LITERATURE REVIEW

Drug Review
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1 INTRODUCTION

This review describes the performance-impairing effects of twenty-six commonly used drugs. It is not intended to list comprehensively all drugs that may affect driving performance. However, it does list and describe several drugs that have been the topic of intense research scrutiny.

2 ALPRAZOLAM

Alprazolam (Xanax) is the most frequently-used benzodiazepine and is one of the 10 most-prescribed drugs in the US. It has a short half-life and is generally prescribed in divided doses from 0.5-10 mg/day. It is used to treat anxiety and panic disorders.

In a crossover study, Verster, Volkerts and Verbaten (2002) dosed 20 healthy participants with 1 mg alprazolam and placebo on 2 days of testing (separated by a 14-day washout period). This study involved acute testing only; there was no testing at steady state. In the standard on-the-road Dutch test, alprazolam was associated with a larger SDLP than placebo. This 9-cm increase in SDLP was likened to the increase that might be seen with a BAC of 0.15%. Speed variability also increased significantly with alprazolam compared to placebo. When participants took alprazolam, they also exhibited significantly more right and left lane excursions than they did with placebo. Participants rated their own driving performance and alertness as significantly worse/greater with alprazolam than with placebo. RMS error in tracking ability (in a computerized task) was significantly impaired by alprazolam. Alprazolam also increased reaction time significantly in the Sternberg memory scanning task. After taking alprazolam, six of the twenty participants fell asleep while attempting to complete the on-road driving task. No participants fell asleep after taking placebo.

Fourteen participants took part in a crossover study comparing the effects of 0.5, 1 and 2 mg alprazolam with placebo (Evans, Troisi and Griffiths, 1994). All alprazolam doses significantly impaired participants’ ability to balance on one foot. All doses were also associated with poor performance on the DSST compared to placebo and slower choice reaction time. Performance on immediate and delayed recall memory tasks was also impaired by all doses of alprazolam, and participants felt significantly more drowsy after taking alprazolam than after placebo. In comparison with pre-drug baseline testing in 12 female volunteers, a single 0.5-mg dose of alprazolam significantly reduced critical flicker fusion threshold (CFFT; Subhan, Harrison and Hindmarch, 1986), as do most sedating drugs (stimulants increase CFFT). After repeated dosing for one week with 0.5 mg tid, however, this effect was no longer observed. Neither the acute nor the more chronic administration led to impairment in reaction times or divided attention performance, but participants did report significant subjective sedation at both times.

In a visual search task, 1 mg alprazolam increased reaction times and decreased hit rate in comparison with placebo (Munte, Gehde, Johannes, Seewald and Heinze, 1996). Twelve male participants completed this crossover study.
3 AMITRIPTYLINE

Amitriptyline (Elavil, Endep) is a tricyclic antidepressant. Typical doses run from 75-200 mg/day.

An acute dose of 50 mg amtriptyline significantly reduces critical flicker fusion threshold (Curran, 1990). Similar effects were found in a different study with 9 healthy female volunteers; CFFT was significantly reduced by an acute dose of 50 mg amtriptyline compared with placebo (Hindmarch, Harrison and Shillingford, 1988). In this study, too, choice reaction time was significantly increased by 50 mg amitriptyline and produced more errors on the Stroop test. Subjective drowsiness was also significantly higher with amitriptyline than with placebo.

In another study, participants taking fluoxetine rated themselves as significantly less drowsy than participants taking amitriptyline 75 mg. This difference was significant for the first two weeks of treatment with the drugs and was observable (but not significant) during the third week of treatment (Evans et al., 1994).

4 BIPERIDEN

Biperiden is an anticholinergic drug sometimes used to combat the extrapyramidal symptoms created by the administration of antipsychotic drugs.

Fourteen healthy volunteers were dosed twice in one day with 4 mg biperiden, placebo and another drug in a crossover study (Guthrie, Manzey, Scott, Giordani and Tandon, 2000). Subjective sedation (VAS) was significantly greater with biperiden than with placebo or the other drug. Backwards digit span was impaired by biperiden, along with performance on a number of memory tasks.

5 BROMPHENIRAMINE

Brompheniramine is an extremely sedating first-generation antihistamine. It is often combined with other drugs in OTC allergy and cold preparations. Since its sedative properties are no longer in question, it is not studied very often.

