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Medications and Impaired Driving: A Review of the Literature

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Abstract

Objective—To describe the association of specific medication classes with driving outcomes and provide clinical recommendations.

Data sources—The MEDLINE and EMBASE databases were searched for articles published from January 1973 to June 2013 on specific classes of medications known to be associated with driving impairment. The search included outcome terms such as automobile driving, motor vehicle crash, driving simulator, and road tests.

Study selection and data extraction—Only English-language articles that contained findings from observational or interventional designs were included. Cross-sectional studies, case series, and case reports were excluded. Studies of ≥ 10 subjects were included in this review.

Data synthesis—Driving is an important task and activity for the majority of adults. Unfortunately, some specific classes of commonly prescribed medications have been associated with driving impairment as measured by road performance, driving simulation, and/or motor vehicle crashes. This review of 30 studies identified findings with barbiturates, benzodiazepines, certain non-benzodiazepine hypnotics, various antidepressants, opioid and non-steroidal analgesics, anticonvulsants, antipsychotics, antiparkinsonian agents, skeletal muscle relaxants, antihistamines, anticholinergic medications, and hypoglycemic agents. Additional studies identifying medication impacts on sedation, sleep latency, and psychomotor function – as well as the role of alcohol – are also discussed.

Conclusions—Psychotropic agents and those with CNS side effects were associated with various measures of impaired driving performance. It is difficult to determine if such associations are actually a result of medication use or perhaps the medical diagnosis itself. Regardless, clinicians should be aware of the increased risk of impaired driving with specific populations and classes of medications when prescribing these agents, educate their patients, and/or consider safer alternatives.

Keywords

automobile driving; driving safety; medication safety; potentially driver impairing medications; drugs and driving

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Introduction

Over six thousand FDA-approved medications are currently on the market.[1] With so many agents available and medication consumption on the rise in an aging demographic, the incidence of adverse drug events is a growing concern. It has been estimated that one in five Medicare beneficiaries have five or more chronic conditions, and over 50% are on five or more medications.[2] Polypharmacy, or the superfluous use of medications without clinical indication, may easily be overlooked by clinicians.

Medications may affect the visual, cognitive, and/or motor abilities needed for safe driving. Human factors determine how smoothly we are able to execute and transition between stages of the driver information processing (DIP) model – perception, decision, and reaction.[3] According to this model, fitness to drive is contingent upon our eyes, brain, and musculoskeletal system working in harmony.[4] Ophthalmic medications may cause blurred vision or dizziness; some medications can cause tremor, impaired coordination, or myopathy; and others can impact the central nervous system (CNS) by causing sedation, confusion, or dizziness.

Cognitive tests are commonly used to assess driving ability, such as Trail Making Test Parts A and B (TMT-A and TMT-B, respectively),[5] maze completion tests,[6] and the Freud Clock Drawing Test.[5] Tests of cognition may be useful in predicting a patient's executive function, route planning, or visuospatial aptitude. Popular tools also include the Digit Symbol Substitution Test (DSST),[7] which assess visual scanning, attention, psychomotor speed, information processing, and general executive function, important skills when roadside signs must be read or obstacles recognized quickly. Sedation can be measured on a variety of subjective scales but is often documented in the form of the Mean Sleep Latency Test (MSLT).[8]

Medications associated with motor vehicle crashes may also be characterized as having the potential to impair driving performance. Perhaps the most cited reference in the realm of medications and driving, LeRoy and Morse[9] examined 33,519 cases involved in motor vehicle collisions, matched by age and gender to over 100,000 control subjects. Medications more prevalent in case participants were assigned a calculated odds ratio (OR), indicating the increased crash rate relative to patients not taking that medication. For example, the use of belladonna alkaloids revealed an OR of 1.85, conferring an 85 percent increase in crash rate.[9]

Numerous studies have also associated the use of certain agents with poor performance on real or simulated driving evaluations. The State Department of Motor Vehicles often uses the road test as the final or major arbitrator to determine licensing. Thus, many authorities recognize the performance-based road test as the *de facto* standard.[10] Brake reaction time (BRT) becomes important in assessing a patient's ability to quickly recognize road hazards and stop the vehicle.[11] Another measurement – the Standard Deviation of Lateral Position (SDLP) – indicates how well the vehicle is controlled and kept in the center of the lane.[12]

Not surprisingly, medications associated with impaired driving have been classified as potentially driver impairing (PDI) medications.[13] There is little agreement on what should be labeled a PDI medication, or whether there is enough evidence to suggest that clinicians modify their prescribing behaviors toward any specific subclass. The primary goal of this review was to review studies that link driving impairment to prescription medications and to educate clinicians regarding medications that might warrant special attention. Prescribing and monitoring recommendations are provided.

Criteria For Selection and Assessment of Literature

Statistically significant results from the LeRoy and Morse[9] study were used as the foundation for this review. Medication classes with a strong association, which we defined as an OR of ≥ 1.40, were further investigated. The MEDLINE and EMBASE databases were searched for English-language articles published from January 1973 to July 2013. Search terms included humans, barbiturate, benzodiazepine, narcotic, opioid, hypnotic, hypoglycemic, anticholinergic, NSAID, antihistamine, antipsychotic, anxiolytic, antiepileptic, antiparkinsonian, skeletal muscle relaxant, antiplatelet, antithrombotic, antihypertensive, antidepressant, potential driver impairment, automobile driving, motor vehicle crash, driving simulator, and road tests. Publications with findings from observational or interventional studies were included, while those describing results of cross-sectional studies, case series, or case reports were excluded. Studies conducted using fewer than 10 subjects were also excluded.

