Abuse Liability of Alprazolam Relative to Other Commonly Used Benzodiazepines: A Review

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RUSH, C. R., S. T. HIGGINS, W. K. BICKEL, AND J. R. HUGHES. Abuse liability of alprazolam relative to other commonly used benzodiazepines: A review. NEUROSCI BIOBEHAV REV 17(3) 277-285, 1993—Nonhuman and human studies comparing the abuse liability of alprazolam to other commonly used benzodiazepines are reviewed. These studies are reviewed to determine to what extent prospective, controlled, experimental studies support opinions that alprazolam’s abuse liability is greater than that of other commonly used benzodiazepines. Studies comparing the self-administration of alprazolam, the discriminative stimulus effects of alprazolam, self-reported effects of alprazolam, physiological dependence on alprazolam, and adverse effects of alprazolam relative to other benzodiazepines are reviewed. Overall, the experimental literature does not support the widely held belief that alprazolam’s abuse liability is greater than that of other benzodiazepines, but much more research is needed. Such research should focus explicitly on alprazolam’s reinforcing effects, and the nature and severity of the discontinuation syndrome associated with its long-term use. Important issues such as selection of an appropriate comparison drug, selection of an appropriate population, dosing regimen and test doses need to be considered in future studies.

ALPRAZOLAM (XANAX™) is the most commonly prescribed benzodiazepine in the United States (75). Some evidence suggests alprazolam is distinguishable from other benzodiazepines in terms of its abuse potential. First, individuals with a history of alcohol and opiate abuse prefer alprazolam to other benzodiazepines (e.g., chlordiazepoxide and oxazepam), and report alprazolam produces a greater “high” (44, 80). Second, 75% of drug-abuser-experienced physicians reported alprazolam as having a greater potential for abuse than other benzodiazepines (40). Third, emergency room admissions involving alprazolam increased 50% between 1985–1988 (16–19). Finally, admissions to substance abuse treatment clinics for alprazolam dependence increased during this same period, with three-fold increases reported in some clinics (24).

The present paper reviewed the existing experimental literature to determine to what extent these concerns are supported by prospective, controlled, experimental studies. Retrospective studies, case reports, and published abstracts are not discussed. Both nonhuman and human studies assessing alprazolam’s liability for abuse (i.e., maintenance of self-administration), as well as its liability of abuse (i.e., adverse effects) relative to other benzodiazepines are reviewed (12,13). The abuse potential of alprazolam and diazepam was recently reviewed (46), but the present paper differs from this report in that studies comparing alprazolam and other commonly used benzodiazepines (e.g., lorazepam and triazolam) are also included.

STUDIES CONDUCTED WITH LABORATORY ANIMALS

Preclinical trials are critical in determining the abuse liability of a drug. First, these trials determine whether a drug maintains self-administration, which is thought to be central to its abuse liability (12,13,37). Second, drug discrimination studies determine a drug’s interoceptive effects, which may be analogous to categorizing the self-reported drug effects in humans (57,58). Finally, studies of a drug’s lethality in overdose and ability to produce physiological dependence characterize its adverse effects.

Self-Administration

One study compared the number of daily self-administrations of alprazolam (0.01–3.2 mg/kg/injection), bromazepam

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Interceptive Stimulus Effects

Interceptive stimulus (i.e., discriminative stimulus) effects of a drug are typically assessed in laboratory animals using drug discrimination procedures (57,58). In these procedures, one response (e.g., press lever A) is reinforced following the injection of drug and a different response (e.g., press lever B) following the injection of saline. Following training, novel compounds can be substituted to determine if subjects respond as if the novel drug is the training drug. The abuse liability of the novel drug can be inferred if it substitutes for a drug with a known abuse liability.

Three studies assessed the discriminative stimulus effects of alprazolam relative to other benzodiazepines (22,28,79). In the first study, four rhesus monkeys were trained to discriminate pentobarbital (10 mg/kg) from saline (27). Alprazolam, bromazepam, diazepam, flurazepam, halazepam, lorazepam, midazolam, oxazepam, temazepam, or triazolam occasioned at least 80% pentobarbital-appropriate responding in all monkeys. In the second study, separate groups of rats were trained to discriminate a low (1 mg/kg) or high (10 mg/kg) dose of diazepam from saline (79). Alprazolam, adinazolam, triazolam, and pentobarbital occasioned 80% diazepam-appropriate responding in both groups. In the third study, five pigeons were trained to discriminate midazolam (1.0 – 3.0 mg/kg) from saline (28). Alprazolam, diazepam, flurazepam, lorazepam, nitrazepam, nordiazepam, and triazolam occasioned at least 80% midazolam-appropriate responding in all pigeons. Overall, these studies suggest alprazolam produces a pharmacological profile similar to that of other benzodiazepines and sedative/hypnotic compounds.

