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Inhaled vs. oral alprazolam: subjective, behavioral and cognitive effects, and modestly increased abuse potential

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Abstract

Rationale—Infrahuman and human studies suggest that a determinant of the abuse potential of a drug is rate of onset of subjective effects.

Objectives—This study sought to determine if the rate of onset of subjective effects and abuse potential of alprazolam would be increased when administered via inhalation vs. the oral route.

Methods—Placebo, inhaled alprazolam (0.5, 1, 2 mg), and oral alprazolam (1, 2, 4 mg) were administered under double-blind, double-dummy conditions using a cross-over design in 14 healthy participants with histories of drug abuse. Participant and observer ratings, and behavioral and cognitive performance measures were assessed repeatedly during 9 hour sessions.

Results—Both routes of administration produced orderly dose and time-related effects, with higher doses producing greater and longer lasting effects. Onset of subjective effects following inhaled alprazolam was very rapid (e.g., 2 vs. 49 minutes after 2 mg inhaled vs. oral). On measures of abuse potential (e.g., liking and good effects), inhaled alprazolam was more potent, as

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evidenced by a leftward shift in the dose response curve. Despite the potency difference, at the highest doses, peak ratings of subjective effects related to abuse potential (e.g., “drug liking”) were similar across the two routes. On other measures (e.g., sedation and performance) the routes were equipotent.

Conclusions—The inhaled route of administration modestly increased the abuse potential of alprazolam despite significantly increasing its rate of onset. If marketed, the reduced availability and increased cost of inhaled alprazolam may render the societal risk of increased abuse to be low.

Keywords

alprazolam; oral; inhalation; Staccato®; abuse potential; liking; performance; drug abusers; humans

Introduction

It is widely believed that the abuse liability of a drug is determined, in part, by its speed of onset (as indicated by time to onset or time to maximum subjective effects). Increasing the speed of drug onset may increase the abuse potential of a drug by decreasing the interval between drug administration and the onset of subjective effects (i.e., the “rate hypothesis”) (Gorelick 1998; Oldendorf 1992). Anecdotally, many commonly abused drugs (e.g., cocaine, and heroin) are preferentially administered using routes of administration that result in a rapid onset of effects such as intravenous injection, inhalation (e.g., smoking), and intranasal (e.g., snorting).

Consistent with the rate hypothesis, drug self-administration studies in infrahuman subjects have shown that drugs are more reinforcing when administered intravenously vs. orally or intragastrically (Griffiths et al. 1985). In studies examining different durations of cocaine infusions in rhesus monkeys, the rate of responding for a fixed dose of cocaine increased as infusion speed increased (Balster and Schuster 1973). Based on these findings, it was proposed that the reinforcing effects of cocaine result from a joint function of dose and infusion rate. Other studies in rhesus monkeys demonstrated that more rapid infusions of cocaine were associated with an increased number of injections per session on a progressive ratio schedule (Woolverton and Wang 2004). In a similar manner, in rhesus monkeys trained to self-administer nicotine, 24 hour self-administration rates increased as the rate of drug delivery was increased (Wakasa et al. 1995). In crab eating monkeys (*Macaca irus*), Kato and colleagues found that the threshold dose for producing cocaine and pentobarbital self-administration decreased as infusion rate increased (Kato et al. 1987). Taken together, these results indicate that in animal models, the reinforcing effects of drugs are increased by more rapid administration. While the precise mechanism(s) underlying this relationship are unclear, more rapid routes of administration typically result in a more rapid onset of drug effects and reduce the delay between self-administration and peak drug plasma levels. This reduces the delay between the response and the reinforcing stimulus, increasing its reinforcing efficacy.

Human studies in drug users have shown that when dose and duration of intravenous cocaine infusions are manipulated, drug liking (e.g., euphoria) is positively related to speed

of infusion (Fischman and Schuster, 1984). In volunteers who use intravenous cocaine and heroin, subjective responses to identical doses of cocaine (but not hydromorphone) were greater when cocaine was administered more rapidly (Abreu et al. 2001). A third study examining the effect of rate of infusion of intravenous cocaine in humans found that the rate of cocaine infusion affected both subjective and cardiovascular outcome measures. Further, positive subjective effects (e.g., “good”, “stimulated”, and “like”) were most affected by rate, even when controlling for dose. The study was unique in that it included variation of both cocaine dose, and rate of infusion (Nelson et al. 2006). In human opioid users, faster infusions of morphine produced greater positive subjective effects, drug effects, and plasma drug levels. The authors suggested that both the dose and rate of drug administration affect abuse liability (Marsch et al. 2001).

Studies that have manipulated the rate of delivery of benzodiazepines and barbiturates in humans have shown that when administered as a single oral dose (that results in relatively rapid peak plasma levels) diazepam and pentobarbital are associated with greater increases in subjective effects related to abuse liability than when given as divided doses (which result in longer time to peak plasma levels) (de Wit et al. 1992; de Wit et al. 1993). It is important to note that similar peak plasma levels of drug were obtained using each dosing regimen, albeit at different time points. Based on these results, the authors concluded that the rate at which blood levels of a drug increase is positively related to subjective effects associated with its abuse.