Data Synthesis

Twenty-five classes of medications were associated with at least a 40% higher crash risk in the LeRoy and Morse[9] study. (The OR mentioned within each section refers to the results from LeRoy and Morse[9] unless otherwise referenced.) A review of the literature corroborated this association for several of these classes, which have been rearranged into the following eighteen sections for consistency. Some sources presented notable contradictory findings, which are included as well. Thirty reference studies are discussed (Table 1).

Psychotropic medications

Barbiturates—Barbiturates have myriad outpatient indications – anxiety, seizure, insomnia – and are also utilized as fast acting anesthetics to sedate patients undergoing surgery. Examples include phenobarbital, amobarbital, and secobarbital. Barbiturates enhance the natural effects of GABA, which can lead to significant sedation and diminished coordination.[14]

Use of these agents has been associated with a motor vehicle collision with an OR of 7.5; in other words, drivers taking barbiturates showed an increased crash likelihood of 7.5 times higher than drivers not taking these medications.[9] Aside from some very dated literature, rigorous studies on driving impairment with barbiturates are rare, demonstrating the obsolescence of these agents in an ever-evolving pharmaceutical market. Thankfully, safer alternatives exist.

Benzodiazepines (BZDs)—While LeRoy and Morse[9] show that BZD use corresponds to double the risk of a motor vehicle crash, further studies have demonstrated that these agents cause measureable impairments in cognitive and motor function as well.[15] Benzodiazepines may cause severe respiratory depression and are thus subject to routine monitoring of vital signs. Other PDI side effects may include weakness, clumsiness, loss of balance, dizziness, and distorted vision.[14] Barbone and colleagues[16] observed more than a two-fold higher risk of automobile collision with use of anxiolytic BZDs such as alprazolam and lorazepam. However, hypnotic BZDs such as flurazepam and temazepam did not show a statistically significant difference.[16]

It is important to consider the approximate rate of elimination in order to schedule an appropriate regimen. BZDs with longer half-lives may invariably produce carry-over effects beyond the dosing period.[17] For instance, midazolam has a half-life of 1-5 hours whereas diazepam concentrations do not fall to 50% until after about 30-60 hours.[18] In general, a

shorter acting BZD is preferred over one that may remain in the body for several days or be metabolized to active metabolites. Nighttime dosing with shorter duration agents may lessen the chance of daytime PDI effects. Indeed, a 1997 study found increased risk of crash with use of long-half-life BZDs (t½ > 24 h) but not with short-half-life BZDs.[19]

A dose dependent association is also worth mentioning. In a study of elderly Medicaid enrollees, the risk of motor vehicle crash was increased with BZD use but was even greater for subjects taking diazepam in excess of 20 mg per day.[20] Physicians should examine other therapeutic options first, and, if a BZD is selected, should initiate at the lowest possible dose.

Non-BZD hypnotics—Zolpidem, zaleplon, and eszopiclone have been around since the 1990s and have become a popular alternative to BZDs in managing sleep disorders. They still may produce dizziness and drowsiness, and were shown to increase collision rate by 48% in the LeRoy and Morse study.[9]

Zolpidem has gained attention for case reports of sleep walking, eating, and even driving during the night without recollection by the next morning. In light of this “known risk,” the FDA announced May 2013 that it would require manufacturer labeling to indicate a lower recommended dose of zolpidem. For instance, the recommended dose of immediate-release products has been reduced from 10 mg to 5 mg for women.[21]

The literature has associated zolpidem with both at-fault and non-at-fault collisions. The risk of motor vehicle accident appears to be greater in patients prescribed more than one 10 mg tablet per day.[22] A placebo comparison study examining zolpidem and zopiclone, the stereoisomer of eszopiclone, noted a quantitatively similar risk with both medications. This risk increased with younger age, perhaps as a consequence of reduced lifetime exposure compared with older patients taking the same medications.[23] Impairment with zopiclone was also seen in an earlier study using a battery of cognitive and driving assessments; this same study found 10 mg zaleplon to produce no impairment over placebo.[24] Eszopiclone has been shown to improve both quality of sleep and sleep latency, but only in healthy volunteers did it cause statistically significant sedation. Insomnia patients were not any more drowsy with or without the medication, supporting the benefit of eszopiclone for patients who have trouble sleeping.[25]

Ultimately, the literature designates no impairment with zaleplon,[24] no impairment with eszopiclone in patients with insomnia,[25] and an increased crash risk overall with use of zolpidem.[22] Perhaps the best option is to prescribe a non-BZD hypnotic at a low evening dose and to dissuade patients from driving during the initiation phase.

Tricyclic antidepressants (TCAs)—Although this class has been replaced by better tolerated agents in the treatment of major depressive disorder, TCAs are still prescribed for neuropathic pain, certain anxieties, and menopausal symptoms. Medications include amitriptyline and imipramine, with active metabolites nortriptyline and desipramine, as well as doxepin. These agents can produce anticholinergic effects, orthostatic hypotension, and varying degrees of central depression and sedation.[14] Additionally, LeRoy and Morse[9] found a 41% greater crash likelihood with the use of a TCA.

