists that some received an antihistamine of the more recently introduced 'nonsedating' generation. In Leveille et al.'s sample,[16] however, the 'sedating' diphenhydramine accounted for 80% of antihistamine use. The controversy may be related to the fact that the use of antihistamines in both surveys was ascertained from prescriptions filled at the pharmacy, and did not include the vast majority of 'sedating' antihistamines that are sold over the counter. As a consequence, misclassification of drug exposure in the study samples could have introduced a conservative bias.

Neutel[7] estimated the RR of becoming involved in an injurious accident as a function of time since their first prescription for most of the adult users of benzodiazepine hypnotics and anxiolytics in Saskatchewan during the period 1979 to 1986. Her results demonstrate that the first prescription for a benzodiazepine is initially followed by a substantially increased risk of a traffic accident (fig. 1). They also illustrate that this risk diminishes with passage of time as a result of developing tolerance to the sedative activity of the drug. During the first week, the RR for hypnotic users and anxiolytic users was 9.1 and 13.6, respectively. By the end of the second week, those RRs declined to 6.5 and 5.6, respectively. At the end of one month, the respective RR values were 3.9 and 2.5. The youngest group of benzodiazepine users (20 to 39 years of age) had substantially higher rates of hospitalisation for traffic accidents than their older counterparts.

In another article, Neutel et al.[8] indicated that for 3 weeks after a first prescription, in comparison with nonusers, users of flurazepam were about 5 times more likely, and users of triazolam, diazepam or lorazepam were about 3 times more likely, to be injured in traffic accidents. Among individual drugs, only oxazepam failed to significantly elevate its users' RR. That triazolam elevated the user's risk in this survey, but not in that by Leveille et al.,[16] is probably attributable to a difference in dosage taken by the participants. The former data[8] were collected before, and the latter[16] after, the manufacturer had reduced the recommended starting dosage from 0.5 to 0.25 mg/day.

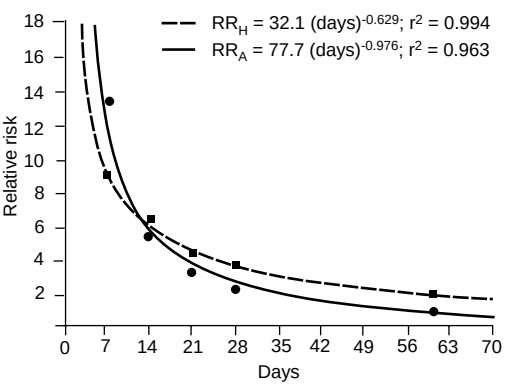

Fig. 1. Relative risk of injurious traffic accidents as functions of cumulative elapsed time after prescription of hypnotics (RR_H) and anxiolytics (RR_A) of the benzodiazepine class, compared with individuals who did not receive these drugs (curve estimations based on data from Neutel[7]).

Insulin and oral antihyperglycaemic agents have also been implicated as causal factors in injurious traffic accidents.[17] This is probably related to the fact that patients with diabetes mellitus treated with such drugs commonly experience mild to moderate hypoglycaemia causing dizziness, cognitive impairment and, as a consequence, accidents.

2.3 Occupational Accidents

Accidents attributable to medication use in working environments have been reported in 2 studies.

Govaarts et al.[20] conducted a postal survey of 2795 employees of 3 Dutch companies (public transportation, clerical and electronics manufacturing) concerning benzodiazepine use and injuries incurred within the preceding 48 hours. Completed questionnaires were received from 62% of the workers. The replies indicated that benzodiazepine users were 2.6 times more frequently involved in occupational accidents than nonusers.

Gilmore et al.[18] reported significant associations between certain types of occupational injuries and the use of either antihistamines or antibacterials. Open wounds and burns were the most prevalent injuries among the users of either drug. The study authors interpreted the relationship involving antibacterials as epiphenomenal: it was more likely that the infections requiring antibacterial use were responsible for the accidents, rather than the drugs themselves. However, the relationship involving antihistamines was interpreted as causal. This was because, at the time and place the survey was conducted, the workers' medical insurance carrier would only support their use of older (i.e less expensive) sedating antihistamines. Gilmore et al.[18] justified their interpretation on the basis of experimental evidence showing that the older drugs possess strongly impairing properties, expected to cause accidents in the workplace.