The effects of a combination of 12 mg brompheniramine, 15 mg phenylephrine and 15 mg phenylpropanolamine (commonly found in Dimetapp) were compared in a between-subjects study with the effects of placebo. Four-choice reaction time increased at 2.75 and 5.5 hours post-dose (Millar and Standen, 1982).

6 BUTORPHANOL

Butorphanol is a narcotic analgesic that can be administered transnasally for relief of migraine headaches and postoperative pain.

In a crossover study with 10 healthy participants, 2 mg butorphanol administered transnasally significantly impaired DSST performance for 120 minutes following dosing (Zacny, Lichtor, Klafta, Alessi and Apfelbaum, 1996). There were no significant effects on two other measures of cognitive performance. Subjective sedation, sleepiness and stimulation were also increased by the same dose, compared to placebo. A 1-mg dose had no significant effects compared to placebo. The authors state that “Certainly, child care,
operating machinery and driving an automobile would be contraindicated at this dose, at least when administered acutely” (p. 934).

7  CETIRIZINE

Cetirizine (Zyrtec) is generally classified as a second-generation antihistamine. However, it is the most “controversial” of the antihistamines in the sense that some studies indicate that it causes sedation and performance impairment; some do not show these effects.

Ten and twenty mg cetirizine did not cause subjective drowsiness (VAS) in a small sample of 4 allergic volunteers, whose ratings were compared to those of 4 other volunteers who took placebo (Gengo and Gabos, 1987). There was also no significant effect of cetirizine on Stroop test performance, and it did not cause changes in CFFT performance. Digit symbol substitution was unaffected by cetirizine at 5, 10 and 20 mg in another study, when compared with placebo (Gengo, Gabos and Machtler, 1990).

Ten mg cetirizine did not cause changes in lateral position in on-the-road driving (the standard, 100-km driving test) when compared with placebo (Patat, Stubbs, Dunmore, Ulliac, Sexton, Zieleniuk, Irving and Jones, 1995). This dose did, however, cause slight but significant impairments in adaptive tracking and divided attention (tracking and vigilance) performance. In another study (Volkerts, van Willigenburg, van Laar and Maes, 1992), 10 mg was not associated with elevated SDLP after acute dosing or after 4 days of dosing. Cetirizine did not affect reaction time or memory performance in this study, either. Van Cauwenberge (1992), however, reported significant elevations in SDLP with 10 mg cetirizine that were comparable to the effects of a 0.1% BAC, in a crossover study with 16 participants. Cetirizine also seemed to potentiate the effects of alcohol when the two were administered together. Significantly more allergy patients reported sedation as a side effect with 10 mg cetirizine than with placebo in a study with 278 participants, involving an allergy challenge situation. Ten mg cetirizine did cause significant increases in subjective sedation in 15 participants in a crossover study (comparison with placebo; Simons, Fraser, Reggin and Simons, 1996).

Walsh, Muehlbach and Schweitzer (1992) took the novel approach of asking participants to complete a simulated assembly line task. The task was essentially a vigilance task, with participants being asked to accept or reject simulated computer parts coming off of a simulated assembly line. However, the task lasted for the duration of a regular work day, 8 hours. This study had a between-subjects design with four participants each receiving 10 mg cetirizine, 25 mg hydroxyzine or placebo. Cetirizine did not affect the number of correct responses or the number of correct rejections of the simulated computer parts. Similar results were found in a second study using the simulated assembly line task and three-day administration of 10 mg cetirizine (Schweitzer, Muehlbach and Walsh, 1994). In this study, cetirizine also did not produce subjective sedation when compared to placebo.

8  CHLOROQUINE

Chloroquine is a drug used for malaria prophylaxis. Unfortunately, it is stored in the retinal pigment epithelium for several years after it is taken, which can lead to irreversible blurred vision, visual field losses and color vision defects.
In twenty-eight patients shown to have chloroquine retinopathy (defined by bilateral scotomas), 26 failed more than one color vision test, while only 5 out of 25 patients who were taking chloroquine but had no retinopathy failed even one of the tests (Vu, Easterbrook and Hovis, 1999). The primary color defect in patients with chloroquine retinopathy is difficulty distinguishing blue, a defect that may not be picked up in standard red-green color blindness testing.