Even higher values have been reported in other literature, ranging from a 220% to 230% risk.[20,26] A convincing dose dependent association was also noted with patients using more than 125 mg amitriptyline per day.[20] Iwamoto, et al.,[27] discovered a correlation with plasma levels of amitriptyline and poor vehicle maneuvering via SDLP. Four hours following

administration of 25 mg amitriptyline, subjects exhibited more lateral weaving and variation in car-following distance.[28]

Brunnauer and colleagues[29] examined 100 subjects treated with antidepressants and found that only 10% of TCA users passed a global driving ability test compared with patients on mirtazepine (50% pass rate). Patients receiving TCAs also performed worse on psychomotor and visual perception assessments, indicating that perhaps TCAs should be a last line of therapy when alternatives exist.[29] If a tricyclic antidepressant must be prescribed, patients should be advised to avoid driving during initial use and after each dosage adjustment.[4]

Selective serotonin reuptake inhibitors (SSRIs)—These agents are the most commonly prescribed class to treat depression and are gaining popularity in the pharmacotherapy of anxiety disorders. SSRIs include paroxetine, fluoxetine, citalopram and its enantiomer escitalopram, and sertraline. Common PDI effects are altered sleep architecture and tremor.[30] LeRoy and Morse[9] noted a motor vehicle crash OR of 1.59 with the use of SSRIs, slightly higher than the risk with TCAs by the same study. However, SSRIs were found to have an advantage over TCAs with tests of selective attention in a 2006 trial of depressed patients.[29] Wingen, et al.,[31] reported increases in SDLP with use of an SSRI or SNRI but did not identify a difference with either class individually. Similarly, crash rate per a Norwegian national registry was increased with SSRIs or venlafaxine, but again, these groups were combined and not assessed according to use of individual medication classes.[32] The same year, results of another randomized study showed no difference in SDLP between paroxetine and placebo.[28] In a meta-analysis, Ravera and colleagues[33] concluded that although data seem “unclear and conflicting,” SSRIs only appear to pose a threat to driving when given at high doses. As many clinicians favor SSRIs, patients should be educated about potential deleterious effects on driving and alertness.

Second generation / related antidepressants—Several antidepressants have been developed with structures and pharmacodynamic mechanisms that do not fit neatly into any previous antidepressant medication classes; these are the second generation antidepressants. Serotonin and norepinephrine reuptake inhibitors (SNRIs) include venlafaxine and duloxetine, and have been associated with a 78% increase in crash rate.[9] However, no consistent or meaningful impact on driving behavior was observed in a blinded controlled trial of venlafaxine against placebo; SDLP and subject ratings of drowsiness did not significantly differ between groups.[34] Partial serotonin antagonists, trazodone and nefazodone, were found to have a 90% higher chance of crash, while bupropion and mirtazapine demonstrated nonsignificant findings.[9] In a crossover trial comparing mirtazapine with placebo, driving performance was affected during the initial treatment period (days 1 to 7) with a lower 30 mg dose, but this effect did not remain for days 8 to 15 when subjects were given 45 mg. It is possible that adaptation or mirtazepine's inverse dose-dependent sedation may have played a role in this outcome.[35] A recent study found that for a combined group of patients prescribed SSRIs, SNRIs, or partial serotonin antagonists, crash risk was increased by 10%, but this was significant only when a BZD had been co-prescribed.[36]

There is inconsistency in the literature regarding second generation antidepressants. Thorough counseling should be provided to patients, and nighttime administration should be scheduled when the risk of sedation is high. Like most PDI medications, patients should monitor for side effects during initial treatment in order to observe potential impacts on driving. If the patient perceives the impairment as too severe, an alternate drug may be considered.

Analgesics

Opioid analgesics—While opioid analgesics are indeed sedating, they offer a number of additional PDI effects. Respiratory depression can occur similar to BZDs. Patients may also experience fatigue, lightheadedness, and miosis or pupillary constriction.[14] These side effects may be ameliorated with extended use, although visual changes persist despite continuous therapy.[37] Crash analysis data have shown that narcotics confer a 2.2 times higher risk,[9] although medication use was not classified as acute versus chronic. Injury and hospitalization for automobile crash, especially for women, has been associated with opioid use.[38] A 2012 cohort study noted a substantial impact on TMT-A and TMT-B in a combined group of BZDs, opioids, and antipsychotics, but it is difficult to parse out which specific subclass may have been responsible for this finding.[39]

In 2000, Galski and colleagues[40] attempted to answer a common clinical question – do chronic opioid users have the same high risk of impaired driving? Patients on chronic opioid therapy demonstrated better threat recognition braking accuracy, visuospatial ability, and DSST scores, as well as an improved ability to follow directions, when compared with other rehabilitated drivers (post stroke or brain injury) who had previously taken and passed the road test battery.[40] Perhaps continued use of opioid analgesics allows for physiologic adaptation to their centrally depressive effects, making the risk for driving impairment greatest during initial therapy.

Fortunately, there are ways to mitigate risk of impaired driving. First, a combination product may be chosen to reduce the required dose for analgesia. Examples include oxycodone and hydrocodone, which may be formulated in smaller doses with acetaminophen.[14] Patients who are naïve to opioid analgesics should be started low and titrated slowly to an appropriate pain score. Prescribers might also advise patients against driving during the first four or five days after initiating or titrating the dose of an opioid analgesic, and that they avoid other sedating products, such as first generation antihistamines, BZDs, and alcohol.[4] If only acute therapy is required, advise temporary driving cessation during use.

Nonsteroidal anti-inflammatory drugs (NSAIDs)—NSAIDs are a frequent choice for relief of pain, inflammation, and fever. They are not often thought about as having an impact on driving and cognition, although drug monographs advise caution when driving or operating heavy machinery with the use of agents like ibuprofen, naproxen, and indomethacin. Dizziness, drowsiness, and blurred vision are possible PDI effects. LeRoy and Morse[9] found a 58% higher crash risk in patients taking NSAIDs, so the potential influence on driving should not be underemphasized. McGwin and colleagues[41] reported a similar (70%) increase in at-fault crashes from a case-control study, a risk which was significantly greater when ACE inhibitors were given concomitantly. This could be explained by the pharmacodynamic interaction between these two classes of medications, or perhaps it is simply the result of medical illness (i.e., congestive heart failure) requiring ACE inhibitor therapy. Unfortuantely, the true relationship of NSAIDs with driving impairment is easily confounded by coadministration with other medications prescribed for pain. Whether we blame driving impairment on the medication or on the condition it treats, physicians should be wary when recommending an NSAID to patients with whom driving is already a concern.