With respect to benzodiazepines, compounds that are rapidly absorbed are preferred to those with slower absorption rates (Griffiths et al. 1984). For example, when comparing the effects of diazepam and oxazepam in sedative abusers, participants preferred diazepam over oxazepam, and were willing to pay more for the former (Griffiths et al. 1984). This finding is consistent with diazepam’s more rapid onset of subjective effects and comments from study participants that cited a rapid onset as a desirable feature of diazepam (Griffiths et al. 1984). Along these same lines, extended release alprazolam was shown to have less potential for abuse than immediate release alprazolam (Mumford et al. 1995a). In that study, the highest dose of extended release alprazolam (3 mg) failed to produce greater ratings of “good effects”, “strength”, and “liking” than the lowest dose of immediate release alprazolam (1 mg). It is notable that there were several instances where equivalent plasma concentrations of alprazolam were achieved between the two formulations, yet only the IR formulation affected subject ratings of drug effects. Based on these results, the authors suggested that the abuse liability of alprazolam is affected by both dose and release rate (Mumford et al. 1995a).

Alexza Pharmaceutical’s Staccato[®] technology is a novel inhalation drug delivery system. The Staccato[®] system consists of a breath-actuated inhaler that incorporates a solid, thin film of drug on an inert metal substrate. By rapidly heating the metal substrate, the drug film is rapidly vaporized to form a highly pure aerosol. The Staccato[®] system has previously been shown to deliver drugs with intravenous-like pharmacokinetics in humans and canines, including a rapid onset of pharmacodynamic effects (Avram et al. 2007; Avram et al. 2009; Avram et al. 2013; Rabinowitz et al. 2004; Rabinowitz et al. 2006). For example, 1 mg of inhaled alprazolam produced peak plasma levels in 3.84 minutes (Alexza Pharmaceuticals

2014a b). Similarly, when Avram and colleagues (2013) administered zaleplon using the Staccato[®] system, peak sedative effects (measured with VAS) occurred about 3 minutes after dosing. This was in contrast to orally administered zaleplon for which peak pharmacodynamic effects occurred approximately 90 minutes after administration. Because increasing the rate of delivery of a drug may increase its abuse potential by increasing the speed of onset of drug effects, the purpose of the present study was to compare the abuse potential of inhaled alprazolam to an oral alprazolam preparation.

Methods

Study Participants

Participants were 8 males and 7 females with a history of sedative abuse or dependence without any other significant medical or psychiatric conditions.

The study was conducted at the Behavioral Pharmacology Research Unit (BPRU) of the Johns Hopkins University School of Medicine. Participants gave their informed consent. The protocol and recruitment materials were approved by the University's Institutional Review Board. The study was conducted in accordance with the Declaration of Helsinki and registered at www.clinicaltrials.gov (NCT00603980). Participants were paid.

Participants were initially interviewed over the telephone. Eligible candidates were scheduled for an in-person screening. During in-person screenings, applicants underwent a physical exam and a medical history review. Participants completed a structured clinical interview for psychiatric conditions (Diagnostic and Statistical Manual—Version IV (DSM-IV)), and had their blood and urine collected for testing. An electrocardiogram was performed along with a drug screen, pregnancy test, alcohol breathalyzer test, and training on study assessments. Participants were required to meet the following entry criteria: (i) have a history of substance abuse or dependence (DSM-IV) on a commonly abused recreational drug (e.g., benzodiazepines, opioids, or cocaine), (ii) be age 18–55, (iii) report non-therapeutic use of barbiturates and/or benzodiazepines for their intoxicating effects at least once in the past year, (iv) be in good general health, (v) have a negative pregnancy test, (vi) have not participated in a clinical trial 30 days prior to screening, (vii) not taking CYP3A inhibitors or inducers, and, (viii) have no history of acute or chronic pulmonary disease. Eligible participants visited BPRU up to three times per week on an outpatient basis.

51 participants signed the informed consent form. Twenty-five participated in the qualifying sessions, 15 completed the qualifying sessions, and 14 completed the study.

Qualifying Sessions

Before test sessions, volunteers completed two double-blind qualifying sessions to identify individuals who demonstrated greater liking for the effects of oral alprazolam relative to placebo.

During both qualifying sessions, participants swallowed four, band sealed, size 0, orange, opaque, hard gelatin capsules at two time points. The first set of capsules were administered

at the beginning of the session and the second set was administered 1 hour later, immediately before administration of inhaled Staccato[®] placebo (Alexza Pharmaceuticals, Mountain View CA). During the placebo session, both sets of capsules contained placebo (lactose). During the active (e.g., non-placebo) qualifying session, the first set of capsules contained oral alprazolam (2 mg) (Murty Pharmaceuticals, Lexington KY) and the second set contained placebo. Active, inhaled drug was not administered during any qualifying session.

During the first qualifying session, half of the subjects received oral placebo, and half of the subjects received oral alprazolam. Only participants who demonstrated greater liking for oral alprazolam versus placebo (as determined by a difference of at least one point on the overall drug liking score on the end-of-day questionnaire) participated in test sessions.

Test Sessions

The timing of procedures for daily test sessions are summarized in ESM Table 1. Eligible subjects participated in up to 3 sessions per week. Sessions were separated by at least 48 hours. Participants arrived at the research unit by 7:00 AM. Before each session, participants performed a breathalyzer test and provided a urine sample that was tested for amphetamines, cocaine, barbiturates, benzodiazepines, and opiates. Participants who tested positive for alcohol or illicit drug use were not allowed to participate in that day's test session.