9 CHLORPHENIRAMINE

Chlorpheniramine (Chlor-Trimeton) is a heavily sedating first-generation antihistamine. After four days of dosing with four mg chlorpheniramine tid, CFFT decreased, compared with placebo, in a between-subjects study with 10 participants per group (Hindmarch and Parrott, 1978). In another study, the same acute dose caused significantly increased scores on the Stanford Sleepiness Scale at three hours post-dose, compared with placebo, and choice reaction time was significantly longer with chlorpheniramine at 1 and 3 hours post-dose (Witek, Canestrari, Miller, Yang and Riker, 1995).

10 CLEMASTINE

Clemastine (Tavist) is a first-generation antihistamine. Two mg (acute) clemastine significantly increased SDLP compared with placebo in the standard 100-km on-road test (Vuurman, Uiterwijk, Rosenzweig and O'Hanlon, 1994). This study was conducted with 24 participants in a crossover design. Clemastine also increased subjective drowsiness ratings, reduced CFFT and impaired tracking performance and both parts of a divided attention test consisting of a tracking and a reaction time task. One and two mg clemastine also impaired auditory reaction time at 2.5 hours post-dose in a crossover study with acute dosing (Peck, Fowle and Bye, 1975). Two mg still slowed reaction time at 5 hours post-dose and impaired DSST performance at 2.25 and 4.75 hours post-dose.

11 DIAZEPAM

Diazepam (Valium) is a very commonly-used anxiolytic with significant CNS depressant properties. In a between-subjects comparison, eight participants who took 10 mg diazepam performed significantly worse in a low-fidelity driving simulation than eight others who took placebo. Additional deficits were noted in participants’ divided attention performance—they exhibited longer reaction times to targets at one hour post-dose, but not at three or five hours post-dose (Moskowitz and Smiley, 1982). After continuous diazepam dosing (15 mg/day) for eight days, when participants were dosed on the eighth day, performance was similarly affected; tolerance to the drug’s effects on performance did not appear to have developed.

Twelve anxious patients were dosed with 5 mg diazepam tid for one week before completing the standard 100-km on-road driving test (van Laar, Volkerts and van Willigenburg, 1992). One participant asked to stop driving due to the sedative effects of the drug in the first week of testing, and another participant asked to stop during the
driving test in the second week of dosing. Diazepam significantly increased SDLP after one, two and three weeks (but not four weeks) of dosing (in comparison to a pre-drug baseline). In an epidemiological study of all motor vehicle fatalities in one Texas county over 18 months (Garriott, DiMaio, Zumwalt and Petty, 1977), diazepam was the drug most commonly detected in blood and urine tests. It was present in 56.5% of samples that were positive for any drug.

Acute doses of 10 mg diazepam decreased CFFT in crossover studies with men in different age groups (compared with placebo; Palva, Linnoila, Routledge and Seppälä, 1982). Moser, Huether, Koch-Weser and Lundt (1978) made a similar finding in 20 healthy male participants.

12 FLURAZEPAM

Flurazepam (Dalmane), a benzodiazepine derivative, is a hypnotic sleep aid.

Moskowitz and Chen (1990) reported on a study in which they administered 45 mg flurazepam to 30 healthy adult males in a crossover study. Forty-five mg is more than the recommended prescription dose of 15-30 mg. Testing was conducted 9 hours post-dose, after participants had a full night’s sleep. Flurazepam 45 mg was associated with significant increases in choice (but not simple) reaction time when compared with placebo. In divided attention testing, tracking error and mean reaction time increased with flurazepam. Reaction time and number of misses in a vigilance task also increased with flurazepam.

In another study of residual impairment with flurazepam (Warburton and Wesnes, 1984), six participants were given 30 mg flurazepam and tested 10 hours post-dose. Each drug treatment was examined twice in this study. Flurazepam significantly reduced the number of correct detections participants made in a vigilance task (compared with placebo) as well as slowing reaction times.

13 HYDROXYZINE

Hydroxyzine (Atarax) is a heavily sedating first-generation antihistamine. It is also used for anxiety reduction and as a sleep aid.