Adverse Effects

Lethality in overdose. Alprazolam, like other benzodiazepines, has a large margin of safety, and death due to overdose is rare (30,33). In the rat, for example, the lethal dose (i.e., LD₅₀) alprazolam is 3312,171 mg/kg (63), while the effective anxiolytic dose (ED₅₀) is 0.5 mg/kg (77). Thus, the therapeutic ratio (LD₅₀/ED₅₀) of alprazolam is 662,4,342.

Physiological dependence. Benzodiazepine physiological dependence and withdrawal is often assessed in nonhuman laboratory animals by administering the drug chronically, abruptly discontinuing it, and assessing withdrawal with a standardized scale. Benzodiazepine withdrawal can also be precipitated with a benzodiazepine antagonist (e.g., flumazenil) in subjects chronically maintained on drug.

In an abrupt discontinuation experiment, 0.025% (percent by body weight) alprazolam was added to the daily food ration of mice, and subjects ingested approximately 40–65 mg/kg/day of alprazolam for 28 days (32). These data were compared to those from a similar experiment in which 0.10% (percent by body weight) diazepam was added to the daily food ration of mice, and subjects ingested approximately 1000 mg/kg/day of diazepam for 52 days (31). Removal of drug from the diet resulted in a physiological withdrawal that was qualitatively similar in both alprazolam- and diazepam-treated mice (31,32). The peak withdrawal scores associated with alprazolam dependence ranged from 19-25 vs. 26-36 with diazepam. Alprazolam withdrawal was discernible 8 h after drug discontinuation, peaked at 32 h, and abated by 2-3 days (32). Diazepam withdrawal onset approximately 24 h after drug discontinuation, peaked at 72 h, and lasted up to 17 days (31). These findings must be viewed tentatively because exposure were not equivalent across the two experiments (alprazolam < diazepam), and these variables are important determinants of the severity of withdrawal (49).

One study explicitly examined the precipitated withdrawal syndrome in dogs (N = 6) chronically treated with alprazolam (48 mg/kg/day) (76). Following at least 1 week of exposure, subjects were challenged with oral administrations of flumazenil (6, 18, or 36 mg/kg). Scores on a modified version of the Nordiazepam-Precipitated-Abstinence Scale and the frequency of seizures generally were an increasing function of flumazenil dose. These data were compared to those from a similar experiment in which dogs were chronically maintained on diazepam (24 or 36 mg/kg/day) and challenged with oral administrations of flumazenil (2, 6, or 18 mg/kg) (54). Nordiazepam-Precipitated-Abstinence-Scale scores for the alprazolam-treated dogs were significantly less than for the diazepam treated dogs following the 6 and 18 mg/kg doses of flumazenil. Seizure activity did not differ significantly across drugs (76).

Another report summarized several experiments from the same laboratory in which dogs were chronically treated with alprazolam, diazepam, flunitrazepam, halazepam, lorazepam, oxazepam, and nordiazepam and then challenged with flumazenil (52). Drugs were administered 4–5 times a day for 210 weeks followed by oral administrations of flumazenil (2–72 mg/kg). Scores on the Benzodiazepine Precipitated-Abstinence Scale and the frequency of seizures generally were an increasing function of flumazenil dose in all benzodiazepine-treated dogs, while benzodiazepine-naive dogs showed no effect. Following flumazenil (18 mg/kg), the benzodiazepines appeared to differ in terms of Benzodiazepine-Precipitated-Abstinence Scale scores (diazepam > flunitrazepam = halazepam > alprazolam = nordiazepam > oxazepam > lorazepam) and the frequency of seizures (flunitrazepam > alprazolam > diazepam > nordiazepam > lorazepam > oxazepam), but the report did not mention whether between-drug differences were statistically significant.

Summary of Studies With Nonhumans

The available preclinical data suggest alprazolam's abuse liability does not differ from that of other benzodiazepines. Alprazolam maintains rates of self-administration similar to
those of other benzodiazepines (38). The interoceptive stimu-
lus effects of alprazolam are similar to those of other benzodi-
azepines as determined in drug discrimination procedures (22,
28,79). The adverse effects of alprazolam are not significantly
different from those of other benzodiazepines. As with other
benzodiazepines, alprazolam has a high therapeutic-lethality
ratio. The withdrawal syndrome associated with chronic al-
prazolam treatment onsets, peaks and abates more rapidly,
but may be somewhat less severe at peak than that of diazep-
am (31,32).

