Title: Medicinal Drugs and Traffic Collisions: Evidence, Issues and Challenges
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Abstract
Although most industrialized countries have been more interested in alcohol and illicit drugs and driving, in recent years attention has begun to focus on the potential impairing properties of medicinal drugs. Descriptive epidemiological studies examining the prevalence of drugs and alcohol have found medicinal drugs, such as benzodiazipines, to be commonly used among crashed drivers. For example, benzodiazapines were found in 12.4% of injured drivers in a Canadian study and was the second most common drug detected and were also the second most common drug found in an Australian study. Despite this high prevalence, which begs the need for case-control studies and continued experimental and laboratory research, only Europe seems to be conducting the bulk of the research on this topic. This is particularly curious, given the ageing population who are more likely to be taking medicinal drugs than alcohol or illicit drugs, and the trends in western countries to de-hospitalization, day-surgeries, and community-based living of frail elderly. This paper will provide a brief synopsis of the epidemiological and experimental research on medicinal drugs and impairment. This will be followed by a discussion of the issues and challenges in conducting research on medicinal drugs and driving.

INTRODUCTION

Traffic collisions are a major cause of morbidity and mortality in the world. Medicinal drugs can impair mental and physical functions and thus contribute to road accidents[1]. Although more information is available on the role of alcohol than drugs in motor vehicle collisions, in recent years there has been a growing interest in the role played by medication in traffic safety[2] . For example, the state of Victoria calculated the economic burden of road crashes that were medicinal and illicit drug-related, either alone or in combination with alcohol. The economic burden was $143 million in 1993, or one-eighth of the total economic burden of road crashes[3]. Similarly, in Europe De Gier[4] estimated that if 10% of the adult population is driving under the influence of behaviourally toxic medications and has double the crash risk, those medications are estimated to cause 4500 deaths, 13,500 injuries and 6.3 billion Euro dollars in damage to European society each year. It is noteworthy that no similar governmental interest in medications and impairment is evident in North America. This is despite the fact that De Gier[5] has estimated that at least 10% of all people injured or killed in road crashes were taking some sort of psychotropic medication. However, unlike alcohol, the relationship between medication and driving is extremely complex and needs to be clarified[2]. Alvarez[6] indicates that there are nine main drug groups that because of their pharmacological properties could impair driving performance, (see Table 1) although for many medications that fall within these groups, the actual research on the degree of impairment is not available. However, many medicinal drugs can directly affect the central nervous system (CNS) and as such can directly affect psychomotor performance and thus driving. For example, the Road Safety Committee Parliament of Victoria[3] in their inquiry into the effects of drugs on road safety indicated that of the 250 most frequently prescribed medications, about A25% are either known or suspected of being capable of impairing their user=s skills.≅ These medications can be categorized very simply into two groups depending on the ways in which they affect the central nervous system (CNS); CNS depressants and CNS stimulants[7]. *Depressants*, which include tranquillizers (e.g., benzodiazepine derivatives, and barbiturates), narcotics (e.g. opiates and methadone), antidepressants, first generation antihistamines, etc., produce the predominant effects of relaxation and sedation[7]. *Stimulants* include drugs such as amphetamines. The main effect of these drugs is to *stimulate* transmission at the synapses that use epinephrine, norepinephrine, dopamine or serotonin as a transmitter[8]. Although drugs within these two categories have similar neurochemical effects, their behavioural effects can differ considerably. All the psychoactive drugs just described, due to their CNS effects, have the potential to impair skills needed for driving and consequently, to be a causal factor in motor vehicle collisions. Moreover, not only can medicinal drugs directly effect psychomotor performance, but the appearance of certain adverse effects during treatment may also impair driving performance (Table 2). Over the last two decades research been conducted on a range of medicinal drugs and its affects of psychomotor performance. A review of all the research is simply not possible in the limited time today. Indeed there are a number of review articles on the topic including an excellent review by Hunter et al., from the Dept. for Administrative and Information Services, South Australia. Moreover, since 1980 the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) has published more than 250 drugs and driving studies on various issues, such as prevalence among drivers, analytical aspects and drug screening, effects on skills and performance drug, and administrative, legal and medical aspects[5]. (see Hunter et al.[9] for a

detailed, tabulated review of samples, methods and findings of epidemiological and experimental studies, Ferrara et al.[1] for a review of laboratory and epidemiological studies of psychoactive substances and driving, and Lillsunde[11] for a review of epidemiological studies. For a general review on the influence of illegal drugs on driving within the context of European Community regulations[7], Woods et al.[12] provide a comprehensive review of benzodiazepines use and consequences, including adverse driving outcomes.)