In a crossover study with 12 male allergy patients, 25 mg hydroxyzine (acute) decreased CFFT and impaired Stroop test scores at 2 and 4 hours post-dose (Gengo, Dabronzo, Yurchak, Love and Miller, 1987). The same dose of hydroxyzine also slowed reaction time performance in a 30-minute vigilance test (Seidel, Cohen, Bliwise, Dement, 1987). This was a between-groups comparison between hydroxyzine and placebo with 15 participants per group. Performance impairment was no longer evident 6 hours post-dose. In another crossover study with 16 healthy participants, the effects of 25 mg hydroxyzine were compared with those of a placebo after 2 and 5 days of twice-daily dosing. Simple and choice reaction times were significantly longer with hydroxyzine than with placebo after 2 days of dosing, and this effect was still present and significant after 5 days of treatment with hydroxyzine (Goetz, Jacobson, Murnane, Reid, Repperger, Goodyear and Martin, 1989). Subjective drowsiness, measured on a 4-point scale, was also significantly greater on both test days with hydroxyzine than with placebo.
In the simulated assembly line study described above (Walsh et al., 1992), 25 mg hydroxyzine given acutely in a between-subjects design had several effects on performance. Participants made significantly fewer correct responses and fewer correct rejections with hydroxyzine than participants who took placebo. There was a significant interaction between time of day and drug administered, in that performance was significantly worse at 9:30 AM and 2 PM with hydroxyzine than with placebo. Participants also rated their own performance as significantly worse with hydroxyzine than with placebo and felt significantly sleepier (VAS).

**14 IMIPRAMINE**

Imipramine (Tofranil) is a tricyclic antidepressant with significant anticholinergic properties.

Van Laar, van Willigenbrg and Volkerts (1995) conducted research with 12 healthy young adults and 12 elderly adults to determine the effects of 50 mg imipramine given twice daily on driving performance. In this crossover study, after acute dosing, imipramine produced a significantly elevated SDLP in the young adults but not in the elderly adults (compared to placebo). The effect in the young adults was still observable and significant but small on the 7th day of dosing. Both groups of participants were significantly sleepier with imipramine than with placebo after acute dosing, but the article did not report on the incidence of subjective sleepiness after 7 days of dosing.

**15 LITHIUM**

Lithium is a drug given primarily to treat bipolar disorder.

In one study (Hatcher, Sims and Thompson, 1990), 16 patients who had been taking lithium for at least three months were compared in their choice reaction time performance with 22 healthy drug-free controls. Reaction times in the patients were significantly longer than in the controls. The patients were taking different doses of lithium, which had been titrated to meet their treatment needs. However, lithium dosage was not significantly related to reaction time. The authors commented that lithium does not cause subjective sedation but appears to interfere with at least one aspect of psychomotor performance.

Lithium also significantly impaired long-term retrieval measures of memory in 22 bipolar patients treated with different doses (Shaw, Stokes, Mann and Manevitz, 1987).

**16 LORAZEPAM**

Lorazepam (Ativan) is an anxiolytic. Its relatively long duration of action makes it useful as a hypnotic and a surgical pre-medication as well.

Two mg lorazepam significantly reduced CFF threshold in acute dosing of twelve female volunteers, but there was no effect after seven days of dosing at 2 mg tid (Subhan et al., 1986). This dose did, however, increase choice reaction times and impair performance in both aspects of a divided attention task (tracking and reaction time) both acutely and after repeated dosing. Subjective sedation was reported by the participants acutely but not after repeated dosing. These comparisons are all in reference to pre-drug baseline testing and ratings.
With acute dosing of 2 mg lorazepam, experienced users of CNS depressants exhibited impaired tracking performance and standing steadiness (balance) for 4 hours following dosing (Sellers, Schneiderman, Romach, Kaplan and Somer, 1992). Memory performance was also impaired; however, none of the tasks completed by participants are described particularly well in the publication. The drug effects are with reference to the effects of placebo in this crossover study.

Mean tracking speed in an adaptive tracking task and divided attention performance were significantly impaired by acute dosing with 0.5 mg lorazepam (Irving and Jones, 1992). Two mg impaired performance on those tasks as well as reaction time to hazards and lateral deviation in curves in a closed-course driving task. The participants were twelve 45-55-year-old female volunteers.

In a parallel groups study with 9 participants per group, 2 mg lorazepam given acutely impaired response time on the Baddeley task, prose recall, digit cancellation, DSST and pursuit rotor when compared to placebo (Curran, Schifano and Lader, 1991). Subjective sedation was also significantly greater with lorazepam than with placebo. Sedation scores were more closely related to psychomotor testing scores than to the scores from memory tasks, and the authors speculated that any amnestic effect of lorazepam was not secondary to the drug’s sedative effects.