Responses to questionnaires were recorded on Macintosh computers (Apple, Cupertino, CA). When not completing an experimental task, participants were allowed to engage in recreational activities (e.g., playing games or reading).

During sessions, participants received one of seven different treatments under double-blind conditions: oral alprazolam (1, 2, and 4 mg), inhaled alprazolam (0.5, 1, and 2 mg), or placebo. The sequence and order of doses were counterbalanced across participants and each participant received all treatments in a crossover design. The crossover sequences were determined according to a 7-treatment, 7-period Latin Square of Williams design balanced for first-order carryover effects. The Circular Lights, Digit-Symbol-substitution task (DSST), Subjective Effects Questionnaire, Observer-Rated Questionnaire, and Drug Effects Questionnaire, were completed before capsule administration. Capsules were administered after baseline assessments. One hour later, a second set of capsules (always placebo) were administered along with inhaled Staccato[®] placebo or Staccato[®] alprazolam. The timing of the drug administrations was scheduled to obscure from participants and staff the differences in rates of onset and to preserve the study blind. To reduce possible taste discrimination between placebo and inhaled alprazolam, participants were given a rapidly dissolving, intensely flavored breath mint strip after each capsule set.

Drug Effect Questionnaire

This previously described participant-rated questionnaire (Mumford et al. 1995b; Evans et al. 1990; Reissig et al., 2012) consisted of 5-point rating scales of drug strength, good effects, bad effects, high, and rush and a 9-point, bipolar drug liking rating scale ("dislike very much," "dislike quite a bit," "dislike somewhat," "dislike, but not very much," "neutral or no effect," "like, but not very much," "like somewhat," "like quite a bit," "like very

much”). This task was completed before and at 2 min, 5 min, 10 min, 20 min, 30 min, 45 min, 60 min, 62 min, 65 min, 70 min, 80 min, 90 min, 105 min, 2 hr, 2.5 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr, and 9 hr after administration of the first capsules.

Sedation (Subjective Effects Questionnaire)

This previously described participant-rated questionnaire (Rush et al., 1999) consisted of 13 adjectives thought to be sensitive to sedative drugs (e.g., “Do you feel sleepy?”). Participants were instructed to rate how they felt on a 5-point scale (“not at all,” “a little bit,” “moderately,” “quite a bit,” and “extremely”). Ratings were summed across the 13 items and expressed as a total score. This questionnaire was completed before and 30 min, 60 min, 90 min, 2 hr, 2.5 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr, and 9 hr after the first capsule administration.

Pharmacological Class Questionnaire

This previously described participant-rated questionnaire (Rush, et al., 1999) listed descriptive titles and examples of 12 classes of psychoactive drugs, including “blank or placebo”, and “other.” Participants were instructed to choose the option that they believed most closely represented the drug they received that day. This questionnaire was completed 9 hr after the first capsule administration.

End of Day Questionnaire

For this previously described questionnaire (Carter et al. 2006; Rush et al. 1999) participants rated the overall effect of the drug they received that day. Subjects rated the overall strength of the drug effect, overall good effects, overall bad effects, and the degree to which they would like to take the drug again on a 5-point scale. Subjects rated their overall drug liking on a bipolar, 9-point scale, estimated the amount of money the drug would be worth on the street, and estimated the amount of money they would pay to receive that drug again. This questionnaire was completed 9 hr after administration of the first capsules.

Observer-Rated Measures

This previously described questionnaire (Rush et al. 1999) consisted of eight items. A staff member rated each participant on: sedation/sleepiness, locomotor and non-locomotor muscle relaxation, posture, slurred speech, confusion/disorientation, stimulation/arousal, and strength of drug effect. Observers rated each dimension on a 5-point scale from 0 (normal) to 4 (very strong drug effect). This task was completed before and at 10 min, 20 min, 30 min, 45 min, 60 min, 70 min, 80 min, 90 min, 105 min, 2 hr, 2.5 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr, 8 hr, and 9 hr after administration of the first capsules.

Circular Lights

This 1-minute psychomotor task, described previously (Mumford et al. 1995a; Mumford et al. 1995b), required participants to press a series of 16 buttons as rapidly as possible in response to a random sequence of illuminated lights. The score was the number of correct button presses during the 1-minute trial. Timing of this assessment was the same as that for the observer-rated measures.

Digit Symbol Substitution Task (DSST)

This task was a computer version of the DSST (McLeod et al. 1982), a 90-second trial that required participants to use a numeric keypad to type keys corresponding to a geometric pattern displayed on a computer screen. The score was the number of correct patterns entered during the 90-second trial. Timing of this task was the same as that for the observer-rated measures.

Word Recall Task

This task consisted of a word encoding phase followed 10 minutes later by a word recall test. For the encoding phase, participants were presented with 16 words that appeared on a computer screen one at a time. Participants classified each word as artificial (i.e., man-made) or natural by clicking a button on the computer screen. Participants were informed that their memory for these words would be tested later in the session. In the recall test, participants were instructed to write down as many words as possible from the list of words they had classified as artificial or natural 10 minutes earlier. The score was the number of words (out of 16) correctly recalled. For details, see (Carter et al. 2009).