Centrally active medications

Antiepileptic drugs (AEDs)—Also known as anticonvulsants, AEDs include carbamazepine, phenytoin, valproate, gabapentin, topiramate, lamotrigine, ethosuximide, and others. Possible side effects include somnolence, slowed speech and psychomotor

function, and mydriasis.[14] Use of anticonvulsants has been associated with a 97% increased collision rate, almost twice the probability of a crash.[9]

However, some studies in epileptic patients have commented on the benefit of therapy. Preventing seizures on the road would certainly reduce the incidence of collision, so optimal therapy is key. Interestingly, Krauss, et al.,[42] reported that having AED therapy switched or doses decreased was associated with a reduced crash incidence, indicating the need for careful monitoring and dose titration. A large multicenter study discovered higher crash rates in patients not taking their AEDs appropriately compared with medication-adherent patients.[43]

The physician must prescribe a dose and frequency that are adequate to maintain nontoxic therapeutic concentrations. As mentioned, a vigilant clinician is a great asset to monitor and fine-tune AED regimens, ensuring quality medication management and reduced danger with operating a motor vehicle.

Antipsychotics—Although some first generation antipsychotics (FGAs) remain in use today, a newer class of second generation antipsychotics (SGAs) has largely replaced them in clinical practice. These include but are not limited to aripiprazole, quetiapine, clozapine, and olanzapine. In addition to extrapyramidal symptoms, SGAs may cause sedation, visual disturbances, confusion, and orthostasis.[14] LeRoy and Morse[9] observed a 120% increase in crash rate with the use of SGAs, while findings for FGAs, such as haloperidol and thiothixene, were nonsignificant. In contrast,quetiapine outperformed haloperidol in measures of psychomotor skill and was associated with fewer driving simulator accidents in hospitalized schizophrenic patients prior to discharge.[44] Despite mixed findings in the literature, detailed patient counseling is advised when prescribing an antipsychotic of any kind.

Antiparkinsonian agents—Medications used to manage Parkinson's disease include carbidopa and levodopa, pramipexole, ropinirole, entacapone, and amantadine, although others may be prescribed. Unfortunately, rigorous studies of antiparkinsonian effects on driving are scarce. Interpretation of such studies is often complicated by the presence of disease and ethical concerns with giving placebo. The majority of patients with Parkinson's disease already receive treatment, making it difficult or impossible to compare medicated with nonmedicated patients. Although our search turned up no references for this medication class, we feel it still warrants a discussion of adverse events.

Patients taking antiparkinsonian agents have reported ‘sleep attacks’ – sudden, unexpected lapses of attention and falling asleep. This may, in part, be due to anticholinergic properties of certain agents like benztropine and trihexylphenidyl.[14] Montastruc and colleagues[45] noted that over 30% of patients on these medications reported experiencing a sleep attack. A recent study in Parkinson's patients examined the frequency of sleep attacks and found it highest when dopamine agonists were combined with levodopa. The highest risk with any single agent was with pramipexole, although ropinirole and ergot-containing agonists were also associated with sleep attacks.[46] Interviews with patients from three movement disorder centers identified 8 involved in automobile accidents; all 8 patients had fallen asleep at the wheel during treatment with pramipexole.[47] Additionally, results from a 2009 blinded trial revealed that pramipexole reduced sleep latency over placebo with no subjective indication of sleepiness. No changes in time to sleep were observed with bromocriptine, however.[48]

Fluctuating drug levels may also interfere with motor function, and some patients are impacted by an ‘on / off’ phenomenon. Thus, timing of driving trips in relation to medication peaks may become critical. Optimally, the drugs suppress involuntary gestures,

but waxing and waning plasma levels may produce slowed or diminished voluntary movement with spastic, involuntary end-of-dose movements, a collective condition called dyskinesia. Naïve patients should be instructed to take the drug for about 5 days before driving, should they experience these effects.[4]

Potential underlying effects of disease should not be disregarded. Compared with healthy controls, medically treated Parkinson's patients already exhibit suboptimal reactivity to stimuli while driving.[49] The benefits of antiparkinsonians to enhance driving ability must be highlighted; they have great potential to improve motor speed, gait, balance, rigidity, and tremor, deficits which could conceivably impede driving ability if untreated.

Skeletal muscle relaxants (SMRs)—The LeRoy and Morse[9] study reported an OR of 2.09 for patients taking SMRs, attributable to PDI effects like drowsiness, ataxia, and blurred vision.[14] Even a single dose of meprobamate, the active metabolite of carisoprodol, has been associated with significantly reduced coordination and reaction time.[50] Carisoprodol was studied in 2011 using healthy subjects, and was found to produce diminished psychomotor response with the DSST. Moreoever, subjective sedation ratings were greater with carisoprodol at both 350 mg and 700 mg. Overall perceived medication effect was high with 700 mg carisoprodol, but subjects did not perceive an effect at the 350 mg dose, indicating a lack of effect discrimination.[50] Unfortunately, our search returned no studies of skeletal muscle relaxants; however, forensic toxicology studies have reported an association with impairment and increased blood levels of these agents.[51,52] While we agree these drugs should be considered PDI medications, additional studies are needed to confirm this relationship.