3. Empirical Evidence and Case Reports

A wide variety of procedures has been used to assess the behaviour-impairing effects of drugs. The earliest were taken from existing psychometric batteries, such as the Digit Symbol Substitution Test (DSST) from the Wechsler Adult Intelligence Scale. Other early tests were those developed to diagnose neurological, ophthalmological and vestibular disorders (e.g. Wisconsin Card Sorting, Maddox wing, Body sway tests, respectively). Later, 'psychomotor' tests, characterised by contingent motor responses to an imposed discrete or continuous signal, were applied [e.g. reaction time (RT), tracking and critical flicker/fusion frequency (CFF) tests]. 'Cognitive' tests were added primarily to measure various mnemonic functions, but also deductive reasoning. Finally, tests were developed to measure some aspects of 'real-life' performance, such as driving in a simulator, through staged manoeuvres on a course closed to other traffic, or on public roads in actual traffic. All of these tests have been applied in single- or multiple-dose, double-blind studies, usually with healthy volunteers, but sometimes with patients. They have used both parallel group and crossover designs, most with both placebo and active drug controls.

The great advantage of the empirical approach is its ability to determine the intrinsic pharmacological effects of drugs on performance without the confounding factors that always obscure or exaggerate the effect in the natural environment. Moreover, experimental studies can be undertaken with drugs in all phases of clinical development and with doses that extend beyond the therapeutic range. They are particularly valuable for identifying and controlling problematic drugs.

However, the empirical approach has limitations as well. All tests employed in experimental studies are more or less artificial. No one knows how to translate the results they provide into the safety-relevant performance impairment of patients in their normal daily living activities. There are just enough comparative data from volunteers and patients to know that both experience similar adverse effects of psychoactive drugs that influence performance,[36-38] but far fewer concerning the therapeutic effects of the drugs that might improve patients' performance.[39] In short, it is not generally possible to predict the net effect of

psychoactive drugs on patients' performance from results obtained in experimental studies.

Finally, the relatively small numbers (i.e. less than 30) employed in these studies are generally insufficient to observe extreme or unusual reactions, particularly those that involve the inhibition of spontaneous behaviour or the provocation of grossly aberrant behaviour. Such unusual reactions are only reported in clinical case studies. Although somewhat anecdotal, they must be regarded seriously. The phenomena they describe are often the most severe kinds of behavioural toxicity afflicting individual patients. Any review of this topic would be incomplete without mentioning them.

3.1 Anxiolytics and Hypnotics

GABA is a major inhibitory, and widely distributed, neurotransmitter in the mammalian CNS. It is released by a web of short-axon interneurons occupying some 40% of all synapses. benzodiazepine ligands affect inhibitory GABA neurotransmission by allosterically modulating the ability of the neurotransmitter to open chloride channels at the $GABA_A$/benzodiazepine receptor complex. The classic benzodiazepine anxiolytics and hypnotics act as agonists and achieve their anxiolytic, anticonvulsant and sedative effects through potentiation of GABA-stimulated chloride flux.

Previous reviews of pharmacodynamic studies employing healthy volunteers and patients have generally shown that benzodiazepine agonists can cause severe impairment in tests designed to measure psychomotor and driving performance.[40-43] Among psychomotor tasks, measures of CFF, DSST, tracking and RT were particularly sensitive to the sedative effects of benzodiazepines. They generally indicate that benzodiazepines reduce their users' overall speed of information processing and motor response.