This paper will briefly review methodological issues related to research on medicinal drugs and driving, summarize some of the key findings on medicines and impairment and discuss emerging issues to be considered within the framework of changes to the health care system and shifting demographics.

1. METHODOLOGICAL APPROACHES

Despite the proliferation of studies on the topic, the determination of medicinal driving impairment is difficult. The combination of laboratory/experimental and epidemiological studies provides the best information to understand the causal connection between medications and traffic crashes[13 14]. Experimental studies, using a double-blind approach and random assignment of subjects to either an active drug group or to a non active drug (placebo) group, can determine the nature of impairment produced by specific medications and its impact on performance tasks. Experimental studies usually require subjects to perform laboratory psycho-motor tasks or driving tasks on simulators or on closed road circuits or regular roadways. The main limitations of laboratory and simulator experiments relate to external validity issues because medicinal drug use and the driving environment in experimental designs may not reflect actual patterns of medicinal drug use and driving in the real world [7 15 16]. Therefore, experiments that assess a driver=s skill performance may not be applicable to real driving situations. Poor generalizability of experimental research to driving and road crashes (i.e., external validity) can also emerge in relation to the use of healthy volunteers (versus actual medication-users), types of control drugs used, duration and dosages of medications, types of psychomotor tasks, and other statistical and methodological issues [7 17]. In recent years, however, experimental research on medicinal drugs and driving through the use of Aon-the-road≅ driving experiments and medication using individuals as subjects has reduced many of the problems described above [15 18 19].

Epidemiological studies address the issue of incidence/prevalence of drug use among various subpopulations of drivers in the real world. The two major epidemiological research goals are descriptive and analytic. Descriptive epidemiology provides an indication of the extent or magnitude of the problem, and as such, guides experimental research by detecting the substances in persons involved in collisions. If a particular medication is not detected in crash-involved drivers, studying the impairing properties of the medication may be of little practical value [13 14]. Descriptive epidemiology can also provide important trend data on the changing patterns of medication use and driving[14].

Analytic epidemiology seeks to determine which medications are over represented in crash-involved drivers. The more methodologically valid approach is the case-control study where crash involved drivers are compared to non-crash involved drivers matched for age, sex and location of crash. Another related approach most typically used for fatal crashes is through responsibility or culpability analysis. Within a group of fatal drivers, the proportion of those judged responsible for crashes in the medication positive group is compared to the proportion responsible in the medication negative group. The resulting odds ratio helps us understand whether the specific medication in question was related to the crash, although a methodological problem with culpability analysis relates to the difficulty in assessing 100% culpability to one driver in multi-vehicle crashes. Both these methods have limitations with the interpretation of causality since the relationship established is one of association [13 14]. Thus, although the relative risk of crash involvement for medication-using drivers could be higher than for non-medication using drivers, other factors, such as the illness for which the medication was prescribed, may explain both medication use and high crash risk. For example, O=Hanlon and Freeman[20], analyzing Nelson=s data from the Mayo Clinic in Rochester found that depressed patients were 1.8 times more likely to be involved in traffic crashes than those suffering from any other disorder. However, patients treated with tricyclics were less likely and those not treated were more likely to become crash victims. Yet, when type of tricyclic was examined, O=Hanlon and Freeman[20] found that patients using amitriptyline drove with a crash risk 4.9 times higher than those taking other tricyclics or nothing.

An additional limitation of case-control drug studies relates to the measurement of pharmacologically active drugs in the crash victim [14 21 22 23]. Current tests, be they urine, blood, saliva, hair, indicate the presence and historical use of a drug but not whether the drug concentration and pharmaco-kinetics was such that it caused behavioural impairment. Blood tests can correlate more closely with impairment depending on the drug; however, they are more invasive[24] and are typically only used in fatal crashes/trauma. Although the police in many jurisdictions have legislation which allows them to ask for blood and urine samples, in most jurisdictions the police do not have the

legislative authority to require a driver to take an impairment test and provide a blood and/or urine sample, and as such many officers are reluctant to obtain samples.