Additional SMRs include baclofen, cyclobenzaprine, dantrolene, metaxalone, and tizanidine.In spite of the lack of non-PDI alternatives, patients being prescribed these medications need strict counseling on the dangers of driving during use.

Others

Antihistamines—First generation antihistamines – diphenhydramine, doxylamine, hydroxyzine, and several others – are more lipophilic and can easily permeate the blood brain barrier. Most second generation antihistamines have been designed to eliminate sedating side effects; loratadine and fexofenadine do not contain label warnings against motor vehicle operation. Due to their hydrophilic nature, these medications remain in the peripheral blood without a pronounced effect on wakefulness. Taking these medications at doses above what is recommended may, however, cause some of the medication to cross into the brain to cause PDI effects.[30] One second generation antihistamine, cetirizine, has been associated with slight impairments.[53]

Yanai and associates[54] suggest that antihistamines be classified by their occupancy of central histamine receptors (H_1R). When subjected to PET imaging in brain tissue, non-sedating antihistamines were classified as having an H_1R occupancy of 0-20% and included fexofenadine, terfenadine, and 10 mg cetirizine. Less sedative agents were, notably, azelastine and 20 mg cetirizine. The most sedating antihistamines included chlorpheniramine and ketotifen.

Subjective symptoms of drowsiness, such as yawning or drooping eyelids, may not be apparent when effects on driving and psychomotor function occur. Authors of a placebo controlled crossover study commented that drivers using sedating antihistamines may not perceive that they are under any sort of impairment. This same study found that subjects taking hydroxyzine had significantly slower brake reaction time than those given fexofenadine.[11]

In a randomized controlled trial, subjects with a blood alcohol content (BAC) one-eighth the legal limit were able to better steer a vehicle simulator than subjects given 50 mg of diphenhydramine.[55] A double blind crossover in healthy males also revealed a significant change in sleep latency with diphenhydramine, as well as increased somnolence for ketotifen, cetirizine, and diphenhydramine but not for astemizole, terfenadine, or loratadine.[53] Driving-related deficits have been noted in a number of other studies, including increased SDLP with clemastine 3 to 4 hours following a morning dose.[56] An isomer of chlorpheniramine produced a similar effect 3 hours after the first dose, but this impairment was absent by the eighth day of treatment.[57]

Patients should be prescribed a non-sedating antihistamine when indicated; otherwise, temporary driving cessation is recommended for patients during daytime use of a first generation agent.[30] Cetirizine, although likely less impairing that first generation antihistamines, should be reserved for drivers who have responded inadequately to loratadine and fexofenadine.

Intestinal and antiemetic agents—Treatment of emesis, intestinal spasticity, and abdominal cramping commonly includes the use of anticholinergic agents. Use of a natural belladonna or an antiemetic conferred a respective 85% and 63% increased crash risk in the LeRoy and Morse[9] study, while crash outcome data with other antispasmodics was nonsignificant. Belladonna alkaloids such as scopolamine, atropine, and hyoscyamine, along with other, newer muscarinic antagonists like dicyclomine and glycopyrrolate, may cause PDI effects including drowsiness, blurred vision, and delirium.[14]

In a large randomized study, atropine demonstrated reduced performance on an attention test despite minimal subject reports of perceived impairment. Glycopyrrolate performed even worse with lower scores on the attention test, poorer coordination, and longer time to complete coordination tasks.[58] A study in healthy male aviation pilots produced similar results with atropine, including significantly greater error in altitude control, control while turning, and tracking accuracy.[59] When possible, these medications are to be avoided, and newer agents should be attempted before prescribing a belladonna alkaloid.

Antiemetics prochlorperazine and droperidol have also been associated with poor performance in driving simulator studies. Betts and colleagues[60] reported a longer time to complete the driving test and more cones hit by prochlorperazine users compared with placebo. Simulator driving test scores were also reduced following an intramuscular droperidol injection; fortunately, subjects could perceive driving impairment 60% of the time when given droperidol but never with placebo.[61]

Hypoglycemic agents—Studies have shown that insulin, which induces a hypoglycemic state, has been significantly associated with falls.[62] Symptoms of hypoglycemia are often patient-specific but may include mental and visual problems, as well as dizziness, shakiness, and lightheadedness.[14] LeRoy and Morse[9] stratified hypoglycemic medications by their physiologic actions – insulin (OR = 1.80), sulfonylureas (OR = 1.50), and bisguanides such as metformin (OR = 1.49).[14] Use of an insulin pump, which carries the risk of symptomatic hypoglycemia, has been associated with driving mishaps such as collision or being stopped for wreckless driving.[63] Similar findings were published in 2006 where an increased crash rate was seen for insulin monotherapy and for dual treatment with a sulfonylurea and metformin. However, no effect was noted when insulin was combined with one of these medications or in patients taking a sulfonylurea or metformin alone.[64]

Physicians must exercise caution when designing a diabetes regimen, especially in elderly drivers or individuals at high risk of hypoglycemia. In some cases, medications less

associated with driver impairment, such as repaglinide or pioglitazone, may be preferred. Conditions of greater risk (e.g., brittle diabetes with recurrent hypoglycemia) should alert clinicians to allow for a less tightly controlled regimen in patients still operating a motor vehicle.

Alcohol effects—All patients should, ideally, be encouraged to avoid or limit alcohol intake, especially when they expect to drive. Physicians have an opportunity and, arguably, a responsibility to counsel patients on the dangers of ethanol. Consumption of alcohol, in adequate doses, is lethal to nearly all living creatures. Humans are no exception. At lower BAC, the body suffers only mild impairment by a lowered sense of inhibition and a decline in concentration and alertness.