The practical relevance of psychomotor impairment under the influence of benzodiazepines has been amply demonstrated in a long series of driving studies employing a standardised test.[36,37,44-50] The test involves operating a specially instrumented vehicle at a constant speed and with a steady lateral position over a 100km circuit on a primary highway in actual traffic. Standard deviation of lateral position (SDLP), a measure of tracking error, is its primary performance measure. Participants have included both healthy volunteers and patients with anxiety; no essential difference was noted to their reactions to the same drugs. Typically, driving performance deteriorated in a dose-related manner in response to same-day treatment with anxiolytics and on the days following hypnotic treatment.

Almost all commonly used benzodiazepines have been tested and practically none has failed to seriously impair driving performance. The maximum effect was usually seen after the initial doses. However, it occurred later in series of repeated doses for those benzodiazepines possessing the slowest rates of elimination.[36] The adverse effects of the drugs on driving diminished, but were still significant for up to 3 weeks of continual administration.

Recognition of the detrimental effects of benzodiazepines on performance has led to the development of newer drugs expected to achieve anxiolysis without concomitant sedation. The first was buspirone, a $5\text{-}HT_{1A}$ receptor partial agonist.[51] Other new classes of benzodiazepine-like drugs acting as partial agonists at the $GABA_A$ receptor complex (the cyclopyrollones, such as zopiclone and suriclone, and the imidazopyridines, such as alpidem) were less successful in achieving that goal. All had detrimental effects on performance similar to those seen for classic benzodiazepines.[52-59]

Benzodiazepine agonists are also known to produce anterograde amnesia in healthy volunteers and patients.[42,60] It is thought that the specific amnesic effect is somewhat independent of the general sedative effect responsible for psychomotor impairment,[61-65] and that the former may outlast the latter.[66,67] There is increasing evidence that most benzodiazepines primarily affect explicit memory systems involved in recall of specific events, but not implicit memory systems involved

in knowledge of language, procedures and motor skills that do not require deliberate recollection.[68-72]

The practical implication of this specific amnesic effect of benzodiazepine may be best illustrated by a number of case reports reviewed by Woods et al.[42] All patients experienced transient anterograde amnesia after taking initial doses of midazolam or triazolam. They were perfectly capable of routinely performing their daily, occupational activities while in this state, but they were completely unable to recall any events occurring for up to 24 hours after ingesting the medication.

Other reports have related how, in anxious but otherwise healthy individuals, benzodiazepines impaired cognitive functions to degrees commonly observed in patients with dementia.[73] Moreover, benzodiazepines occasionally provoked aberrant behaviour, such as hostility, and in some cases overt aggression, self-harming behaviour and mania.[74] The practical importance of these reports cannot easily be disregarded. Similar case reports were the reason for the forced withdrawal of triazolam from the market in several countries.

In summary, empirical studies have consistently demonstrated that behavioural toxicity occurs during benzodiazepine administration. Short-acting benzodiazepines affect psychomotor performance in the same way as long-acting benzodiazepines and do not necessarily represent an advantage in avoiding behavioural impairment. Clearly, residual impairment is less persistent for single doses of short-acting benzodiazepines, but this may be irrelevant to patients who receive multiple doses of short acting benzodiazepine anxiolytics to achieve steady-state plasma concentrations. Similarly, none of the newer benzodiazepine receptor ligands appears devoid of behavioural toxicity.

3.2 Antidepressants

Most antidepressants are thought to achieve their efficacy by increasing postsynaptic concentrations of monoamines. TCAs relieve depression by inhibiting the reuptake of noradrenaline (norepinephrine) and serotonin, whereas SSRIs preferentially inhibit reuptake of serotonin. Other antidepressants, such as mianserin and mirtazapine, enhance noradrenergic release by blocking presynaptic α_2 adrenergic receptors, or increase monoamine release by inhibition of monoamine oxidase type A (MAO-A), as with moclobemide.