STUDIES CONDUCTED WITH HUMANS

Human abuse liability assessment trials should determine
whether a drug maintains self-administration and its adverse
effects. Self-administration procedures adapted for use with
human subjects, unfortunately, are under utilized in such tri-
als (8,36). Instead, self-report instruments are commonly used
to assess the abuse liability of drugs in humans (45). Com-
monly studied adverse effects of benzodiazepines include
physiological dependence, impairment of recall, learning and
performance, and interactions with alcohol (81–83).

Self-Reported Effects

One study examined self-reported preference for alprazo-
lam over diazepam in patients (N = 7) undergoing benzodia-
epine-withdrawal therapy (2). Patients were stabilized on 5
mg/day of diazepam (t.i.d.). Alprazolam (0.5 mg) was then
substituted for the morning or noon medication and patients
reported their preference 1 h prior to the evening medication.
Subjects preferred alprazolam over diazepam on 13 of 14 test
occasions. A second experiment was conducted in these same
patients with a lower dose of alprazolam (0.37 mg), but alpra-
zolam was not preferred to diazepam.

Another experiment compared the self-reported effects of
alprazolam (2 mg), diazepam (20 mg), lorazepam (4 mg), me-
thaqualone (300 mg), and placebo in recreational sedative
users (N = 30) using a within-subject, randomized, double-
blind design (56). Each benzodiazepine increased subject rat-
ings of sedation and scores on the Morphine-Benzedrine
Group (MBG) scale of the Addiction Research Center Inven-
tory, a putative measure of euphoria. Diazepam and lora-
zapam did not differ from each other in terms of MBG
scores. Alprazolam, diazepam and lorazepam did not differ in
terms of estimated street value or subject ratings of “high.”

Adverse Effects

Physiological dependence. Terminating benzodiazepine
therapy results in a recognizable discontinuation syndrome,
and this syndrome is purportedly more common and severe
when treatment involved a short half-life benzodiazepine
(e.g., alprazolam or lorazepam) (59,64,67). Despite these re-
ports and several case studies of severe withdrawal syndrome
following the discontinuation of alprazolam (14,24), only
three controlled discontinuation studies with humans included
alprazolam and other benzodiazepines (65,68,74).

In one study, the discontinuation syndromes of short half-
life (SHL) (alprazolam and lorazepam) and long half-life
(LHL) (clorazepate and diazepam) benzodiazepines were com-
pared following abrupt termination in outpatients currently
undergoing treatment with these drugs (65). The groups dif-
ferred in terms of amount of daily medications and length of
treatment (SHL < LHL), but not clinical features. Patients
withdrew with SHL benzodiazepines exhibited higher rates of
attrition and relapse, and higher scores on the Hamilton Anxi-
ety Scale for Anxiety and the Physician-Withdrawal Checklist.
Peak severity of the discontinuation syndrome occurred 2–3
and 4–8 days after the termination of medication for most
patients treated with SHL and LHL compounds, respectively.
Specific between-drug comparisons (i.e., alprazolam vs. diaze-
pam or alprazolam vs. clorazepate) were not reported. Alpra-
zolam-treated patients experienced slightly lower peak scores
on the Physician-Withdrawal Checklist than lorazepam-
treated patients even though the pharmacokinetics of these
two drugs are similar (20,35), but this may be attributable
to differences in amount of daily medications and length of
treatment (alprazolam < lorazepam).

A second study examined the effects of a gradual taper
(i.e., 25%/week) in outpatients currently undergoing treat-
ment with SHL (alprazolam and lorazepam) and LHL (clora-
zepate and diazepam) benzodiazepines (74). Again, the groups
differed in terms of the amount of daily medication and length
of treatment (SHL < LHL), but not clinical features. Pa-
ients treated with SHL benzodiazepines exhibited higher rates
of attrition and relapse. Patients treated with SHL benzodiaze-
pines experienced lower peak scores on the Hamilton Anxiety
Scale for Anxiety and Physician-Withdrawal Checklist scales.
Specific between-drug comparisons were not reported. The
authors of this study combined their data with that from the
Rickels et al. (1990) study (65) and found a statistically signifi-
cant interaction of half-life and mode of discontinuation
across most measures. Patients treated with SHL benzodiaze-
pines experienced a more severe discontinuation syndrome
than patients treated with LHL benzodiazepines when the
drugs were abruptly terminated, but not when they were gradu-
ally tapered as is medically recommended.