Another epidemiological approach involves *survey research*, where subjects are asked to report on medication use and driving. For example, they might be asked to indicate if they believe their medication use contributed to a traffic crash. Here again, any identified relationship between self-reported medication use and traffic collisions would be correlational and not causal. Survey methods are generally considered less valid than methods using drug tests because many people under report, forget or lie about their medication use.

Another problem of determining crash risk associated with different medications in epidemiological studies relates to multiple medication use, which is common. Multiple medication use makes it difficult to disentangle individual medication risks and to assess possible additive affects. A final element with regards to medicinal drugs relates to the therapeutic impact of the drug. Studies are needed where the potential dangers of medications such as behavioural impairments are weighed against the potential improvement in the condition for which the medication was prescribed[25]. As Del Rió and Alvarez[7] summarize, medications can cause deterioration of driving skills of varying degrees depending on factors, such as method and type of medication taking, expectations, multiple medication taking and issues of dependence related to withdrawal and overdose, all of which is exceedingly hard to measure and consequently to determine the causal link between medication use and motor vehicle collisions.

2. INCIDENCE OF MEDICATIONS AMONG DRIVERS

There have been a number of descriptive epidemiological studies examining the incidence of drug use in traffic collisions and violations. These studies have noted the proportion of drivers with positive drug tests in collisions[26 27 28 29 30 31 32 33 34 35 36], driver fatalities [33 37 38 39 40 41 42 43 44 45 46], reckless driving[47], suspicion of driving while impaired by drugs [27 48 49 50 51 52], impaired driving [33 53] and impaired pedestrians[54]. A few roadside studies involving drug tests have also been conducted with general drivers [29 55 56 57].

Recent roadside survey studies from Italy and the Netherlands found illicit drugs most common 56 58, while a roadside study from Quebec, Canada found cannabis, benzodiazapines, cocaine, opiates, barbiturates and amphetamines in that order [58]. Women and drivers over 35 were overrepresented as benzodiazapine users.

Studies of driver casualties find that although alcohol always is the most prevalently identified drug, both therapeutic drug categories of depressants and stimulants, have also been detected. Benzodiazepines were found in 12.4% of injured drivers, second only to cannabis in a Canadian study[35]. Similarly Longo et al.[31] found that benzodiazapines were second to cannabis in their study of injured drivers, but benzodiazapines were detected in 2.7% of injured drivers in an Australian study. In summary, generally cannabinoids and benzodiazepines were the most frequently detected drugs, after alcohol, in driver casualty studies, although in the US benzodiazepines were rare: rather illicit drugs (cannabinoids and stimulants) were more common [11 33 59].

Studies of impaired driving offences have observed similar patterns, despite the fact that these data could be biased by sample selection: that is, they do not represent a random sample of drivers but rather a sample that the police identified as possible impaired drivers. In New South Wales, Australia, for drivers suspected of being drug impaired, the most common drug detected was cannabis, followed by minor tranquillizers, heroin and amphetamines [60]. In Denmark, the most commonly detected drugs from samples of police suspected drug impaired drivers were overwhelmingly benzodiazepines, followed by morphine, methadone, cannabinoids and amphetamines[61]. Similarly, in Norway benzodiazapines were found in 30%-64% of suspected drugs and driving cases [27 48]. The prevalence of drugs among suspected drug-impaired drivers is similar to the driver casualty studies. Cannabis or depressants (including benzodiazepines, opiates, morphine) are typically the most commonly found drugs, although in some jurisdictions stimulants are more common than depressants [52 62]. Rates of benzodiazepines generally ranged from less than 1% to 64% among arrested, injured and fatally injured drivers within different jurisdictions [12 27 48]. Moreover, although alcohol-related impaired driving and fatalities seem to be decreasing, drug-related impaired driving and fatalities seem to be increasing [3 58].

These studies of drug use among collision-involved drivers or violators only provide prevalence data. They present no information on whether these drug-using drivers involved in collisions or violations are over-represented in their drug use compared to drivers not involved in crashes and violations. Experimental and analytic epidemiological studies provide greater clarity on various drugs and their impairment properties and crash risk.