Apart from reversible inhibitors of MAO-A (RIMAs) and some SSRIs, most antidepressants possess binding affinities for postsynaptic α_1 adrenergic or H_1 histaminergic receptors. These binding affinities are thought to play a major role in the development of sedation, causing cognitive, psychomotor and driving impairment during treatment.[39,75-78] TCAs also antagonise muscarinic acetylcholine receptors, and may cause amnesia.[79] Among the TCAs, impairment is most pronounced for the tertiary amines (e.g. clomipramine, amitriptyline, doxepin, imipramine, dothiepin) and less so for secondary amines (e.g. desipramine, nortriptyline), which posses very modest anticholinergic activity.[80]

These adverse effects are predominant, and superimposed on behavioural disturbances related to depression itself during the first weeks of treatment. Adverse effects are expected to dissipate after 2 to 4 weeks of treatment at about the same time as the therapeutic effect begins.[81-85] Most studies indicate that tolerance to the acute sedative effects of amitriptyline, mianserin, doxepin and maprotiline on psychomotor and driving performance develops in both healthy volunteers and patients within 1 to 3 weeks of treatment.[86-92] However, it is doubtful that tolerance completely abolishes the initial deficits or that new deficits fail to emerge during the course of maintenance antidepressant therapy. The persistence of certain kinds of impairment has been shown in several empirical studies with both volunteers and depressed patients.[93-97] Moreover, as discussed in section 2, epidemiological surveys have shown that patients using long term antidepressant therapy are at a relatively high risk of becoming involved in various types of accidents. Similarly, specific anticholinergic effects of antidepressants on memory functions seem resistant to tolerance.[98,99]

The latest generation of antidepressants, such as RIMAs (e.g. moclobemide and befloxatone), SSRIs or venlafaxine, have little or no affinity for histaminergic, adrenergic or muscarinic receptors. This is the main reason why therapeutic dosages of RIMAs have never been shown to adversely affect cognitive and psychomotor function.[87,93,100-103] Generally, SSRIs have little effect on performance as well.[86,95,96,104] Mild psychomotor and memory impairment is most likely to occur for those agents possessing some affinity for muscarinic receptors, such as paroxetine and fluvoxamine,[86,90,105-109] or α_1 receptors, such as nefazodone.[110,111]

This is not to say that performance impairment can never occur with the more selective reuptake inhibitors that have no specific affinities for muscarinic, adrenergic or histamine receptors, as in the case of venlafaxine and fluoxetine. Volunteers' performance in actual driving and psychomotor tests remained virtually unaffected by both drugs, but their vigilance progressively decreased over 2 weeks' treatment with venlafaxine and 3 weeks' treatment with fluoxetine.[112,113] The relevance of this finding is unknown, but it cannot yet be disregarded. Plasma fluoxetine concentrations are known to accumulate over 4 to 8 weeks before steady-state is achieved.[114,115] Accumulation over time may well account for a belated emergence of adverse events.

The long term use of SSRIs has been associated with unusual adverse behavioural reactions in a number of case reports. Most of them implicate fluoxetine for the simple reason that it is the most widely prescribed. Anxiety, insomnia and agitation have been most frequently reported,[116-121] sometimes in combination with confusion and amnesia,[122-125] in patients taking fluoxetine. Inhibitory reactions, such as apathy, indifference and loss of initiative have been reported in patients taking either fluoxetine or fluvoxamine.[124] In one case, a 60-year-old woman retired as a piano teacher when she failed to learn piano pieces and a foreign language in preparation for a trip. Withdrawal of fluoxetine resulted in the resumption of her career as a piano teacher, along with learning the language she had been unable to master.[126] Fluoxetine has also been reported to provoke aberrant behaviour, such as paranoia, hostility and aggression;[127,128] cessation of fluoxetine resulted in an abatement of the respective problem, which usually returned on rechallenge.

In summary, empirical data consistently demonstrate that most antidepressants impair psychomotor or memory function and diminish their users' driving performance as measured in a standard driving test. Impairment is most pronounced for antidepressants possessing multiple antagonistic affinities for histaminergic, adrenergic and muscarinic receptors, such as the TCAs, which generally produce a higher level of sedation than antidepressants that have selective affinity for serotonin and noradrenaline transporters. However, even in the absence of sedation, behavioural toxicity can still occur with the more selective drugs, as shown by their effects on vigilance and the adverse motivational and emotional reactions noted in case reports.