This task was given twice. The first time corresponded to the expected time of peak effect for inhaled alprazolam (encoding occurred 10 minutes after inhalation administration, which was 70 minutes after administration of the first capsules). The second time corresponded to the expected time of peak effects for the oral administration (encoding occurred 2 hours after administration of the first capsules, which was 1 hour after inhalation administration). In both cases, recall occurred 10 minutes after encoding.

Data Analysis

Time course data were analyzed with repeated-measures regressions using SAS PROC MIXED. Drug condition and time were included in the model. Planned comparison *t* tests were conducted between placebo and active doses at each time point.

For the 9-point, bipolar drug liking scales (the End of Day Questionnaire and Drug Effect Questionnaire) data were divided into separate measures of “liking” and “disliking.” For purposes of data analysis, ratings of liking were assigned a score of 0 if a participant indicated disliking. Conversely, ratings of disliking were assigned a score of 0 if a participant indicated liking. For participant- and observer-rated measures assessed at multiple time points, peak effect for each session was defined as the maximum value recorded within 9 hours after administration of the first set of capsules. For psychomotor performance and cognitive assessment measures (i.e., DSST, word recall, and Circular Lights), the peak effect for each session was defined as the minimum value scored during the 9 hours. Data from the peak effect calculations and from assessments that were completed once per session were analyzed using SAS PROC MIXED (SAS Institute, Cary, NC). Fisher’s LSD post hoc tests were used to compare drug conditions. Data from the Word Recall Task were analyzed using SAS PROC MIXED with Fisher’s LSD post hoc tests to compare all conditions within each time point. For all analyses and statistical tests, $p < 0.05$ was considered significant.

For purposes of summarizing drug effect time course, means and SEMs were calculated at each time point for the 15 measures (shown in Tables 1 and 2, and ESM Table 2) that were assessed at multiple time points (6 participant ratings, 7 observer ratings, and the Circular Lights and DSST). Time to onset was defined as the first time point after drug administration that was significantly different from placebo. Time to peak effect was defined as the time point corresponding to the peak of the group data. Time to offset was defined as the time point after the last significant difference from placebo.

Relative potency between oral and inhaled alprazolam was calculated according to the methods of Finney on measures assessed at a single time point and on peak effects for measures assessed at multiple time points. Tests for linearity, parallelism, preparation (route) differences, and significant regression (i.e., significant dose effects) were conducted. Relative potency estimates are not reported for variables that did not meet these validity criteria.

For all analyses and statistical tests, $p < 0.05$ was considered significant.

Data from the Pharmacological Class Questionnaire were calculated as the percentage of participants that chose each drug class for each of the seven drug conditions.

Results

Time Course

Figure 1 shows time course data for inhaled and oral alprazolam on two participant-rated measures reflecting abuse potential (liking and good effects) and on two measures of behavioral performance (Circular Lights and DSST). Both routes of administration produced orderly, dose and time-related effects, with higher doses producing greater and longer lasting effects.

Inspection of the data indicated that the onset of drug effects after inhaled alprazolam was very rapid and generally more rapid than after oral administration. For example, at the same dose of alprazolam (2 mg), the mean (SEM) time to onset of drug effects across 15 participant-rated, observer-rated, and performance measures (see Data analysis section and ESM Table 2) was 11.3 (2.3) minutes after inhaled administration vs. 62.8 (3.9) minutes after oral administration (ESM table 2). These onset times tended to be shortest for the 5 participant ratings assessing positive subjective effects related to abuse potential (Drug Effects Questionnaire ratings of strength, liking, good effects, high and rush): a mean of 2.0 minutes (no variation) after inhaled vs. 49.4 minutes (range 30 to 65) after oral administration.

As shown in Figure 1, for ratings of liking and good effects, the two highest doses of inhaled alprazolam (1 and 2 mg) were significantly different from placebo at the first time point (2 minutes after inhalation) and reached 80 to 90% of peak mean rating by the second time point (5 minutes).

Likewise, inspection of the data showed that time to peak effect was generally shorter after inhaled vs. oral administration. For example, for the 2 mg dose of alprazolam across the 15

measures noted above, the mean (SEM) time to peak effect was 51.7 (14.3) minutes after inhaled vs. 120.1 (5.9) minutes after oral administration (ESM Table 2).

The time to offset of participant-rated drug effects was only somewhat shorter after inhaled vs. oral administration. For the 2 mg dose of alprazolam across the 15 measures noted above, the mean (SEM) time to offset was 216.0 (19.2) minutes after inhaled vs. 262.0 (19.0) minutes after oral administration (ESM Table 2).

Participant-rated measures related to abuse potential

Table 1 and Figure 2 summarize participant ratings of measures of drug strength and various measures related to abuse potential that were assessed throughout the session (peak effects) or at the end of the session. Strength ratings are reported here because these questions were asked in the context of ratings of abuse potential. Both oral and inhaled alprazolam produced dose-related and significant effects on most items. Inhaled alprazolam was generally more potent than oral alprazolam (i.e., the dose effect function was shifted to the left), and valid relative potency estimates for inhaled vs. oral alprazolam were calculated for 10 of 11 measures. The mean relative potency difference was 2.01 (ranging from 1.53 to 2.94). Consistent with these potency differences, at identical doses (i.e., comparing 1 mg oral vs. inhaled, and 2 mg oral vs. inhaled), inhaled alprazolam almost always (21 of 22 comparisons) produced greater effects than oral alprazolam. These effects were generally not statistically significant except that on the End of Day Questionnaire, 1 mg of inhaled alprazolam produced increases on overall liking, and overall good effects that were significantly greater than 1 mg of oral alprazolam.