A final study assessed the effects of a partial taper and
abrupt discontinuation of alprazolam, diazepam, and placebo
in panic patients (68). Alprazolam- and diazepam-treated pa-

tients were ingesting a comparable number of tablets, while
placebo patients were taking significantly more tablets. The
number of tablets were gradually tapered to approximately
half over 2 weeks. The remaining medications were then
abruptly discontinued. Following the 2-week taper and the
Hamilton Anxiety Scale for Anxiety did not differ signifi-
cantly across the three groups. Following abrupt discontinua-
tion, however, scores on the Hamilton Anxiety Scale for Anxi-
ety were significantly higher for the alprazolam group than
the diazepam and placebo groups. There was not a significant
increase in panic attacks following the partial or abrupt dis-
continuation of drug.

Impairment of recall (anterograde amnesia). Benzodiazep-
pines impair recall of information presented after drug admin-
istration (i.e., anterograde amnesia) (66,69). Significances be-
 tween benzodiazepine differences have been reported (4,
9,60,61,71–73). Five studies examined the effects of alprazo-
lam relative to other benzodiazepines including diazepam
(11,51), lorazepam (10,34,49), prazepam (34), and quazepam
(11) on recall. These studies were similar in terms of subjects,
procedures and measures (see Table 1). One study found
alprazolam (2 mg) was more disruptive than diazepam (10 mg),
but these doses are not clinically equivalent, and the results
must be viewed tentatively (11,20,51). In another study, alpra-
zolam was more disruptive than prazepam (34). Alprazolam
did not differ from lorazepam or quazepam (34,49). Impair-
ment of learning. Benzodiazepines impair human
learning (5–7,21,41,42,70). The only available study that
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<tbody>
<tr>
<td>Block and Berchou (1984)</td>
<td>Alprazolam (1 mg)</td>
<td>Acute</td>
<td>Double-blind, placebo-controlled, crossover</td>
<td>Healthy volunteers Age: 25–44 N = 9</td>
<td>Buschke memory task, word-list free-recall</td>
<td>Both drugs differed from placebo, but not each other.</td>
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<td>Lorazepam (2 mg)</td>
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<td>Diazepam (10 mg)</td>
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<td>Quazepam (15 mg)</td>
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<td>Greenblatt et al. (1988)</td>
<td>Alprazolam (1 mg)</td>
<td>Acute</td>
<td>Double-blind, randomized, parallel groups</td>
<td>Healthy volunteers Age: 19–44 N = 39</td>
<td>Word-list free-recall</td>
<td>Alprazolan and lorazepam did not differ from each other, but both were more disruptive than prazepam.</td>
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<td>Lorazepam (2 mg)</td>
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<td>Frazepam (20 mg)</td>
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<td>Linnola et al. (1990)</td>
<td>Alprazolam (0.5 and 2 mg)</td>
<td>Acute</td>
<td>Double-blind, placebo-controlled, crossover</td>
<td>Healthy volunteers Age: 21–25 N = 10</td>
<td>Word-list free-recall</td>
<td>Alprazolam (2 mg) was more disruptive than diazepam (10 mg).</td>
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<td>Diazepam (10 mg)</td>
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<td>Kumar et al. (1987)</td>
<td>Alprazolam (0.5 mg)</td>
<td>Chronic</td>
<td>Double-blind, placebo-controlled, crossover</td>
<td>Healthy volunteers Age: 25–37 N = 30</td>
<td>Word-list free-recall</td>
<td>Alprazolam and lorazepam did not differ from each other.</td>
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<tr>
<td></td>
<td>Lorazepam (1 mg)</td>
<td>(3 times a day for 5 days)</td>
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tested the effects of alprazolam and another benzodiazepine on learning (i.e., acquisition of new information) found alprazolam to be more disruptive than diazepam (6). Alprazolam (0, 1, 2, 3 mg/70 kg), diazepam (0, 10, 20, 30 mg/70 kg), and triazolam (0, 0.25, 0.5, and 0.75 mg/70 kg) dose-dependently increased the overall percentage of errors in learning new material on a modified version of the repeated acquisition of behavioral sequences procedure, but the highest doses of alprazolam and triazolam were more disruptive than the highest dose of diazepam. These results must be viewed tentatively because this study was not designed to explicitly compare the effects of alprazolam and diazepam, and subjects were entered sequentially into a drug condition.