3.3 Antipsychotics

Phenothiazines, such as thioridazine and chlorpromazine were the first dopamine D_2 receptor antagonists used in the treatment of schizophrenia. Most produce profound sedation by blocking dopaminergic neurotransmission required to sustain arousal. Additional blockade of histaminergic, anticholinergic and adrenergic neurotransmission further contributes to the sedative potential of phenothiazines and results in a high prevalence of concentration difficulties, fatigue and daytime sleepiness among users.[129] Studies examining the effects of phenothiazines on psychomotor performance are rare, but those that have been conducted confirm the expected detrimental effects on psychomotor performance and wakefulness.[130-134]

Since their introduction in the 1950s, these drugs have largely been replaced by more selective and potent dopaminergic drugs such as haloperidol. Like any dopaminergic receptor antagonists, haloperidol produces sedation, which is responsible for psychomotor impairment observed in

empirical studies employing patients or healthy volunteers.[133] Nevertheless, selective dopaminergic antipsychotics cause less profound sedation, and are less capable of affecting a variety of mental functions and dependent behaviours, compared with antipsychotics that also block postsynaptic receptors within other monoamine systems. This was repeatedly demonstrated for the substituted benzamides, which selectively block dopaminergic neurotransmission at D_2/D_3 receptors. The first of its kind, sulpiride, only produced minimal psychomotor and cognitive impairment in conventional tests.[130,135,136] Therapeutic dosages of its successors, remoxipride and amisulpride, consistently impaired psychomotor performance in healthy volunteers, but generally less so than subtherapeutic dosages of chlorpromazine or haloperidol.[137-142]

Reappraisal of clozapine treatment, has led to the development of a new generation of comparable antipsychotics that, besides affinity for dopaminergic receptors, possess multiple mechanisms of action. Clozapine, risperidone, olanzapine and quetiapine (seroquel) are potent antagonists of 5-HT_{2A}, H_1 and α_1 receptors, and, in the case of clozapine and olanzapine, muscarinic acetylcholine receptors as well. Sertindole was shown to possess strong antagonistic activity at α_1 receptors.[143-145] None of these antipsychotics has been properly investigated in studies designed to reveal effects on psychomotor and cognitive function, although in theory, all of them should produce deficits in performance similar to those observed with the earlier phenothiazines. Clozapine, for example, was shown to cause EEG changes indicative of sedation.[146] Another indication came from a multicentre clinical trial evaluating the effectiveness of 5 dosages (1, 4, 8, 12 and 16 mg/day for 8 weeks) of risperidone in over 1300 patients.[147] At the lowest dose, 23.5 to 28.8% of the patients complained of concentration difficulties, increased fatigue and sedation, while 19% complained of memory problems. At the highest dose, these percentages rose to 42 to 48% and 34% respectively.

Antipsychotics may also induce additional inhibitory behavioural reactions, such as indifference, and diminished concentration, affect and motivation, by blocking central D_2 receptors.[148,149] These psychological adverse effects, nowadays referred to as neuroleptic-induced deficit syndrome (NIDS),[150] are among the most neglected in patients with schizophrenia, because of their similarity to the negative symptoms of the disorder. As a consequence, the former may easily be mistaken for the latter and go undetected. This apparently confounding situation contributes to the currently growing belief that the principal action of antipsychotics may be best studied in healthy volunteers.[151] The latter do not experience negative symptoms and may thus serve as a better sample to establish the existence of NIDS.