Peak participant ratings of bad effects were modestly, but significantly, increased relative to placebo after all three doses of oral alprazolam, but not increased by any dose of inhaled alprazolam. The mean (SEM) peak rating of bad effects after the highest dose of oral alprazolam (4 mg) was 1.07 (0.27), and significantly higher than all three doses of inhaled alprazolam. However, participant ratings of drug disliking (peak and end of day) and end of day ratings of bad effects were not significantly different across experimental conditions.

Participant- and observer-ratings and performance measures

Table 2 and Figure 3 summarize other participant-rated, observer-rated, and performance measures. Similar to the participant ratings related to abuse potential, oral and inhaled alprazolam produced dose-related and significant effects on most of these measures. In contrast to the abuse potential measures, inhaled alprazolam was not reliably more potent than oral alprazolam. For most of these measures, inspection of the data and relative potency calculations indicated that the potency of inhaled and oral alprazolam were similar (Figure 3). Furthermore, for the five measures for which valid relative potency measures could be calculated, the mean relative potency was only 1.36.

Relative to placebo, both inhaled and oral alprazolam produced dose-related impairment on the Word Recall Task, as demonstrated by a decrease in the number of words recalled at both time points, with no differences between the two occasions the task was administered (Table 2). Criteria were not fulfilled for calculation of valid relative potency analyses.

Pharmacological Class Questionnaire

As shown in Table 3, placebo was correctly rated as placebo by 79% of study participants. With increasing doses of inhaled and oral alprazolam there was a generally increasing frequency of rating drug conditions as being active (i.e., not placebo) and being either a barbiturate/sleeping medication or a benzodiazepine, with 57% to 71% of subjects selecting either class across the two highest doses of both formulations.

Discussion

The objective of this study was to assess the abuse potential of inhaled alprazolam (delivered via Staccato[®] technology) relative to oral alprazolam. Both infrahuman and human studies provide evidence for the belief that the abuse potential of a reinforcing drug is increased by increasing its speed of onset. However, the current study determined that, despite a much more rapid time of onset, the abuse potential of inhaled alprazolam is only modestly greater relative to the oral formulation.

As expected, inhaled alprazolam resulted in a much more rapid onset of drug effects, with significant subjective effects detected at the first time point after administration (2 minutes vs. 49 minutes after 2 mg of inhaled and oral alprazolam, respectively). Likewise, inhaled alprazolam generally resulted in a shorter time to peak subjective and behavioral effects (52 minutes vs. 120 minutes after 2 mg inhaled and oral alprazolam, respectively). On participant ratings most relevant to abuse potential (e.g., liking and good effects), inhaled alprazolam was generally more potent than oral alprazolam, as evidenced by a leftward shift in the dose response curve (Table 1; Figure 2). This is in contrast to the absence of potency differences across various measures unrelated to abuse potential (Table 2; Figure 3). For the abuse potential measures, valid relative potency differences, which averaged 2.01, were calculated for 10 of the 11 abuse potential measures (Table 1). Consistent with the relative potency differences between inhaled and oral alprazolam, at the same absolute dose, inhaled alprazolam almost always produced numerically greater effects than oral alprazolam. Although these effects were generally not statistically significant, the consistency of the findings across the different measures of abuse potential suggests that at identical doses, inhaled alprazolam has an increased abuse potential relative to the oral formulation, albeit to a moderate degree. However, despite the increase in potency, the highest values produced by the highest dose of each formulation (e.g., 4 mg of oral and 2 mg inhaled) did not differ on the majority of abuse potential measures examined. Based on anecdotal reports suggesting large increases in abuse potential with rapidly administered drugs (e.g., intravenous or smoked cocaine), it might have been expected that changing the route of alprazolam administration from oral to inhaled would result in an increased abuse potential of many orders of magnitude. It did not.

It is of interest to consider the implications of the above findings for predicting the actual abuse of inhaled vs. oral alprazolam. We hypothesize that given equivalent availability and cost, inhaled alprazolam would engender more abuse. However, the Staccato[®] delivery device permits administration of only a single dose of drug. It seems likely that, if marketed, Staccato[®] alprazolam would cost more, and the number of dosage units dispensed would be

substantially fewer relative to the oral dosage form. If these assumptions are correct, the amount of Staccato[®] alprazolam available for diversion and abuse would be quite low.

In contrast to measures reflecting abuse potential, the comparison of inhaled vs. oral routes on participant-rated sedation, observer rated behavioral effects, and measures of psychomotor and cognitive performance were not generally associated with potency differences (Figure 3; Table 2). For example, although both inhaled and oral alprazolam produced dose-related decreases in performance on the Circular Lights and DSST, similar doses produced similar decrements in performance (e.g., 2 mg inhaled produced effects comparable to 2 mg oral). When examined in the context of the abuse potential assessments, it may be that increasing the rate of onset of a drug affects some types of measures (e.g., abuse potential) and not others (e.g., psychomotor effects).

