Relative Abuse Liability of Indiplon and Triazolam in Humans: A Comparison of Psychomotor, Subjective, and Cognitive Effects

Lawrence P. Carter, Roland R. Griffiths, Patricia E. Suess, John H. Casada, Christopher L. Wallace, and John D. Roache

Departments of Psychiatry and Behavioral Sciences (L.P.C., R.R.G., P.E.S.) and Neuroscience (R.R.G.), Johns Hopkins University School of Medicine, Baltimore, Maryland; and Departments of Psychiatry (J.H.C., C.L.W., J.D.R.) and Pharmacology (J.D.R.), University of Texas Health Science Center at San Antonio, San Antonio, Texas

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ABSTRACT

Indiplon ([N-methyl-N-[3-[3-(2-thienylcarbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]acetamide; NBI 34060] is a positive allosteric GABA<sub>A</sub> receptor modulator that is under development for the treatment of insomnia. This study compared the abuse potential of indiplon, a compound with preferential affinity for GABA<sub>A</sub> receptors containing an α<sub>1</sub> subunit, with triazolam in 21 volunteers with histories of drug abuse. Placebo, triazolam (0.25, 0.5, and 0.75 mg), and indiplon (30, 50, and 80 mg) were studied in counterbalanced order under double-blind conditions at two different residential research facilities. Both drugs impaired psychomotor and cognitive performance and produced similar dose-related increases in participant and observer ratings of drug strength. The onset of action of both drugs was rapid (30 min); however, the duration of action of indiplon (3–4 h) was shorter than that of triazolam (4–6 h). The profiles of subjective effects of triazolam and indiplon were similar; however, a maximum of 52% of participants identified indiplon as a benzodiazepine or barbiturate, compared with 81% of participants after 0.75 mg of triazolam. On participant-rated subjective effects relevant to sedation, the slope of the triazolam dose-effect curve was significantly steeper than that of indiplon. Neither the largest doses of indiplon and triazolam nor the slope of the indiplon and triazolam dose-effect curves were significantly different from each other on any of the same-day or next-day measures of positive drug effects or next-day measures of reinforcing effects. Together, these data suggest that although the abuse potential of indiplon is not different from that of triazolam at these doses, psychomotor and cognitive impairment after large doses of indiplon might be less.

Chronic insomnia is estimated to affect 10 to 15% of the adult population (Thase, 2005). The most commonly prescribed drugs for the treatment of insomnia are benzodiazepines (e.g., triazolam and temazepam) and nonbenzodiazepines (e.g., zolpidem and zaleplon) compounds that bind to GABA<sub>A</sub> receptors and that enhance, or positively modulate, the effects of GABA. Although positive GABA<sub>A</sub> receptor modulators are effective sedative/hypnotic compounds, use of these drugs can also result in unintended effects such as psychomotor and cognitive impairment, and the abuse of, or dependence upon, these drugs. Thus, the development of sedative/hypnotic compounds that retain the desired therapeutic effects (induction and maintenance of sleep), while having fewer undesired effects, would increase the therapeutic utility and safety of these compounds.

GABA<sub>A</sub> receptors in brain are pentameric chloride ion channels most commonly composed of α<sub>1,3</sub>, β<sub>1,3</sub>, and γ<sub>1,3</sub> subunits in a 2:2:1 ratio (Mehta and Ticku, 1999). Benzodiazepines bind at the interface of an α and γ subunit of a GABA<sub>A</sub> receptor, and the isoform (1–6) of the α subunit has been shown to be a critical determinant of the selectivity of benzodiazepine binding (Mehta and Ticku, 1999). Moreover, preclinical studies have suggested that GABA<sub>A</sub> receptors containing an α<sub>1</sub> subunit mediate the sedative effects of benzodiazepines (Rudolph et al., 1999; McKernan et al., 2000), whereas receptors containing α<sub>2</sub>, α<sub>3</sub>, and α<sub>5</sub> subunits are thought to mediate the anxiolytic, amnesic, and myorelaxant effects of these drugs (Löw et al., 2000; Paronis et al., 2001; Licata et al., 2005). Therefore, compounds that have preferential affinity for GABA<sub>A</sub> receptors containing the α<sub>1</sub> subunit would be expected to have fewer side effects.
Materials and Methods

Study Sites

This study was conducted at two different sites. Ten participants were enrolled and completed the study at the University Clinical Psychopharmacology Laboratory of The University of Texas Health Science Center at San Antonio (San Antonio, TX). Eleven participants were enrolled and had completed the study at the Behavioral Pharmacology Research Unit at Johns Hopkins University (Baltimore, MD).