In another parallel groups study with 12 participants per group, 2.5 mg lorazepam given acutely impaired performance on a number of measures, including number cancellation, symbol copying, simple reaction time and memory for images (File, 1992). A crossover study with 12 healthy participants found that 1 mg lorazepam impaired simple reaction time 1 and 2 hours post-dose and choice reaction time, word and picture recognition speed 1-6 hours post-dose (Hanks, O’Neill, Simpson and Wesnes, 1995). Subjective sedation was not significantly greater with lorazepam than with placebo.

One mg of lorazepam three times daily was given to 12 female participants in a study of cognitive and driving performance (Hindmarch and Gudgeon, 1980). Dosing continued for three days before participants were tested. Lorazepam caused significant subjective sedation compared to placebo, and it impaired mental arithmetic and letter cancellation performance as well. Car driving ability was rated by driving instructors on the following tasks: reverse parking, a three-point turn, a slalom around cones and brake reaction test. These abilities were all significantly impaired by lorazepam compared with placebo.

17 METHAMPHETAMINE

Methamphetamine is a stimulant drug of abuse; it also has limited therapeutic applicability use in weight control.

Chronic users of methamphetamine (who did not, however, abuse other drugs) demonstrated memory impairment and had difficulty with the DSST and Trails B tests compared to drug-free controls (Simon, Domier, Carnell, Brethen, Rawson and Ling, 2000). The pattern of results exhibited by the drug users in Stroop testing was similar to that exhibited by people with “isolated pre-frontal [brain] injuries” (p. 226).
18 MORPHINE

Morphine is a strong opioid analgesic often used to treat cancer pain.

In a crossover study of 12 participants, 10- and 15-mg doses of morphine were associated with significant memory impairment at one hour post-dose (Hanks et al., 1995). Subjective alertness was not altered by morphine, but the participants’ critical flicker fusion threshold was significantly reduced by both morphine doses.

19 OXYBUTYNIN

Oxybutynin (Ditropan) is a tertiary amine ester with anticholinergic/antimuscarinic, spasmylytic and local anesthetic properties. It is commonly used to treat urinary frequency and urgency, nocturia and urge incontinence arising from overactive detrusor function or instability. The recommended dose is 5 mg BID or TID with a maximum dose of 5 mg QD.

The most common side effect of anticholinergic drugs is dry mouth; this effect has been reported by 50% of patients taking oxybutynin in some studies (Pietzko, Dimpfel, Schwantes and Topfmeier, 1994). Blurred vision and constipation are also reported, but less frequently (Davila, Daugherty and Sanders, 2001).

Cognitive impairment as a possible adverse effect of oxybutynin has been investigated in only a few studies. In one such study (Katz, Sands, Bilker, DiFilippo, Boyce and D’Angelo, 1998), oxybutynin was associated with reduced performance on certain cognitive measures. Twelve normal individuals (7 men and 5 women) aged 65-76 were given placebo, 5 mg oxybutynin, 10 mg oxybutynin, or 50 mg diphenhydramine across four separate visits before completing a series of cognitive tests. These tests included the Buschke Selective Reminding Test, Digit Span, Verbal Fluency - Letters, Trailmaking Parts A and B, and Digit Symbol Substitution administered by an interviewer, and several tests from the Neurobehavioral Evaluation System administered by computer.

The results of the study indicated that oxybutynin (dose not identified) resulted in a statistically significant reduction in performance on 7 of 15 cognitive measures. The effects of oxybutynin were at least as great as those produced by diphenhydramine. Two tests, the Buschke Selective Reminding Test and the Reaction Time Test (part of the Neurobehavioral Evaluation System), were especially sensitive to performance decrements caused by oxybutynin. The authors encouraged caution in interpreting the results due to the small sample used but encouraged physicians to monitor patients on oxybutynin for possible cognitive effects.

Elsewhere, oxybutynin was compared to trospium chloride (a drug similar to oxybutynin that is not available in the United States) to evaluate central nervous system effects (Pietzko et al., 1994). The participants, 12 healthy males, were randomly assigned to one of three treatments: oxybutynin (20 mg), trospium chloride i.v. (1.2 mg), or trospium chloride p.o. (45 mg). Oxybutynin was found to lower heart rate and affect EEG results.