It is widely believed that the rate of onset of subjective effects is an important determinant of the abuse potential of a drug and it is often presumed that the primary determinant of rate of onset is the speed of drug delivery to plasma or brain. However, other pharmacokinetic factors may play a significant role including peak plasma levels, (C_{max}), absorption, and overall drug exposure (area under the curve or AUC). Thus, a major limitation of the current study was the lack of assessment of drug plasma levels following administration. We cannot rule out the possibility that the differences in abuse potential measures (or lack thereof) are due to differences in absorption, peak drug plasma levels or other pharmacokinetic (PK) parameters (e.g., C_{max}, T_{max}).

However, prior clinical assessments of Staccato[®] alprazolam have demonstrated that the 1 mg dose produces peak plasma levels of drug in 3.84 minutes (Alexza Pharmaceuticals 2014a b), a finding that is consistent with the rapid onset of drug effects (~ 2 min, ESM Table 2) observed in the present study. These data are consistent with clinical and preclinical PK analyses of several different drug substances delivered via the Staccato[®] system. These studies have generated consistent results, with peak plasma levels observed 3–5 minutes after inhalation, regardless of the drug substance administered (Alexza Pharmaceuticals 2014c; Avram et al. 2007; Avram et al. 2009; Avram et al. 2013; Macleod et al. 2012; Rabinowitz et al. 2004; Rabinowitz et al. 2006; Spyker et al. 2010). Another limitation of the present study is the relatively small sample size (N=14). Future studies designed to differentiate among different routes of administration should use larger samples.

In contrast to the inhalable formulation, the effects of orally administered alprazolam peaked around 120 minutes and produced dose-related sedation, findings consistent with its pharmacokinetic profile (Greenblatt and Wright 1993; Smith et al., 1984), and prior studies examining the pharmacodynamics and abuse potential of immediate release alprazolam (Mumford et al. 1995a; Fleishaker et al., 1980).

The novelty of the Staccato[®] drug delivery system may also have affected the study results. For most benzodiazepine users, the oral route of administration is the most common method of recreational use (Roset et al. 2001). The unfamiliarity with the Staccato[®] system might have affected its abuse potential, although the Pharmacological Class Questionnaire results suggest that volunteers identified each formulation as a sedative-like drug (Table 3).

In this study, we demonstrated that despite a marked difference in rates of onset, differences in abuse liability measures between inhaled and oral alprazolam were modest. The modest increase in abuse liability resulting from the rapid onset of drug effects after inhaled administration via the Staccato[®] system must be weighed against possible therapeutic advantages. Currently approved immediate release alprazolam tablets reach peak plasma concentrations 1 to 2 hours after administration. Oral spray products containing non-benzodiazepine compounds (e.g., ZolpiMist[™]) also produce peak plasma concentrations about an hour after administration (Neubauer 2010). The relatively slow onset of effects after the oral administration of drugs precludes their use in situations in which rapid effects are desired (e.g., treating an acute panic attack in a public setting). Administration systems that result in intravenous-like onset of drug effects may offer significant therapeutic advantages in therapeutic areas in which rapid drug onset is desirable such as in the treatment of panic attacks, migraine headaches, epileptic seizures, and the management of acute psychosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Time course of effects of inhaled alprazolam (left panels) and oral alprazolam (right panels) on participant ratings of drug liking and good effects from the Drug Effect Questionnaire (top 2 rows) and performance on the Circular Lights Task and the Digit Symbol Substitution Task (bottom 2 rows). Y axes: mean participant rating of liking and good effects (0 to 4 point scale), mean score on the Circular Lights Task, and mean trials correct on the Digit Symbol Substitution Task. X axes: Left panels show the time in minutes after inhaled administration; Right panels show the time in minutes after the first set of oral capsules were administered; 0 shows the pre-administration time point. Data symbols show means (N=14). Filled symbols indicate values that are significantly different from the corresponding placebo value at the same time point ($p < 0.05$, planned comparisons).

Figure 2.

Effects of placebo (circles), inhaled alprazolam (squares) and oral alprazolam (triangles) on participant ratings of several measures specific to abuse potential. Left panels show peak ratings of drug liking, good effects, and high from the Drug Effect Questionnaire. Right panels show ratings of liking good effects, and monetary street worth from the End of Day Questionnaire. Y axes: participant rating (0 to 4 point scale) and Street Worth (in dollars). X axes: dose in mg; P designates placebo. Data points show means (N=14) brackets show plus or minus 1 SEM. Filled symbols indicate values that are significantly different from

placebo; data points that do not share a common letter are significantly different from one another ($p < 0.05$, Fisher's LSD).

Figure 3.

Effects of placebo (circles), inhaled alprazolam (squares) and oral alprazolam (triangles) on observer ratings, participant ratings, and performance measures that do not specifically assess abuse potential. Left panels show peak effects of observer ratings of locomotor relaxation, confusion/disorientation, and slurred speech. Right panels show peak effects of participant ratings of sedation and performance on the Circular Lights and Digit Symbol Substitution Tasks. Y axes: observer ratings (0 to 4 point scale); participant rating of sedation (0 to 52 point scale); Circular Lights Task score and Digit Symbol Substitution

Task trials correct; X axes: dose in mg; P designates placebo. Data points show means (N=14) brackets show plus or minus 1 SEM. Filled symbols indicate values that are significantly different from placebo; data points that do not share a common letter are significantly different from one another ($p < 0.05$, Fisher's LSD).