Impairment of performance. Benzodiazepines impair varied aspects of human performance (25,53,81–83). Nine studies with humans included alprazolam and at least one other benzodiazepine (3,10,11,26,27,29,34,55,78). These studies were similar in terms of subjects, procedures, and measures (see Table 2). Alprazolam did not produce significantly greater impairment than the other benzodiazepines tested in any of the studies. Definitive conclusions are difficult because most of these studies compared only a single dose of each compound, and often the doses studied were not clinically equivalent (1,20).

Interactions with alcohol. Combined use of alcohol and benzodiazepines pose a substantial risk because benzodiazepine-induced impairment is greater when alcohol is also ingested (15,50). One study examined the effects of alprazolam (0.5 and 2.0 mg) and diazepam (10 mg) alone and in combination with alcohol (0.8 g/kg) in 10 healthy volunteers on a battery of performance tasks (51). Alcohol exacerbated the effects of both drugs, but combining alprazolam (2 mg) and alcohol was more deleterious than combining diazepam (10 mg) and alcohol. The authors did not report whether these differences were statistically significant. Another study examined the effects of alprazolam (0.25 or 0.5 mg), diazepam (5 or 10 mg) and placebo alone and in combination with alcohol (0.5 and 0.8 ml/kg) in 10 healthy volunteers using similar performance tasks (43). Diazepam (10 mg) combined with alcohol impaired performance relative to placebo, but neither dose of alprazolam combined with alcohol did. Meaningful conclusions are difficult based on these studies because most of the doses of alprazolam and diazepam were not clinically equivalent (1,20). Discerning differential interactions of benzodiazepines with alcohol require the doses or the range of doses to be clinically/functionally equivalent.

Summary of Studies With Humans

The human experimental literature, like the nonhuman experimental literature, does not provide a basis for distinguishing alprazolam from other benzodiazepines in terms of abuse liability. In patients with a history of long-term benzodiazepine use, differences in alprazolam's abuse potential relative to diazepam were not consistently demonstrated across a range of doses (2). The adverse effects of alprazolam are the same as those of other commonly used benzodiazepines. The discontinuation syndrome associated with chronic alprazolam use is more intense than that of LHL compounds when alprazolam is abruptly terminated, but not when gradually tapered. Finally, most studies found the effects of alprazolam on measures of recall, learning, and performance to be qualitatively and quantitatively similar to those of other commonly used benzodiazepines.

CONCLUSIONS AND DIRECTION OF FUTURE RESEARCH

Many clinicians believe the abuse liability of alprazolam is greater than that of other commonly used benzodiazepines, but this opinion is not supported by the available scientific information (40). While pointing out that the available experimental literature does not suggest the abuse liability of alprazolam is greater than that of other benzodiazepines, it is important to note a lack of prospective, experimental studies that explicitly address this question. Moreover, only limited conclusions can be drawn from the existing studies because most tested only a single dose of each compound, and in many instances these doses were not clinically equivalent. Well-controlled studies that explicitly compare the effects of alprazolam to those of other commonly used benzodiazepines are clearly needed.

Studies conducted with nonhumans suggest the abuse liability of alprazolam is qualitatively and quantitatively similar to that of other commonly used benzodiazepines, as determined by its ability to maintain self-administration, discriminate stimulus effects, and adverse effects including physiological dependence. Studies with humans also suggest alprazolam's abuse liability is similar to that of commonly used benzodiazepines. The only difference is that the discontinuation syndrome associated with alprazolam may onset more rapidly and be more severe if drug is abruptly terminated. Thus, clinicians should clearly instruct patients who are prescribed alprazolam to avoid situations in which they are unable to take their medications and not to spontaneously stop taking them.

Perhaps future studies that explicitly address alprazolam's abuse liability relative to other commonly used benzodiazepines will find differences, but this awaits confirmation. Future research with nonhumans should focus on alprazolam's relative reinforcing effects and the severity of the discontinuation syndrome associated with its long-term use. With regard to the relative reinforcing effects of alprazolam, before such studies can be conducted the procedures used to compare the reinforcing effects of drugs need to be refined (47). The lack of adequate procedures to compare the relative reinforcing effects of drugs may explain the failure to detect significant differences between commonly used benzodiazepines (48).

With regard to the discontinuation syndrome, studies that carefully control the dose and duration of drug exposure are needed because these variables affect the severity of the discontinuation syndrome (49).