To date, only one group of investigators[142] has followed this approach. They treated 17 volunteers for 5 days with haloperidol 4 mg/day, amisulpride 50 or 400 mg/day, or placebo, in order to investigate the effects of the drugs on, among other things, affective function. This was assessed using the Positive and Negative Symptom Scale (PANSS) and Naber's Subjective Well-Being under Neuroleptics (SWN) scale. Haloperidol, but not amisulpride, significantly elevated ratings of negative symptoms and general psychopathology on the PANSS, and reduced feelings of well-being on the SWN scale. Since both haloperidol and amisulpride are selective D_2 receptors antagonists, the absence of negative symptoms during amisulpride treatment was remarkable. It may be explained by evidence suggesting that amisulpride preferably attaches to receptors in the limbic system, rather than the striatal system, whereas haloperidol does not discriminate between regional subpopulations of dopamine receptors.[152,153]

In summary, empirical studies have demonstrated the ability of antipsychotic drugs to produce profound sedation and disrupt psychomotor and cognitive function through blockade of central dopaminergic receptors. The adverse effects of these agents on performance may further increase if neurotransmission within other monoamine or cholinergic systems is simultaneously blocked. Other dopaminergically regulated adverse reac-

tions, such as psychological disturbances, may additionally diminish a patient's ability or motivation to initiate behaviour. These adverse reactions seem least likely to occur during treatment with the substituted benzamides, although comparative data are currently rather limited.

3.4 Antihistamines

Histamine is another neurotransmitter responsible for the maintenance of waking arousal. First-generation antihistamines, such as diphenhydramine, triprolidine, clemastine or chlorpheniramine, are strong antagonists of muscarinic and H_1 receptors. All first-generation antihistamines induce somnolence and have repeatedly been shown to diminish cognitive, psychomotor and driving performance in healthy volunteers.[35,76,154] Impairment might be of even greater clinical significance in patients when the allergic disorder *per se* adversely affects CNS function, as suggested by studies in which a reduced learning ability of children and young adults with allergic rhinitis was exacerbated by diphenhydramine.[155,156]

Second-generation antihistamines are less lipophilic and cross the blood-brain barrier more slowly than their predecessors. Their impairing properties have been extensively assessed using the standardised actual driving test described in section 3, usually after both single and repeated doses of up to 4 times those currently recommended.[35,157] Results of these studies show that the extent to which these antihistamines cause sedation varies with the drug, its dosage and the duration of therapy. Several agents (acrivastine, cetirizine and mizolastine) mildly affected driving performance when given at therapeutic doses. Others (ebastine, fexofenadine, loratadine and terfenadine) did not have significant effects after being taken in recommended doses, but had measurable effects after doses that were twice as high. Mild impairment is sometimes overcome by coadministering the sympathomimetic decongestant pseudephedrine,[35,158] but the combination may also be associated with a higher frequency of subjective adverse effects, such as insomnia and other symptoms of CNS stimulation.[76]

Interestingly, nocturnal doses of chlorpheniramine have failed to affect actual driving performance when assessed the next morning.[159] This result is somewhat surprising, given the fact that the drug possesses an elimination half-life (>24 hours) long enough to sustain its pharmacological activity for a considerable period over the day. Similarly, as noted before, Ray et al.[9] found no association between the use of antihistamines to promote sleep (half-lives ≤13 hours) and the risk of hip fracture in elderly patients in their epidemiological survey. A possible explanation for this discrepancy may come from another study examining the effects of sleep on performance of volunteers previously treated with diphenhydramine.[160] Performance was initially impaired, but this resolved after a 60-minute sleep.

These results suggest that antihistamines specifically activate sleep mechanisms, which in turn may be reversed by a period of sleep. The mechanism by which this occurs is still largely unknown, but might be mediated by restoring the balance between histamine release and synthesis. Histamine is synthesised in cell bodies located in the posterior hypothalamus, and transported to axon terminals throughout the cerebral cortex and limbic system.[161] Transmitter release without reuptake is more or less constant during the waking period, but ceases abruptly with the onset of slow-wave sleep. Synthesis continues unabated and may even be greater during sleep. Thus, histamine availability at postsynaptic H_1 receptors may be greatest shortly after awakening. In that case, antihistamines would be less likely to block histaminergic transmission at this time than others.