Another study compared immediate-release oxybutynin administered orally to that administered via a transdermal patch (Davila et al., 2001). In this study, 76 older patients (70 women and 6 men) were randomly assigned to receive either the oral medication or
the transdermal patch. Adverse effects related to the central nervous system for transdermal and oral medication, respectively, included: drowsiness (18% vs. 37%), dizziness (16% vs. 26%), and blurred vision (18% vs. 24%).

One review of the effectiveness and adverse effects of extended-release oxybutynin (Goldenberg, 1999) has been published. One of the studies reviewed examined oxybutynin in 257 patients and found that dry mouth was reported by 57% of participants, constipation by 10% of participants and drowsiness by 7% of participants. Across the studies reviewed, dosages of oxybutynin ranging from 5 to 30 mg resulted in the following reports of adverse effects: dry mouth (61%), constipation (13%), drowsiness (12%), headache (10%), blurred vision (8%), and dizziness (6%). No information was provided regarding sample sizes or the comparison treatments (e.g., active drug or placebo) used in these clinical trials.

The elderly are more sensitive to the adverse effects of anticholinergic drugs than the younger population (Feinberg, 1993). Older people are also likely to suffer from multiple chronic conditions requiring treatment. When multiple drugs are prescribed for multiple conditions (one of which, in the elderly, is likely to be overactive bladder), the side effects can be additive, leading to behavioral or pharmacologic toxicity. For this reason, it is particularly important to understand the effects of all of the anticholinergic drugs.

20 PROMETHAZINE

Promethazine (Phenergan) is a sedating, first-generation antihistamine that is also used as an anti-emetic. In a crossover study with 6 participants, 10 mg promethazine given acutely impaired visual vigilance performance and reaction time compared with placebo (Nicholson and Turner, 1998). It also increased subjective sleepiness and decreased sleep latency from 1.5-5.5 hours post-dose. Another crossover study with 24 participants showed that 30 mg promethazine given acutely significantly decreased CFFT 3-9 hours post-dose (Hindmarch, Shamsi, Stanley and Fairweather, 1999).

21 SECobarbital

Secobarbital is a barbiturate, used to treat insomnia and sometimes given before surgery to relieve anxiety.

In a study of the effects of secobarbital on reactions to letter stimuli presented with different levels of visual masking or degradation, secobarbital, at doses of 2 and 2.9 mg/kg body weight, was associated with increased recognition reaction time and a significant drug x visual degradation interaction, in comparison with placebo (Logsdon, Hochhaus, Williams, Rundell and Maxwell, 1984). Secobarbital had greater negative effects on recognition reaction time as stimuli were more heavily masked. Secobarbital was also associated with significantly more recognition errors than placebo, and a drug x visual degradation interaction similar to the one mentioned previously was also found. This study was conducted with 18 male participants in a crossover design.

Another study reported on the administration of 100 mg secobarbital to 30 male participants in a between-groups study comparing secobarbital, d-amphetamine and placebo (Schroeder, Collins and Elam, 1974). Participants were asked to perform a
compensatory tracking task while stationary and while undergoing angular acceleration. There were no between-group differences in tracking accuracy while participants were stationary, but tracking accuracy was significantly worse in the secobarbital group than in the placebo group in the angular acceleration condition.

22 TEMAZEPAM

Temazepam is a benzodiazepine with a moderate half-life of approximately 12 hours. Ten to twenty mg of temazepam is a typical dose for the treatment of insomnia.

Van Steveninck, Schoemaker, Pieters, Kroon, Breimer and Cohen (1991) published a study comparing the effects of 5, 10 and 20 mg temazepam with placebo. All of the temazepam doses slowed saccadic eye movements; the 10- and 20-mg doses increased subjective drowsiness compared to placebo. The accuracy of saccades to a rank of LEDs was also significantly diminished by all 3 temazepam doses. The 20-mg dose also impaired adaptive tracking performance compared to placebo.

23 TRIAZOLAM

Triazolam (Halcion) is a benzodiazepine hypnotic with a very short half-life of only about 3 hours.

In a crossover study comparing 0.25 mg triazolam with placebo, triazolam significantly decreased immediate and delayed recall at 1.25 and 8.25 hours post-dose (Troy, Lucki, Unruh, Cevallos, Leister, Martin, Furlan and Mangano, 2000). This study employed 24 participants and also showed that 0.25 mg triazolam impaired performance on the DSST at both testing times.