Similar studies with humans explicitly addressing alprazolam's reinforcing effects and the severity of the discontinuation syndrome are needed, but must consider important issues such as selection of a appropriate comparison drug, population selection, dosing regimen, and dose. For example, comparison studies of alprazolam and other benzodiazepines typically used diazepam or lorazepam as the comparison drug, and these compounds may also have greater abuse liabilities than other benzodiazepines (e.g., oxazepam) (40,44,80). Studying alprazolam's relative abuse liability in chronically anxious patients using a chronic dosing regimen would seem most clinically relevant. However, patients in general practice often use benzodiazepines intermittently to treat temporary anxiety related to environmental demands (e.g., college entrance exams or job interviews). Thus, studies of intermittent dosing are also relevant. Human benzodiazepine-comparison studies must test a wide range of doses of both compounds to determine whether there are differences in maximal effects or
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<th>Study</th>
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<tr>
<td>Aranko et al. (1985)</td>
<td>Alprazolam (0.25 mg)</td>
<td>Acute and Chronic</td>
<td>Double-blind, placebo-controlled, crossover</td>
<td>Healthy volunteers N = 24 Age: 18-33</td>
<td>DSST, CFF, Tracking, RT Maddox Wing</td>
<td>No between drug differences reported under acute dosing. Diazepam was more impairing under chronic dosing.</td>
</tr>
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<td>Blom et al. (1990)</td>
<td>Alprazolam (1 mg)</td>
<td>Acute</td>
<td>Double-blind, placebo-controlled crossover</td>
<td>Healthy volunteers Age: 22-29 N = 9</td>
<td>CFF, CRT</td>
<td>No between drug differences reported.</td>
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<td>Ellinwood et al. (1985)</td>
<td>Alprazolam (0.028 mg/kg)</td>
<td>Acute</td>
<td>Double-blind, balanced, Latin Square</td>
<td>Healthy volunteers Age: 21-26 N = 8</td>
<td>DSST, SCT</td>
<td>No between drug differences reported, but alprazolam appeared somewhat more impairing.</td>
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<tr>
<td>Ellinwood et al. (1987)</td>
<td>Alprazolam (0.014 &amp; 0.028 mg/kg)</td>
<td>Acute</td>
<td>Double-blind, placebo-controlled, crossover</td>
<td>Healthy volunteers Age: 21-26 N = 8</td>
<td>DSST, SCT</td>
<td>No between drug differences reported, but alprazolam appeared somewhat more impairing.</td>
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<tr>
<td>Fernandez-Guardiola et al. (1984)</td>
<td>Alprazolam (0.25 mg)</td>
<td>Acute</td>
<td>Double-blind, placebo-controlled, crossover</td>
<td>Healthy volunteers Age: 21-29 N = 11</td>
<td>RT</td>
<td>No between drug differences reported, but alprazolam appeared somewhat more impairing.</td>
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<td>Nikaddo et al. (1990)</td>
<td>Alprazolam (0.75 &amp; 1.5 mg)</td>
<td>Acute</td>
<td>Double-blind, placebo-controlled, crossover</td>
<td>Healthy volunteers Mean Age: 25.7 N = 19</td>
<td>DSST, SCT</td>
<td>No between drug differences reported.</td>
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<tr>
<td>Subhan et al. (1986)</td>
<td>Alprazolam (0.5 mg)</td>
<td>Acute and Chronic</td>
<td>Double-blind, placebo-controlled, crossover</td>
<td>Healthy volunteers Age: 28-45 N = 12</td>
<td>CFF, CRT, Stimulated-car tracking</td>
<td>No between drug differences reported, but lorazepam may have been more impairing under acute and chronic dosing.</td>
</tr>
</tbody>
</table>

CFF = Critical Flicker Fusion; CRT = Choice Reaction Time; DSST = Digit-Symbol-Substitution Test; RT = Reaction Time; SCT = Subcritical Tracking.
only in dose equivalencies (23). The inclusion of supratherapeutic doses is also necessary because higher doses are often involved in abuse and overdose (23,39). Finally, with regard to the discontinuation syndrome associated with alprazolam, human studies that carefully match the groups on the basis of daily dose and duration of drug exposure are needed.

In conclusion, the commonly held belief that the abuse liability of alprazolam is greater than that of other commonly used benzodiazepines is not supported by the available scientific literature. Rigorous experimental studies are needed that explicitly compare alprazolam and other commonly used benzodiazepines to determine if differences exist. Until such research is available, definitive conclusions concerning the relative abuse liability of alprazolam are not possible.

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