In summary, it can be concluded from empirical studies that second-generation antihistamines possess a major advantage over first-generation agents in that they produce considerably less behavioural toxicity. The differences between the different second-generation antihistamines should not be exaggerated, but cannot be ignored. Regulatory authorities from Europe and the US have recognised these

differences and produced appropriate warnings for some of the second-generation antihistamines.

3.5 Other Drugs

Other classes of drugs are known to cause adverse behavioural reactions in individual cases. It is generally accepted that β-blockers can cause depression and that common adverse events such as fatigue, somnolence and dizziness diminish patients' quality of life.[162,163] Anticholinergic agents, opioids, NSAIDS, other antihypertensives and H_2 antagonists have all been implicated in disturbances of consciousness and changes in cognition that are indicative of drug-induced delirium or dementia.[73,164] Manic reactions have been associated with antiparkinsonian agents, antimalarials and sympathomimetics.[165]

4. Management and Avoidance

Any solution to the problem of behavioural toxicity should start with recognising the fact that some drugs place patients at risk during normal day-to-day activities or limit their social and cognitive functioning in an unacceptable manner. Much of the epidemiological or empirical evidence cited in this review has contributed to the growing awareness of this problem among physicians. In particular, inappropriate drug prescription in the elderly has received considerable attention from experts in fields of geriatrics and pharmacology. Beers et al.[166] have explicitly identified individual drugs (e.g. diazepam, flurazepam, chlordiazepoxide, amitriptyline, dextropropoxyphene) that should be totally avoided in the elderly because of their detrimental effects on behaviour.

Today, Beers et al.'s list[166] is widely accepted and was recently used to estimate the amount of inappropriate drug prescribing for elderly individuals living in the US in 1987.[167] Among the study population, 23.5% received at least one of the drugs considered inappropriate; benzodiazepines (long term) and amitriptyline were among the most commonly prescribed of the contraindicated drugs. These findings may not be totally relevant to the situation in 1998, since overall patterns of drug prescription are different today. Nevertheless, there is also little reason to assume that physicians are currently more aware of the impairing properties of any of the alternative, more recently developed, drugs.

To be maximally effective, lists of contraindicated drugs require regular updating to incorporate recently published material, particularly empirical studies that identify problematic drugs before they become widely available. It is of crucial importance, therefore, for drug manufacturers to conduct research to determine whether the drugs they advance through the registration process are in any way behaviourally toxic, and for drug regulators to ensure that physicians are properly informed of its results. Physicians should subsequently consider alternative treatments in the light of this research, or try to minimise behavioural toxicity when no alternative is available. The following recommendations may be helpful to achieve that goal.

1. Minimise the number of drugs prescribed to reduce the chances of behavioural toxicity. Various studies have shown that it is common for elderly patients to take 7 or 8 prescription drugs daily.[168] Obviously, these patients are at increased risk of experiencing adverse drug reactions. Unfortunately, it is not as common for geriatric polypharmacy to be carefully monitored. The consequences can be severe, as illustrated by Larson et al.,[169] who identified 35 patients with drug-induced cognitive impairment among 308 outpatients evaluated for suspected dementia; 27 were taking one drug known to cause cognitive impairment and the others were taking 2 or 3 such drugs. Benzodiazepines were implicated in nearly half of these patients, with antihypertensives and major tranquillisers as the other main offenders. The number of different drugs prescribed was a major risk factor in those experiencing drug-induced cognitive impairment. In all patients, cognition improved when these drugs were withdrawn.

2. Determine the likelihood of a pharmacokinetic interaction between drugs if polypharmacy cannot be totally avoided, and adjust treatment accordingly. An increasing body of evidence has