3. PHARMACOLOGICAL EFFECTS, EXPERIMENTAL AND ANALYTIC EPIDEMIOLOGICAL STUDIES

Experimental psychopharmacological studies have shown adverse effects of many drugs on driving in controlled environments and driving-related performance variables [7 22 25 63]. Based on current knowledge, certain classes of psychotropic medications capable of producing impairment in experimental studies are: anaesthetics, antidepressants, antihistamines, cardiovasculars, hypnotics, narcotics, phycosometics, sedatives, and stimulants [64 65 66 67 68 69 70 71 72]. Experimental studies have also shown that some medications produce large performance deficits, while other medications produce minor changes in performance or even performance improvements.

Multiple drug studies:

A limited number analytic epidemiology studies have been conducted where different drugs are examined in the same study, either using the case-control method [29 73 74] or methods used to ascribe crash responsibility [31 75]. Both types of studies have found increased odds-ratios for a variety of crash-related measures, such as crash involvement, injury severity, and fatality for some drugs, but the results of the studies are mixed.

Generally speaking, case-control studies indicated that compared to non-crashed drivers, injured or fatally injured drivers were more likely to test positively for benzodiazipines [29 73 74], although these findings must be tempered by the fact that various methodological problems exist with these studies such as small sample sizes, multiple drug use or lack of statistical analyses. Notably, alcohol was frequently found in combination with medicinal and illicit drugs.

Culpability studies have found mixed results for benzodiazapines and possible effects for stimulants. Two recent studies were conducted by Drummer[75] and Longo et al.[31] in Australia. Drummer[75], examining the blood samples of driver fatalities, found those with opiates were 2.4 times more likely to be judged to be responsible for crashes; however, this was not significant. Those with stimulants or benzodiazepines also had non-significant odds ratios of 1.4 and 1.0, respectively. Longo et al.[31], on the other hand, conducting a case-control study with blood samples from 2500 non-fatally injured drivers in South Australia found a clear clausal role for alcohol and benzodiazapines when those with very low concentrations were excluded. Few drivers tested positive for stimulants and no clear evidence was available for stimulants. Thus the results are mixed and may well reflect the differing impairing properties of different types of benzodiazapines which have been documented in the experimental literature.

Single drug studies: depressants and stimulants.

(a) Depressants

The most commonly studied subclass of depressants on psycho-motor performance are benzodiazepine derivatives [12 76 77]. It is also the medicine most commonly detected in descriptive epidemiological studies. Woods et al.[12] have noted over 20,000 papers on benzodiazepines since the 1960's and concluded that the degree of effect depends on the type of benzodiazepine and the types of psychomotor tasks used. As well, Berghaus and Guo[78], conducted a meta analysis of over 1,000 experimental studies of drug induced performance problems for prescribed drugs and also concluded that performance varied, depending on the type of benzodiazepine. Greater sensitivity was found in measuring impairment for on-the-road tests of benzodiazepine use than for simulator driving or laboratory psychomotor tasks[13 15 79 80]. Newer benzodiazepines showed fewer behavioural side effects than older ones [13 63]. Interestingly, O=Hanlon et al.[80] found that anxious patients undergoing treatment showed no important differences between volunteer=s and patients= baseline and/or placebo performances and both groups responded similarly to comparable drug/doses. Moreover, the impairment observed by at least some of the benzodiazapines did not diminish with continued treatment.

Several analytic epidemiological studies have been conducted where traffic records of groups with prescriptions for tranquillizers were compared to non-prescribed groups. Generally, significantly increased odds ratios for crash risk have been found for benzodiazapine users [81 82 83]. For example, Hemmelgarn et al.[82], conducting a nested case-control design with a cohort of 224,734 Quebec (Canada) drivers over the age of 67, found that long half life benzodiazepines were associated with about a 45% increased risk of crashes, with a 26% increased risk for those who had been using benzodiazepines for a longer time period. Short half life benzodiazepines were not associated with an increased risk of crashes. However, Leveille et al.[84] found no relationship between benzodiazepine use and crashes. Burns[64] summarizes the literature on benzodiazapines stating that A the role of these drugs in traffic crashes should not be dismissed...Because the very large number of prescriptions written annually for these drugs is largely for outpatients, they affect people going about their daily routines. For most outpatients that includes driving. All the evidence taken together suggests the response to the question Ashould we worry?≅ is Ayes≅ for this category of drugs≅.