Participants

Participants were 18 adult males and 3 adult females without significant medical or psychiatric illness (other than substance abuse or dependence). Eleven participants were white (52%), seven were African-American (33%), and three were Hispanic (14%). The median age of all participants was 25 (range 19–46 years), and the median body mass index was 25.9 (range 18.1–41.9). Inclusion criteria for this study required that all participants have a history of substance abuse or dependence (Diagnostic and Statistical Manual—Version IV criteria for abuse or dependence on a commonly abused psychoactive drug [e.g., benzodiazepines, opioids, or cocaine] and that they report using a sedative/hypnotic drug, other than alcohol, recreationally within the past 12 months. All participants met Diagnostic and Statistical Manual—Version IV criteria for abuse or dependence on a commonly abused psychoactive drug within the past 12 months, and they reported using a sedative/hypnotic drug, other than alcohol, recreationally within the past 12 months. Most participants reported using a benzodiazepine (76%), opioid (76%), cannabis (76%), or cocaine (57%) within the past 30 days. This study was approved by the Institutional Review Boards of The University of Texas Health Science Center at San Antonio and Johns Hopkins University School of Medicine. Participants gave their written informed consent before beginning the study, and they were paid for their participation.

General Procedures

After completing the screening procedures, eligible individuals were admitted to the residential research unit. Participants were informed that during their participation they would receive placebo, varying doses of alprazolam, indiplon, triazolam (both sites), and other possible drugs (at Johns Hopkins University). Participants were told that the purpose of the study was to learn more about the effects of certain sedative drugs by administering them to individuals who take these drugs for nonmedical reasons such as “to get high”. Other than this general explanation of purpose, participants were not told what outcomes might be expected.

Before admission to the residential unit, participants performed a breathalyzer test and provided a urine sample that was screened for the presence of amphetamines, cocaine, barbiturates, benzodiazepines, and opiates. One participant tested positive for cocaine upon admission to the residential unit; however, this participant (and all other participants) tested negative before beginning the study. On the first session day, participants received placebo under single-blind conditions for training and acclimation to the experimental procedures (e.g., psychomotor and computer tasks). On the second session day, participants received 2 mg of alprazolam under single-blind conditions to determine whether they reported liking the effects of this dose of alprazolam. Participants who reported liking alprazolam (n = 21) on the Next-Day Questionnaire (described below) were allowed to continue in the study. Seven participants were screened for the study, but they did not report liking 2 mg of alprazolam and were discontinued from the study; demographic and other data for those participants are not included in this report.

Experimental sessions were conducted 5 to 7 days per week, and participants followed a daily routine. Participants were awoken by 7:00 AM, and they were allowed to smoke cigarettes until approximately 8:00 AM, but they were not allowed to smoke again until after

subunit (e.g., zolpidem [Ambien], and zaleplon [Sonata]) have been developed and marketed as effective sedative/hypnotics with purportedly fewer undesired effects.

Despite the apparent selectivity of some compounds for GABA<sub>\alpha</sub><sub>1</sub> receptor subtypes, several behavioral effects of the selective compounds are similar to nonselective benzodiazepines and barbiturates. In drug discrimination studies, zolpidem occasioned lorazepam-, midazolam-, and pentobarbital-appropriate responding in nonhuman primates (Griffiths et al., 1992; Rowlett and Woolverton, 1997; McMahon et al., 2002) and triazolam- and pentobarbital-appropriate responding in human participants (Rush et al., 1997; Smith and Bickel, 2001). Likewise, triazolam, midazolam, and pentobarbital occasioned zolpidem-appropriate responding in rats (Sanger and Zivkovic, 1986), nonhuman primates (Rowlett et al., 1999), and human participants (Rush et al., 2000). In self-administration studies in baboons, zolpidem and zaleplon were self-administered at rates equal to or greater than those of triazolam (Griffiths et al., 1992; Weerts and Griffiths, 1998; Ator, 2000). In human sedative drug abusers, neither zolpidem nor zaleplon was different from triazolam in subjective ratings of the drug’s good effects, liking the drug effect, and the degree to which participants reported they would take the drug again (Evans et al., 1990; Rush et al., 1999a,b). Thus, although the behavioral effects of compounds that are selective for GABA<sub>\alpha</sub> receptors containing an \( \alpha_1 \) subunit can be differentiated from nonselective compounds under circumscribed conditions (Rowlett et al., 2003), the in vitro selectivity of compounds for different GABA<sub>\alpha</sub> receptor subtypes has not resulted in markedly different discriminative stimulus effects, subjective effects, or reinforcing effects under most conditions.