shown that drugs inhibiting catabolic enzymes of the cytochrome P450 (CYP) system cause elevated plasma concentrations of any concurrently administered drug that depends on the same enzyme for oxidation.[170] For example, SSRIs are inhibitors of CYP2D6 and CYP3A4 and have the potential to cause clinically important interactions with substrates of these particular isozymes (e.g. TCAs, benzodiazepines, antipsychotics, β-blockers and opioids). Moclobemide is a potent inhibitor of CYP2C19, implicated in the demethylation of diazepam and the hydroxylation of its metabolite, nordiazepam. The practical implications of such interactions have recently been demonstrated in a number of empirical studies. Combination of fluoxetine or nefazodone with alprazolam resulted in accumulation of the latter in plasma and progressive psychomotor impairment in healthy volunteers.[171,172] In a group of depressed outpatients treated for 6 weeks with fluoxetine or moclobemide, driving performance deteriorated in those who were concurrently receiving a benzodiazepine metabolised by a CYP isozyme that would be inhibited by their respective antidepressant.[38]

3. Behavioural impairment may be minimised when drugs are administered in nocturnal doses. Sedating anxiolytics have to be taken in divided daily doses, but other psychoactive drugs do not. Residual effects of sedative antidepressants and antihistamines might be reduced or avoided when administered in nocturnal doses. Several studies[93,112,173-175] have shown that daytime driving or psychomotor performance during medium term treatment with nocturnal doses of amitriptyline, dothiepin, mianserin and mirtazapine were was virtually indistinguishable from that during placebo treatment. Similarly, nocturnal administration of the antihistamine chlorpheniramine to healthy volunteers did not impair their driving performance when tested the next morning.[159]

4. Adjust the recommended dosage regimen to a patient's individual response to the drug in order to minimise the possibility of behavioural toxicity. In particular, the elderly are more vulnerable to drug effects than their younger counterparts because of age-related decrements in metabolic, psychomotor and cognitive function.[73,176] Short periodic evaluations of the latter, before and during treatment, are helpful in establishing and verifying the choice of dosage. If the means of objective assessment are not available, much valuable information can be gained from a patient's subjective experience, or from observations by persons in close contact with the patient.

5. Educate patients on the potential risks of the drugs they receive. Prescription of potentially impairing drugs should be avoided when possible. When impossible, as in the absence of a viable alternative, the patient should receive an appropriate warning from the prescribing physician concerning the possible detrimental effect of the drug on normal daily performance at work, on the road or at home. The patient should be instructed to avoid driving a car or to operate hazardous machinery, in general, and always restrain from these activities whenever he or she feels unusually sleepy, dizzy, lethargic or otherwise 'not themselves'. The benefit of educating potential users was shown by a group of investigators[177] who reported the absence of a significant association between psychoactive drug use and work-related accidents in 1989 to 1990 among employees of the Utah Bacchus work facility of Hercules Aerospace in the US. This study was undertaken to confirm the effectiveness of a medication self-reporting programme that was introduced by the plant's management in 1987. Because of the recognised high cost of human errors in this workplace, a list of commonly used, potentially impairing over-the-counter and prescription drugs was compiled and distributed to the workers. They were advised to use less-impairing alternatives. If they had to use impairing drugs because of a lack of better alternatives, the workers were assigned to less hazardous duties. These workers were not only protected from risks associated with the use of impairing drugs, they were also better informed than most about the existence of those risks.

5. Conclusion

Behavioural toxicity is relatively common among medicinal drug users. Results of epidemiological and empirical research converge on the fact that drugs frequently produce adverse effects that prevent their users from performing everyday operations in an efficient or normal manner. As a consequence, they are at higher risk of becoming involved in accidents, which in turn may lead to injuries and, even worse, death.

Unfortunately, behavioural toxicity often goes unnoticed by users themselves and their prescribing physician. Clearly, more effort from regulatory authorities is needed to increase patients' and physicians' awareness of the detrimental drug effects on behaviour in general, and of differences between the effects of different drugs and dosages. Much of this information can be gained from experimental literature comparing individual drugs' effects on performance. However, this is presently incomplete, since most research conducted until now pertained to psychiatric drugs. Other drug classes have not yet been properly investigated, although many are suspected or known to decrease a patient's quality of life.

In the interest of the patients, it should be the responsibility of drug manufacturers and regulators to always identify the potential of a drug to produce adverse effects that can be considered behaviourally toxic.

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