Another subclass of depressants commonly detected in among crashed and/or arrested impaired drivers are narcotics, which include a wide class of drugs from natural substances such as opium, morphine, and codeine, to synthetically produced substances, such as methadone and meperidine. Opiates depress neurotransmitter functioning

and yet low to moderate doses of opiates do not greatly affect human performance[8]. Tolerance to these drugs develops quickly, and first time doses are much more likely to produce cognitive impairments than subsequent doses[76].

Studies on the impact of methadone on driving performance and crashes have been mixed [85 86 87], but again methodological problems limit the conclusions that can be drawn.

Although not commonly detected among crashed and/or arrested impaired drivers are depressants such as antidepressants and antihistamines. Tricyclic antidepressants have been found to impair driving-related skills in experimental studies. As Burns[64] indicates, it is the associated drowsiness of medications such as amitriptyline and trazodone, that induce the impairment. However Robbe and O=Hanlon[88] reported that the effects of amitriplyine were almost gone by the eighth day of dosing. The newer generation of antidepressants such as fluoxetine, have not been found to cause drowsiness or impairment of driving-related skills[64]. Burns[64] concludes that given the widespread use these newer generation of antidepressant medications, Ait can be assumed that the problem of antidepressants and impaired driving is less than it was a decade ago≅.

Benzodiazapines, narcotics and antidepressants are only available by prescriptions in most countries, which restricts accessibility. In contrast, many antihistamines are available over-the-counter (OTC). Although a high prevalence of antihistamines have not been detected among crashed and/or arrested impaired drivers, the first generation H-1 blockers cause drowsiness, a finding demonstrated in both laboratory and on-road studies[64]. Diphenhyramine, in particular has been shown to impair driving performance and it can be purchased OTC in many products including allergy and cold symptoms, OTC sleeping and motion sickness pills. However, wide variation has been found in susceptibility to drowsiness and the newer generation of antihistamines show little driver-related impairment[70].

(b) Stimulants

A commonly used stimulant is amphetamine, but also includes such widely used substances as caffeine and cocaine. Most laboratory studies have failed to find performance deficits associated with this class of drugs[1]. In fact, performance improvements have been found in some studies for endurance tasks [8 76 89 76]. Laboratory evidence on the performance enhancing effects of stimulants is inconclusive and researchers have suggested that subjects may perceive performance improvements while no real improvements have been noted [90]. Experiments have shown that five types of stimulants, including caffeine, did not differ in terms of their impact on performance[91], although as Burns[89] states with regards to her research on cocaine, the effects are not unidimensional in direction in that the effects of overstimulation on performance may be qualitatively, as well as quantitatively different from the effects of mild-to-moderate stimulation. As well time-of-day appears to be a critical variable. Moreover, stimulants in combination other drugs have been found to cause impairment of driving and performance in secondary tasks[92 93]. Ellinwood and Nikaido[93] write: Athe realistic understanding of the nature of stimulant-induced effects requires the scientific perspective of all aspects of drug use, including acute and chronic dosing conditions, behavioural sensitization and tolerance and drug withdrawal.≅

CONCLUSIONS

One clear conclusion from a large number of laboratory and experimental studies is that the pharmacological properties and effects on psycho-motor performance for the medications examined in this paper vary quite considerably. Laboratory studies have shown that benzodiazepines, and older generation antidepressants and antihistamines impair performance, while the findings for methadone are mixed and stimulants may enhance performance. The epidemiological evidence of medications as a causal agent in collisions is largely inconclusive but this evidence along with experimental studies allows us to draw tentative conclusions. Experimental studies show decreased performance with use and epidemiological studies generally show that benzodiazepine users are up to 6 times more likely than non-users to be in crashes although some studies failed to find it a significant risk factor. The risk of crashes likely varies depending on the specific type of benzodiazepine, the half life of the drug, and duration of use. The results of methadone studies are more variable and definitive conclusions can not be drawn regarding the risks related to driving.

Stimulants have not been shown to adversely affect performance in experimental studies and can actually enhance performance, particularly for endurance tasks. However, long term use could affect personality characteristics, which could increase the likelihood of crashes. Also these medications can be addictive and withdrawal could enhance traffic risks. Epidemiological studies have not conclusively shown stimulant use to be a major contributor to crashes. Similar conclusions can be drawn for methadone, although performance deficits have been demonstrated in some experimental studies.