In a between-subjects study with 10 participants per group, two doses (0.25 and 0.5 mg) of triazolam were compared with placebo (Wesensten, Balkin and Belenky, 1996). The larger drug dose was associated with the completion of fewer logical reasoning trials than placebo, and decision time in the logical reasoning task increased with this dosage as well. Similar effects of the drug were seen on a mental arithmetic task, in which the percentage of trials completed was significantly lower with 0.5 mg triazolam than with placebo, and significantly more errors were made. Additionally, two participants who received the larger triazolam dose were too sedated to complete the test battery.

24 TRIHEXYPHENIDYL

Trihexyphenidyl (Artane) is an anticholinergic drug used to treat the extra-pyramidal symptoms caused by antipsychotic drugs.

In a crossover study of 14 healthy volunteers given 5 mg trihexyphenidyl and placebo, the drug was associated with significant decreases in digit span performance and memory impairment on the Buschke selective reminding task (Guthrie et al., 2000).

25 TRIPLENNAMINE

Tripelennamine (PBZ) is a widely-abused antihistamine. A 50-mg dose was administered to 18 adult volunteers in a crossover study and compared with placebo (Stern, Chait and
Johanson, 1989). Tripelemamine was associated with significantly higher subjective ratings of fatigue, confusion and sedation than placebo. A 25-mg dose did not significantly elevate subjective ratings on these scales.

26 TRIPROLIDINE

Triprolidine is a first-generation antihistamine and is very sedating. It is commonly combined with pseudoephedrine in OTC allergy medications.

Triprolidine was shown to impair performance in a number of domains in a study conducted by Volkerts et al. (1992). Performance testing was conducted on days 1 and 4 of dosing, when the drug had been administered at 5 mg bid. SDLP increased significantly on days 1 and 4 compared with placebo in the standard 100-km test. Subjective driving performance was significantly worse with triprolidine on day 1 but not on day 4. Triprolidine prolonged reaction time significantly on day 1 in two out of three choice reaction time tasks; no significant impact of triprolidine on reaction time was observable on day 4. In a similar study (O’Hanlon, 1988), 10 mg triprolidine caused significant increases in SDLP 1 and 3 hours post-dose, but participants stopped reporting subjective sedation prior to the test session at 3 hours post-dose. The author compared the SDLP impairment with a 0.05% BAC.

Three acute doses of triprolidine (1.25, 2.5 and 5 mg) were associated with decreased vigilance performance in an hour-long task; fewer signals were detected with triprolidine than with placebo in a crossover study with 24 participants (Peck et al., 1975). All of these doses also impaired auditory reaction time at 2.5 hours post-dose, but only the two higher doses were still impairing 5 hours post-dose. The highest dose impaired DSST performance at 2.25 and 4.75 hours post-dose. Five mg also caused subjective sedation in a placebo-controlled crossover study 1.5 hours post-dose (Alford, Bhatti, Rombaut, Curran and Hindmarch, 1989).

In a crossover study with 7 female participants, 10 mg triprolidine was associated with impaired visual-motor coordination and dynamic visual acuity (Bradley and Nicholson, 1987). It also decreased the number of correct substitutions in the DSST and significantly increased CFFT when compared with placebo. Subjective drowsiness was also significantly higher after dosing with triprolidine than with placebo.

27 ZOLPIDEM

Zolpidem (Ambien) is a hypnotic drug used to treat insomnia. It is rapidly absorbed (Tmax 1-2 hours) and has a short half-life of only 1-2 hours.

In a crossover study comparing 10 and 20 mg zolpidem with placebo, zolpidem significantly decreased immediate and delayed recall at 1.25 and 8.25 hours post-dose (Troy et al., 2000). The 20-mg dose significantly decreased digit span length at 1.25 hours post-dose and impaired DSST performance at both testing sessions. The 10-mg dose impaired DSST performance only at 1.25 hours post-dose. Both doses significantly impaired divided attention performance (in terms of tracking, variability and reaction time) at 1.25 but not 8.25 hours post-dose. This study employed 24 participants.
A second study, employing 18 adult volunteers, dosed participants with 5, 10 and 20 mg/70 kg of zolpidem and tested them in a negative priming task (Mintzer and Griffiths, 1999). The two higher doses were associated with significant memory impairment compared to placebo; correct responses in a recognition task were also decreased to a significant extent by the highest dose.

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