Table 1

Participant ratings of measures specific to abuse potential

Outcome Measure	Placebo 0	Inhaled Alprazolam			Oral Alprazolam			Relative Potency [*]
		0.5 mg	1 mg	2 mg	1 mg	2 mg	4 mg	
Participant-Rated Drug Effects								
Strength (Peak)	1.07 (0.40)	1.64 (0.31) ^a	2.43 (0.33) ^{ab}	3.07 (0.25) ^b	1.79 (0.32) ^a	2.79 (0.32) ^b	2.93 (0.22) ^b	1.76 (0.95–3.04)
Liking (Peak)	0.86 (0.40)	1.50 (0.29) ^a	2.36 (0.32) ^{b,c}	3.07 (0.25) ^c	1.86 (0.35) ^{ab}	2.86 (0.31) ^c	3.00 (0.18) ^c	1.53 (0.87–2.42)
Good Effects (Peak)	0.86 (0.39)	1.21 (0.26) ^a	2.36 (0.37) ^{b,d,e}	2.79 (0.28) ^{c,d,e}	1.71 (0.37) ^{ab}	2.71 (0.29) ^{c,e}	2.64 (0.29) ^{c,d}	1.54 (0.76–2.67)
High (Peak)	0.93 (0.38)	1.21 (0.28) ^a	2.29 (0.34) ^{b,c}	3.07 (0.32) ^c	1.64 (0.32) ^{ab}	2.36 (0.32) ^{b,c}	2.71 (0.30) ^c	1.91 (1.02–3.49)
Rush (Peak)	0.79 (0.33)	0.64 (0.13) ^a	1.36 (0.37) ^{ab}	1.79 (0.41) ^b	0.71 (0.32) ^a	1.07 (0.32) ^{ab}	1.29 (0.24) ^{ab}	2.94 (1.48–8.78)
End of Day Questionnaire ***								
Overall Strength	0.64 (0.29)	1.43 (0.29) ^{ab}	2.14 (0.27) ^{a,c}	3.00 (0.23) ^d	1.79 (0.32) ^{a,e}	2.50 (0.29) ^{c,d,e}	2.57 (0.31) ^{c,d}	1.79 (0.99–3.05)
Overall Liking	0.71 (0.40)	1.36 (0.31) ^a	2.50 (0.31) ^{b,c}	2.86 (0.23) ^b	1.79 (0.33) ^a	2.43 (0.27) ^b	2.07 (0.29) ^{ab}	2.69 (3.26–7.09)
Overall Good Effects	0.64 (0.39)	1.14 (0.31) ^a	2.29 (0.32) ^b	2.79 (0.30) ^b	1.43 (0.29) ^a	2.43 (0.25) ^b	2.43 (0.34) ^b	1.95 (1.13–3.32)
Willingness to Take Again	0.57 (0.39)	1.07 (0.37) ^a	1.64 (0.31) ^{ab}	2.21 (0.35) ^b	1.71 (0.44) ^{ab}	2.00 (0.35) ^{ab}	1.86 (0.40) ^{ab}	--
Monetary Street Worth	0.64 (0.84)	4.11 (1.62) ^a	6.21 (1.52) ^{ab}	8.14 (2.00) ^b	4.11 (1.05) ^a	6.79 (1.67) ^{ab}	7.21 (2.63) ^{ab}	2.09 (0.17–44.81)
Willingness to Pay for Drug	0.71 (0.78)	3.86 (1.65) ^a	5.36 (1.17) ^{ab}	8.11 (2.01) ^b	3.93 (1.06) ^a	6.79 (1.67) ^{ab}	6.86 (2.77) ^{ab}	1.94 (0.27–11.81)

Data are mean scores with SEMs shown in parentheses (N=14); for placebo and drug conditions within a row, bold font indicates significant difference from placebo; for active doses, values not sharing a common letter are significantly different (Fisher's LSD $p<0.05$)

* Relative potency estimates for oral vs. inhaled alprazolam, with confidence limits in parentheses; absence of an estimate indicates that the validity criteria for that measure were not fulfilled

Table 2

Participant- and observer-ratings and performance measures excluding participant-ratings specific measures to abuse potential