This review has been restricted to the two categories of medications. Other types of medications may also impair performance and pose a traffic safety hazard. As well, this review has focussed on the independent effects of each medication and the probable impact on driving. Synergistic and dangerous effects on performance can occur when some medications are used in combination with each other or with alcohol. The potential additive effects of medications is especially important to recognize because multiple medication use is common. Moreover, other confounding or impairing situations may also exist, such as the medical conditions for which the medication is being prescribed, or ageing.

What is clear from this review is that research has been limited for medications other than benzodiazapines. Yet, as mentioned previously, nine main drug groups, because of their pharmacological properties could impair driving performance. Impairment and medications is an emerging issue of research which needs to be pursued. Medication use increases with age. For example, Kaba et al.[94] found that in Austria, 50-59 year olds consume 27 packages of medication, 60-69 year olds consume 38 packages and the 70-79 consume 54 packages a year. With the population ageing in industrialized countries, the current trend of medicine-related impaired driving and fatalities will only increase. Kaba et al.[94] found from 1992 to 1996 a 25% increase for cardiovascular therapy and a 15% increase for psychiatric medications. Their most prescribed medications were antihypertensives (17.9%), cardiovascular (10.8%) and psychiatric (8.5%) medications. Most likely these trends are similar in other industrialized countries. Moreover, increased medical problems, reduced cognitive abilities and motor functioning such as reaction times among the elderly will only compound the problem. In addition, many elderly are multiple medication users. The risk of injuries, not only due to motor vehicle injuries but as pedestrians, or due to falls can only increase and research is needed to monitor these trends in relation to medicinal drug use. For example, Odell[95] reviewing coroner=s records for drivers aged over 70 who died in crashes between 1996-1997 in Victoria, found that many drivers were taking medications that could have affected their driving skills. In particular the author noted that although total numbers were small, the proportionately large numbers of drivers taking the anticoagulant Warfarin suggests that further studies are needed.

In addition to the ageing population, health care restructuring and advances in medical technologies and pharmaceuticals could exacerbate the potential impact of impairing medicinal drugs and injuries. Hospital days of stay have been reducing and day surgeries have been increasing as cost-saving methods. For example, a study of day surgery in Australia[96] found a 77% increase in private freestanding centres between 1993-1998. Furthermore, the case studies of various clinics= post-operative procedures indicate that few seem to explicitly prohibit their patients from driving or going home alone, although most mention the need for a care-taker. Yet, the mobility of these post-operative individuals has not been examined. Although presumably implicit clinic and hospital policies are to not allow post-operative patients drive or go home alone because of risk of falls, and motor vehicle crashes, this cannot always be enforced. The increased risk of injury of patients recuperating alone at home, with sporadic home care services has not been examined to my knowledge.

Similarly, independent living, encouraged in the elderly, developmentally disabled and persons suffering from mental illness also necessitates independent means of transportation and mobility. Various medical conditions, such as neurodegenerative and musculoskeletal diseases, have been significantly correlated with increased injury risk, a problem that will only increase with the ageing population and continued de-institutionalization. Even the frail elderly are being encouraged to live at home, with home care service provision. Yet, as health care dollars are stretched, services become sporadic, necessitating the frail elderly, who are generally using many medications, to complete errands themselves at risk of falls, motor vehicle crashes, etc.

In conclusion, except for benzodiazapines, the research on medicinal drugs and impairment is limited. Clearly with the increased medicinal use of our ageing population and health care trends to out-patient services and surgeries, there is a clear need to augment the research on medicinal drugs and traffic collisions.

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Table 1 Principal Drug Groups Affecting Driving Performance

Beta-blockers
Analgesic-narcotic drugs
Antidiabetics
Antihistamine H-1
Antipsychotic drugs
Anxiolitic-Hypnotics
Antiparkinsonian drugs
Antiepileptics

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Table II Drug related side-effects which can impair driving performance

*Anticholinergic effects: drowsiness, confusing, blurring of vision, photophobia
*Neurological and Psychiatric disturbances: drowsiness, confusion states, dizziness, headache, affective reactions: depression, hypomania and mania, psychotic reactions, hallucinations;
*Involuntary movement disorders: Parkinsonism, acute dystonic and dyskinectic reactions, seizures, ataxia;
*Disturbances of balance and hearing: buzzing, tinnitus, hearing loss, dizziness, ataxia;
*Heart and vascular system disorders: arrhythmias, hypotension;
*Hypoglycaemia;
*Disturbances of vision: blurring of vision, accommodation disorders, decreased visual acuity;

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