Although the definition of 'moderate alcohol use' varies among patients, typically no more than one alcoholic beverage (14 grams)[65] should be ingested per day by a female, with a limit of two for males. In patients who consume more than the recommended amount of alcohol, further depressive effects may be expected. Plasma levels rise, allowing more alcohol to cross the blood brain barrier to access the central nervous system.

Health care professionals should discourage alcohol while driving or in combination with centrally active agents, as it can exacerbate the PDI effects of certain medications. Alcohol augments and subsequently increases the risk of overdose with BZDs, causing further deficits in psychomotor function, respiration, and alertness. It may also trigger hypoglycemia induced by sulfonylureas and bisguanides, orthostasis by sympatholytic agents, and drowsiness by skeletal muscle relaxants.[66] Yet another medication, ranitidine, blocks liver enzymes that metabolize alcohol as it arrives via the hepatic portal system, resulting in a more elevated BAC.[67] Several medications interact with ethanol and demand tailored counseling (Table 2).

Limitations

While the majority of literature is based upon retrospective vehicle crash claims, novel studies are beginning to investigate their relationship with practical, real-time impairments. As the definition of a PDI medication continues to evolve, more studies of medication use with driving simulators and road tests would be helpful in determining actual risks. Unfortunately, most current studies examine real patients and may present several biases. Reported PDI associations may be confounded by disease state and/or other medications and are highly susceptible to response and reporting bias by the subject.

Additionally, this review was conducted purely as a systematic literature search and did not involve any rigorous statistical analysis. The methods used for this review were not exhaustive of the driving literature and should not be the sole consideration when recommending pharmacotherapy for motorists. An association with impaired driving does not necessarily imply causation, as other factors may be at play, such as chronic disease, acute emotional or physical stress, and performance bias or the related Hawthorne effect.

Conclusions

Driving impairment was observed with medication use in numerous studies. Theses medications may create stress, frustration, and inconvenience when they seemingly control whether a patient can safely operate a vehicle. While this article discusses several deleterious effects of medication use, positive outcomes should not be underestimated. Medications improve or stabilize many medical conditions, which may also enhance the ability to drive. The risk-to-benefit ratio must be evaluated for each patient before

prescribing. As long as anticipated benefits outweigh risks of use, medications should be prescribed with clear, comprehensible and, individualized counseling. When alternatives are preferable but not an option, the lowest effective dose should be given so that therapeutic efficacy is achieved while minimizing adverse outcomes on driving.

Driving has become an essential skill in today's society to facilitate work, social connectedness, and everyday life. Thus, the impact of medications on driving is an important consideration in designing a medication regimen. This literature review article, coupled with the availability of clinical trial data and drug monographs, should equip prescribers with the tools to make informed, ethical decisions in selecting medication therapy.

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Table 1

Published crash and simulator studies of specific medication classes

First author (year)	Medication class	Design	Subjects	Outcome*	Comments / findings
LeRoy[9] (2008)	All	Case-control	33,519 U.S. crash cases matched 1:3 with > 100,000 controls	C	Elevated OR reported for several medication classes with respect to motor vehicle crash
Hemmelgarn[19] (1997)	BZDs	Nested case-control	5,579 elderly crash cases randomly matched 10:1 with 13,256 controls	C	Increased risk of motor vehicle crash with long-half-life BZDs (OR = 1.45 within 1 week of exposure; 95% CI 1.04, 2.03). No difference was noted for BZDs with a half-life ≤ 24 h.
Barbone[16] (1998)	BZDs	Case-crossover	19,386 drivers involved in first road traffic accident	C	BZDs associated with elevated OR of 1.88 (95% CI 1.36, 2.60) for at-fault collisions compared to a one-year references period without medication. This risk was greater with anxiolytic BZDs (OR = 2.39), such as alprazolam, diazepam, and lorazepam. Nonsignificant findings for at-fault collisions with hypnotic BZDs including flurazepam and temazepam.
Ray[20] (1992)	BZDs; TCAs	Retrospective cohort	16,262 elderly Medicaid enrollees	C	Noted association with motor vehicle crash and BZD use (RR = 1.5; 95% CI 1.2, 1.9), with patients prescribed at least 20 mg diazepam at greater risk (RR = 2.4; 95% CI 1.3, 4.4) compared with no medication. Similar findings for TCAs (RR = 2.2, 95% CI 1.3, 3.5) and for amitriptyline dosed ≥ 125 mg per day (RR = 5.5; 95% CI 2.6, 11.6).
Oriolls[22] (2011)	Non-BZD hypnotics	Mixed case-control and case-crossover	72,685 drivers involved in an injurious crash	C	Zolpidem showed an adjusted OR of 1.29 (95% CI 1.09, 1.52) for at-fault collisions, although rate was significantly higher in those taking more than 10 mg per day (OR = 2.46; 95% CI 1.70, 3.56). Findings for zopiclone were nonsignificant.
Gustavsen[23] (2008)	Non-BZD hypnotics	Retrospective cohort	3.1 million Norwegian citizens	C	SIR of road traffic accidents = 2.2 for zolpidem (95% CI 1.4, 3.4), similar to the crash risk in subjects taking zopiclone (SIR = 2.3; 95% CI 2.0, 2.8). Noted trend towards increased impairment in younger subjects for both medications.
Vermeeren[24] (2002)	Non-BZD hypnotics	3-way crossover RCT	30 healthy volunteers	T	Authors reported worse outcomes with 7.5 mg zopiclone, including reduced recognition speed (868 vs. 793 msec; $p < 0.025$) and increased SDLP (21.6 vs. 18.2 cm; $p < 0.001$). Outcomes with 10 mg zaleplon were not significantly different from placebo.
Iwamoto[27] (2008)	TCAs	3-way crossover RCT	17 healthy male volunteers	T	Serum concentrations following a single 25 mg dose of amitriptyline correlated positively with grades for SDLP ($r = 0.543$; $p < 0.05$).
Iwamoto[28] (2008)	TCAs; SSRIs	3-way crossover RCT	17 healthy male volunteers	T	Impaired performance was noted 4 hours post amitriptyline with increased SDLP (51.3 vs. 36.9