Outcome Measure	Placebo	Inhaled Alprazolam			Oral Alprazolam			Relative Potency [*]
		0	0.5 mg	1 mg	2 mg	1 mg	2 mg	
<i>Participant-Rated Effects</i>								
Sedation (Peak) ^{**}	7.36 (4.01)	6.21 (1.49) ^a	13.86 (3.26) ^b	16.29 (2.49) ^b	12.36 (2.91) ^{ab}	18.21 (2.97) ^b	18.93 (3.10) ^b	0.96 (0.21–1.90)
<i>Observer Rated Effects</i> ^{***}								
Drug Strength (Peak)	0.71 (0.34)	1.14 (0.23) ^a	1.71 (0.27) ^{ab}	2.14 (0.25) ^{b,c}	1.07 (0.27) ^a	2.00 (0.26) ^{b,c}	2.57 (0.29) ^c	1.58 (0.83–2.66)
Locomotor Relaxation (Peak)	0.21 (0.15)	0.21 (0.11) ^a	0.50 (0.25) ^{ab}	1.00 (0.23) ^{b,c}	0.29 (0.13) ^a	1.00 (0.26) ^{b,c}	1.50 (0.25) ^c	--
Non-locomotor Relaxation (Peak)	0.21 (0.15)	0.14 (0.10) ^a	0.57 (0.25) ^{ab}	0.86 (0.27) ^{b,c}	0.29 (0.13) ^{ad}	1.00 (0.23) ^{b,c,e}	1.43 (0.27) ^e	--
Confusion/Disorientation (Peak)	0.43 (0.25)	0.57 (0.17) ^a	0.79 (0.26) ^{ab}	1.36 (0.25) ^{b,c}	0.64 (0.25) ^a	1.50 (0.34) ^c	2.00 (0.26) ^c	1.08 (0.49–1.78)
Slurred Speech (Peak)	0.36 (0.25)	0.36 (0.17) ^a	0.57 (0.23) ^{ab}	1.50 (0.23) ^c	0.43 (0.23) ^{ad}	1.21 (0.30) ^c	1.71 (0.29) ^c	--
Posture (Peak)	0.36 (0.17)	0.21 (0.15) ^a	0.79 (0.26) ^b	0.93 (0.20) ^b	0.21 (0.15) ^a	0.93 (0.29) ^b	1.29 (0.22) ^b	1.54 (0.64–2.99)
Sedation/Sleepiness (Peak)	1.50 (0.42)	1.93 (0.35) ^{ab}	2.36 (0.29) ^{ac}	2.93 (0.07) ^c	2.07 (0.37) ^{ad}	2.64 (0.25) ^{cd}	2.93 (0.07) ^c	1.62 (0.62–3.38)
<i>Performance Measures</i>								
Circular Lights Task (Peak)	69.57 (4.59)	69.29 (2.76) ^a	58.07 (5.72) ^{abc}	51.79 (4.81) ^{b,c}	61.36 (4.44) ^{ab}	48.57 (5.25) ^{cd}	36.86 (5.21) ^d	--
Digit Symbol Substitution (Peak)	29.64 (4.02)	28.36 (3.24) ^a	18.86 (3.14) ^b	16.29 (3.61) ^{b,c}	21.93 (3.12) ^{ab}	14.79 (3.64) ^{bd}	8.93 (4.00) ^{cd}	--
Word Recall (1st time point) [†]	2.86 (0.61)	3.50 (0.67) ^a	1.29 (0.32) ^b	0.77 (0.53) ^b	3.50 (0.84) ^a	1.23 (0.30) ^b	0.86 (0.49) ^b	na ^{†††}
Words Recall (2nd time point) ^{††}	3.86 (0.60)	3.07 (0.79) ^a	1.00 (0.35) ^b	1.07 (0.35) ^b	1.38 (0.51) ^b	0.54 (0.31) ^b	0.86 (0.71) ^b	na ^{†††}

Data are mean scores with SEMs shown in parentheses (N=14); for placebo and drug conditions within a row, bold font indicates significant difference from placebo; for active doses, values not sharing a common letter are significantly different (Fisher's LSD $p<0.05$)

* Relative potency estimates for oral vs. inhaled alprazolam, with confidence limits in parentheses; absence of an estimate indicates that the validity criteria for that measure were not fulfilled

** Sedation is a total score of the sum of items from the Subjective Effects Questionnaire (see Methods)

*** Data for Observer Rated Stimulation/Arousal was low across all conditions and not statistically significant

[†] Word task encoding at the 1st time point occurred 70 minutes after oral capsules and 10 minutes after inhalation; recall occurred 10 minutes later

^{††} Word task encoding at the 2nd time point occurred 2 hours after oral capsules and 1 hour after inhalation; recall occurred 10 minutes later

^{†††} Relative potency could not be calculated due to missing data

Table 3

Pharmacological Class Questionnaire results

Drug Class	Placebo		Inhaled Alprazolam				Oral Alprazolam			
	0	0.5 mg	1 mg	2 mg	4 mg	1 mg	2 mg	4 mg	1 mg	4 mg
Placebo	79	29	14	0	14	29	0	14	29	0
Opioid	0	7	7	21	14	14	14	0	14	0
Muscle Relaxant	0	21	21	14	7	14	7	7	14	7
Barbiturate/Sleeping Medication	7	14	21	21	43	14	29	43	14	43
Benzodiazepine	14	21	36	43	21	29	43	21	43	21
Antidepressant	0	0	0	0	7	0	0	7	0	7
Other	0	7	0	0	0	0	0	0	0	0
Barbiturate or Benzodiazepine	21	36	57	64	64	43	71	64	43	64

At the end of the session, volunteers were required to identify the drug effect as being most similar to one of several categories of psychoactive drugs. The data show the percentage of volunteers (N=14) that selected a given drug category. Those categories that were not selected (antipsychotic, hallucinogen, stimulant, alcohol, cocaine, marijuana, and phencyclidine) by any volunteer in any condition are not shown.