Indiplon is a positive allosteric modulator of GABA<sub>\alpha</sub> receptors that is under development for the treatment of insomnia (Sullivan et al., 2004). Like zolpidem and zaleplon, indiplon binds preferentially to GABA<sub>\alpha</sub> receptors containing the \( \alpha_1 \) subunit; however, its potency and selectivity at these receptors are greater than that of zolpidem and zaleplon (Petroski et al., 2006). In rodents, indiplon decreased locomotor activity, rotarod performance, and memory/retention performance, and increased punished responding (Foster et al., 2006). In rodents, indiplon decreased locomotor activity, rotarod performance, and memory/retention performance, and increased punished responding (Foster et al., 2006). Indiplon also seems to be an effective sedative/hypnotic in clinical trials. In a double-blind study in elderly patients (65–85 years old) with insomnia, indiplon significantly decreased self-reported latency to sleep onset, number of awakenings, and time spent awake after sleep onset, and it significantly increased patient ratings of quality of sleep and total sleep time (Lydiard et al., 2006).

If selective binding to \( \alpha_1 \) subunit-containing GABA<sub>\alpha</sub> receptors confers greater sedative/hypnotic effects, then indiplon might have greater sedative effects or fewer undesired effects than equivalent doses of a nonselective benzodiazepine. The aim of this study was to compare the abuse potential of indiplon with triazolam, which has well documented positive-reinforcing effects and abuse potential in humans (Griffiths et al., 1985; Zawertailo et al., 2003; Griffiths and Johnson, 2005). Behavioral, subjective, and cognitive effects of a range of doses, including supratherapeutic doses, of each drug were assessed repeatedly over time to characterize the time course and peak effects of indiplon and triazolam at different doses (Griffiths et al., 2003).
1:30 PM. Participants were maintained on a caffeine-free diet for the duration of the study and were not allowed to eat food or drink caloric beverages from midnight the night before a session until noon (3 h after dosing). There was no evidence of acute withdrawal (e.g., from nicotine or caffeine) over the course of these studies. Test rooms contained a desk and chairs, an Apple Macintosh computer, and an automated ECG and blood pressure monitor. A crash cart was available in case of a medical emergency. When not actively completing an experimental task, participants were allowed to engage in recreational activities (e.g., watching television or reading).

On each of the seven test days (session days 3–9), participants received one of seven different compounds (lactose/placebo; 0.25, 0.5, and 0.75 mg of triazolam; and 30, 50, and 80 mg of indiplon) in four capsules, under double-blind conditions, at approximately 9:00 AM each day. On the last session of the study (i.e., the consequence day), participants received a randomly selected consequence from one of all choices from the Drug versus Money Multiple Choice Procedure (described below), and they completed a standard experimental session. The sequence and order of doses were counterbalanced across participants by randomly assigning participants to one of the sequences from three different 7 × 7 Latin squares. The balance task, Circular Lights, Digit-Symbol-Substitution task (DSST), Digit Enter and Recall, and subjective effects questionnaire were completed before capsule administration (approximately 8:30 AM) and at 1, 2, 3, 4, 6, 8, 10, and 24 h after administration. The observer-rated questionnaire, Drug Effect Questionnaire (DEQ), and Visual Analog Scales were completed at 0.5 h after administration in addition to each of the time points listed above. The study phase of the Word Recall/Word Recognition task was completed 2 h after administration; the test phase of the task was completed 6 h after administration. The Addiction Research Center Inventory (ARCI) and Profile of Mood States (POMS) were completed before administration and at 2 and 8 h after administration. The Pharmacological Class Questionnaire was completed 2, 8, and 24 h after administration. The Next Day Questionnaire and Multiple Choice Questionnaire were completed 24 h after administration.

**Behavioral Performance: Psychomotor and Cognitive Measures**

**Balance.** This task began with the participant raising one foot off of the floor with his or her eyes closed. The time that a participant remained on one foot without opening his or her eyes or touching the floor or another part of his or her body with the raised foot was measured for 30 s with each foot and summed across both feet (60 s in total).