First author (year)	Medication class	Design	Subjects	Outcome*	Comments / findings
					cm; $p < 0.01$) and greater variation in car-following distance (36.1 vs. 25.7; $p < 0.05$). Paroxetine had no effect on driving or cognitive performance.
Bramness[32] (2008)	TCAs; SSRIs; second generation antidepressants	Retrospective cohort	3.1 million Norwegian drivers	C	The rate of motor vehicle accident was increased for subjects prescribed TCAs or mirtazapine with SIR = 1.4 (95% CI 1.2, 1.6) as well as for those prescribed SSRIs or venlafaxine with SIR = 1.6 (95% CI 1.5, 1.7). No additional investigation was done regarding the effect of disease or risk with individual medication classes.
Rapoport[36] (2011)	TCAs; SSRIs; second generation antidepressants	Case-only, time-to-event analysis	159,678 elderly Canadian subjects involved in a motor vehicle crash	C	Crash associated with use of antidepressants including SSRIs, SNRIs, and partial serotonin antagonists (HR = 1.10, $p < 0.0001$). Concomitant use of BZDs accounted for this risk; HR with BZD and antidepressant = 1.23 (95% CI 1.17,1.28) and HR with antidepressant only = 1.01 (95% CI 0.98, 1.04). No significant findings reported with TCA users.
Brunnauer[29] (2006)	TCAs; SSRIs; second generation antidepressants	Nonrandomized clinical trial	100 inpatients with MDD	T	Only 10% of subjects assigned to TCAs passed a global driving ability test compared with patients on SSRIs or second generation antidepressants (20-50% pass rate). The difference was significant for TCAs compared with mirtazapine only ($z = -2.49$; $p < 0.05$). Patients on venlafaxine were significantly older (mean age 53.4 vs. mid-40s for other drug classes).
Leveille[26] (1994)	TCAs; opioids	Case-control	234 older subjects treated for 7 days following automobile crash matched 1:2 with 447 controls	C	Increased rate of crash in TCA users per an adjusted OR of 2.3 (95% CI 1.1, 4.8). Adjusted OR for injurious accidents was 1.8 (95% CI 1.0, 3.4) for current opioid users; no increased risk remained with past opioid users.
Wingen[35] (2005)	SSRIs; second generation antidepressants	3-way crossover RCT	18 healthy subjects	T	Mirtazepine at a lower dose of 30 mg showed a significant impact on divided attention and subjective feelings of alertness. Tracking error on day 2 was 19.1 vs. 17.0 mm ($p = 0.032$) and SDLP was 21.8 vs. 17.9 cm ($p < 0.001$). This was not seen with mirtazapine 45 mg given on days 8-15. Escitalopram did not affect road test performance throughout.
Wingen[31] (2006)	SSRIs; second generation antidepressants	Prospective cohort	24 depressed subjects treated with medication matched 1:1 with 24 healthy controls	T	Greater SDLP or lane weaving observed with antidepressant use ($F = 8.29$; $p < 0.01$). No significant differences detected with individual subclasses of SSRI or second generation antidepressant, perhaps due to decreased sample size for this subanalysis. Control subjects did not have depression; disease may have confounded this association.
O'Hanlon[34] (1998)	Second generation antidepressants	4-way crossover RCT	22 healthy volunteers	T	No significant differences between venlafaxine and placebo were detected for SDLP, regardless of dose

First author (year)	Medication class	Design	Subjects	Outcome*	Comments / findings
					given (75 mg vs. 150 mg). Consistent nonsignificant findings were also reported for measures of cognition including divided attention and visual processing.
Meuleners[38] (2011)	Opioids	Case-crossover	616 older Australian drivers hospitalized for automobile crash	C	The OR of opioid use in subjects hospitalized for an automobile crash was 1.5 (95% CI 1.0, 2.3) overall and even greater for women (OR = 1.8; 95% CI 1.1, 3.0).
Galski[40] (2000)	Opioids	Retrospective cohort	16 subjects on chronic opioid therapy compared with 327 'cerebrally compromised' controls	T	For chronic opioid patients, superior visual scanning was seen with higher scores on a digit symbol test (8.81 vs. 6.30; $p < 0.05$) and visuospatial ability was evident with shorter mean time to complete a complex figure task (142.06 vs. 237.38 sec; $p < 0.05$). Opioid patients also had better braking accuracy for threat recognition (82.50% vs. 60.47%; $p < 0.05$). But, the control group presents significant bias since residual deficits of disease may have exaggerated or worsened test performance.
McGwin[41] (2000)	NSAIDs	Case-control	244 drivers involved in at-fault collisions within past year, 182 non-at-fault collisions, 475 controls	C	Authors reported an increase (OR = 1.7; 95% CI 1.0, 2.6) in at-fault crashes in patients using NSAIDs after adjusting for age, sex, race, and annual miles driven. Noted interaction with ACE inhibitors; OR with NSAID and ACE inhibitor = 3.40 (95% CI 1.1, 10.9) and HR with NSAID only = 1.50 (95% CI 1.0, 2.5).
Krauss[42] (1999)	AEDs	Case-control	50 epileptic crash cases matched 1:1 with 50 epileptic controls	C	Having AED therapy switched or doses decreased resulted in a reduced crash incidence (OR = 0.111) but no statistical significance was reported. A combination of factors – including reliable aura prior to seizure, history of fewer crashes, hours driving, and having AED changed – was assessed using multivariate analysis and was associated with reduced risk for motor vehicle accident ($r^2 = 0.49$, $p = 0.001$).
Faught[43] (2008)	AEDs	Retrospective cohort	33,658 epileptic patients	C	Nonadherence to AED therapy (MPR < 0.80) associated with IRR = 2.08 (95% CI 1.81, 2.39) for motor vehicle accident injuries.
Brunnauer[44] (2009)	Antipsychotics	Prospective cohort	80 schizophrenic inpatients receiving AED monotherapy	T	Haloperidol group showed poorer performance on tests of vigilance ($F = 6.34$; $p < 0.05$) and concentration ($F = 4.19$; $p < 0.05$) compared to quetiapine. Quetiapine also associated with fewer simulator accidents ($z = -1.92$; $p < 0.05$). However, haloperidol patients were older (41.3 vs. 29.6 years; $p < 0.05$) and may have been predisposed to poor performance.
Weiler[55] (2000)	Antihistamines	4-way crossover RCT	40 healthy volunteers	T	No differences noted between fexofenadine and placebo. Coherence, or ability to match the speed of a leading car, was assessed as a correlation between

First author (year)	Medication class	Design	Subjects	Outcome*	Comments / findings
					subject velocity and lead vehicle velocity. Coherence was poorest with diphenhydramine at 0.877 (95% CI 0.837, 0.911) and was significant compared with alcohol (mean difference 0.043 ± 0.012).
Tashiro[11] (2005)	Anthistamines	3-way crossover RCT	18 healthy male volunteers	T	Subjects were instructed to perform simple calculations during simulated driving. Those who received hydroxyzine had slower BRT than placebo (95% CI of difference 18.23, 83.43 msec; p = 0.002) or fexofenadine (95% CI of difference 18.96, 82.52 msec; p = 0.001). No significant differences occurred between fexofenadine and placebo.
Vermeeren[56] (1998)	Antihistamines	6-way crossover RCT	24 healthy volunteers	T	Significantly greater SDLP with clemastine on days 1 (p = 0.006) and 4 (p = 0.0309) vs. placebo during a 5-day treatment period; raw data not available.
Theunissen[57] (2005)	Antihistamines	4-way crossover RCT	16 healthy volunteers	T	Subjects treated with dexchlorpheniramine 6 mg twice daily drove with increased SDLP over placebo (21.2 vs. 19.2 cm; p < 0.017) on day 1. Measures of SDLP were exactly the same as placebo (19.9 ± 1.0) by day 8. Cetirizine subjects did not show a significant difference on any of the driving tests throughout the study.
Fulton[61] (2006)	Intestinal and antiemetic agents	2-way crossover RCT	20 healthy volunteers	T	Overall driving simulator scores were lower with a 2.5 mg IM droperidol injection compared to placebo (68.8% vs. 73.6%; p < 0.015). Volunteers perceived impairment 60% of the time following droperidol but never with placebo (p < 0.001).
Betts[60] (1991)	Intestinal and antiemetic agents	3-way crossover RCT	12 healthy female volunteers	T	Authors reported a longer time to complete the driving test (median 215 vs. 191 sec; p < 0.05) and more cones hit (median 9 vs. 4; p < 0.05) in prochlorperazine users over placebo.
Hemmelgarn[64] (2006)	Hypoglycemics	Nested case-control	5,579 elderly crash cases matched 1:2 with 13,300 controls	C	Insulin monotherapy dispensed within the month prior conferred an ERR for crash = 1.4 (95% CI 1.0, 2.0) and 1.3 (95% CI 1.0, 1.7) for dual treatment including a sulfonylurea with metformin. No increases noted with combinations of insulin with either of these agents, or for sulfonylureas or metformin alone.
Cox[63] (2009)	Hypoglycemics	Prospective cohort	452 type 1 diabetic drivers with recent ‘driving mishap’	C	Use of an insulin pump associated with higher risk of driving incidents such as being stopped by police for wreckless driving, immediate cessation of driving for safety concerns, or loss of vehicle control. Adjusted RR = 1.35 (95% CI 1.12, 1.64; p = 0.002).

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Table 2

PDI medications that interact with alcohol

Medication	PDI effect(s)[66]	Recommendation
Benzodiazepines	Increased risk for overdose, sedation, slowed breathing, impaired motor control	Avoid alcohol
Non-BZD hypnotics	Somnolence, dizziness, impaired motor control	Alcohol in moderation
Skeletal muscle relaxants (cyclobenzaprine and carisoprodol only)	Increased risk for overdose, dizziness, ataxia, slowed breathing, increased seizure risk	Avoid alcohol
Antihistamines (all classes)	Drowsiness, dizziness	Alcohol in moderation
Hypoglycemic agents (sulfonylureas and bisguanides only)	Hypoglycemia	Alcohol in moderation
Antihypertensive agents (ACE inhibitors and sympatholytics only)	Orthostatic hypotension, palpitations, drowsiness	Alcohol in moderation
Opioid analgesics	Increased risk for overdose, sedation, slowed breathing, impaired motor control	Avoid alcohol during acute phase; Alcohol in moderation with chronic dosing
Antidepressants (all classes)	Increased risk for overdose, drowsiness, dizziness	Avoid alcohol