**Circular Lights.** This task, which has been described previously (Mumford et al., 1995), began with the participant pressing a button in the center of 16 lights that were equally spaced around a 54-cm-diameter circle and the subsequent random illumination of one of the peripheral lights. The participant was instructed to press the buttons corresponding to the randomly illuminated lights as quickly as possible for the next 60 s. Lights were illuminated sequentially and were not extinguished until the corresponding button was pressed. The dependent measure was the number of correct presses (i.e., lights extinguished) in 60 s.

**Digit-Symbol-Substitution Task.** This task was a computer version of the digit-symbol-substitution task (McLeod et al., 1982). A 90-s trial began with the display of nine numbers and corresponding 3 × 3 geometric patterns across the top of a computer monitor and one randomly selected number in the center of the monitor. Participants were instructed to reproduce the geometric pattern that corresponded to the number in the center of the screen using the 3 × 3 numeric keypad at the right of the keyboard. The reproduction of the geometric patterns always required three key presses, contained only one key press per horizontal row, and was completed from top to bottom. Dependent measures were the number of correct patterns that were reproduced within 90 s.

**Digit Enter and Recall.** This task was a version of the number recall task that has been adapted for use on Apple Macintosh computers (Mumford et al., 1995). In the first component of the task (enter), participants were instructed to reproduce the number using the keyboard while the number remained on the monitor. In the second component of the task (recall), the participants were instructed to reproduce the number after 0 s (five trials) or 10 s (five trials) after the number disappeared from the monitor. The session ended after 10 eight-digit numbers were correctly reproduced in the first component (i.e., 10 trials were initiated) or after the incorrect entry of 25 eight-digit numbers. The dependent measure was the number of eight-digit numbers that were correctly recalled in each delay condition.

**Word Recognition and Recall.** For these tasks, 16 words were presented sequentially on a computer monitor 2 h after drug administration. Participants were required to rate the pleasantness of each word on a scale of 1 (least pleasant) to 7 (most pleasant) to encourage them to read and think about the words for later recall. Four hours after the presentation of the words (6 h after drug administration), the Word Recall task commenced in which participants were asked to recall as many words as they could remember from the words presented earlier. The dependent measure was the number of correct words recalled (written down) within 5 min. The Word Recognition task followed Word Recall task and consisted of the randomly sequenced presentation of the 16 words presented earlier (old) and 16 words not previously presented (new). Participants pressed buttons labeled “old” if they recognized the word or “new” if they did not recognize the word from the prior presentation. The dependent measure for the Word Recognition task was the number of words recognized by the participant from new and old words, which is calculated from the number of old words identified as old and the number of new words identified as old (Snodgrass and Corwin, 1988).

**Observer-Rated Measures**

An observer-rated questionnaire, which has been described previously in detail (Rush et al., 1999b), consisted of eight items. A staff member rated the participant on the following: sedation/sleepiness, locomotor and nonlocomotor muscle relaxation, abnormal posture, impaired speech, confusion/disorientation, stimulation/arousal, and strength of drug effect. Observers (i.e., staff) rated each of these dimensions on a 5-point scale from 0 (normal) to 4 (very strong drug effect). Brief descriptions of each point for each dimension were provided (e.g., sedation/sleepiness: 0, awake and alert; 1, awake and relaxed; 2, drowsy; 3, asleep, but arousable; and 4, asleep, not arousable) to increase the consistency of the observer ratings. Observers also recorded the number of minutes in which participants were asleep.

**Participant-Rated Measures**

Unless otherwise stated, all questionnaires were completed on an Apple Macintosh computer by using a mouse to point to and select response options displayed on the computer monitor.

**Drug Effect Questionnaire.** This previously described questionnaire (Mumford et al., 1995) consisted of a 5-point drug strength rating (“No drug effect at all,” “Possible mild effect but not sure,” “Definite mild effect,” “Moderate strong drug effect,” and “Very strong drug effect”) and a 9-point drug liking-disliking rating (“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”). For purposes of data analysis, ratings of drug liking were assigned a score of 0 if participants indicated disliking (Mumford et al., 1995).

**Subjective Effects Questionnaire.** For this previously described questionnaire (Rush et al., 1999b), participants were instructed to rate how they felt at present on a 5-point scale (“not at all,” “a little bit,” “moderately,” “quite a bit,” “extremely”). The ques-
tions of ratings of 34 somatic and other subjective effects such as, “Do you feel sleepy?” or “Do you feel talkative?”.

Visual Analog Scales. For this questionnaire, participants were instructed to rate how they felt in the past hour and at the current time by making a perpendicular mark on each of nine 100-mm lines labeled “not at all” and “extremely” at the left and right ends of the scale, respectively. The nine scales were described by the following phrases: “feel drug effect,” “like drug effect,” “feel good effects,” “feel bad effects,” “feel drowsy,” “feel sedated,” “feel impaired,” “feel forgetful,” and “have difficulty concentrating.” This task was completed using pencil and paper.

Addiction Research Center Inventory. The short form of the ARCI consists of 49 true/false questions from which three empirically defined subscales were scored: morphine/benzodiazepine group (MBG, considered to be a measure of euphoria); pentobarbital/chlorpromazine/alcohol group (PCAG, considered to be a measure of sedation); and LSD-specific group (LSD, considered to be a measure of dysphoria) (Martin et al., 1971; Jasinski, 1977).

Profile of Mood States. The POMS is a 65-item adjective rating scale that is a standardized method of measuring mood states ( McNair et al., 1971). Participants rated each item on a 5-point scale from 0, “not at all” to 4, “extremely”. From the 65 items, six previously defined factors were determined: Tension/Anxiety, Depression/Dejection, Anger/Hostility, Vigor/Activity, Fatigue/Inertia, and Confusion/Bewilderment.

Pharmacological Class Questionnaire. This previously described questionnaire (Rush et al., 1999b), which was completed approximately 2, 8, and 24 h after drug administration, listed descriptive titles and examples of 12 classes of psychoactive drugs, “blank or placebo”, and “other”. Participants were instructed to choose the option that they believed most closely represented the compound that they had received that day (2 and 8 h) or the previous day (24 h).

Next-Day Questionnaire. This previously described questionnaire (Rush et al., 1999b), which was completed approximately 24 h after drug administration, consisted of five items (“overall strength of the drug effect”, “overall liking of the drug effect”, “overall good effects of the drug”, “overall bad effects of the drug”, “degree to which you would like to take again”) rated on scales similar to those described above for the Drug Effect Questionnaire, and two items (“amount of money you think the drug you took yesterday would be worth on the street” and “What would you be willing to pay for yesterday’s drug?”) answered with a numerical value in dollars and cents.

Drug versus Money Multiple Choice Procedure. This paper-and-pencil questionnaire was an adaptation of a procedure that has been described in detail previously (Griffiths et al., 1993; Mintzer and Griffiths, 1998). It involved the participant making discrete choices to receive the previously administered dose of drug/placebo versus an amount of money. Approximately 24 h after drug administration on each of the test days, participants completed a series of 70 questions asking whether they would prefer to receive yesterday’s dose of drug or an amount of money. Monetary values ranged from $0.25 to $25.00. The maximal price that participants were willing to pay for the compound that was administered on the previous day was determined as the crossover point for that compound. Before the first test day, participants were trained to understand that the Multiple Choice Procedure questionnaire represented real choices between drug/placebo and money and to expect that at the end of the experiment, they would receive the consequence of one of those choices. On the last session of the study (i.e., the consequence day), one of the choices from this procedure across all sessions (i.e., 490 choices) was selected at random, the consequence of that choice was delivered (i.e., if the participant chose drug, the dose of drug or placebo was administered; if the participant chose money, the amount of money was credited to the participant’s account). Regardless of their choice, participants completed a standard experimental session so that there was no bias introduced for drug or money choices and so that the consequence did not affect the duration of the study.

Drugs
Alprazolam, triazolam, indiplon, and matching placebo were orally administered in four identical capsules with 200 ml of water. The capsules were filled with the drug substance, common pharmaceutical excipients, a dye, and an opacifier. Doses of triazolam and indiplon were selected on the basis of a pilot study. Drugs and placebo were supplied by Neurocrine Biosciences Inc. (San Diego, CA).

Data Analyses
Analyses were performed using SAS Proc MIXED (SAS Institute, Cary, NC). For all analyses, site was included as a factor. The effect of site was generally not significant, and it is not reported here. For all statistical tests, p < 0.05 was considered significant.

Time Course Comparisons. The time course of effects that were measured repeatedly (more than three times during the session) were analyzed using a two-factor repeated measures analysis of variance (ANOVA) with condition (placebo; 0.25, 0.5, and 0.75 mg of triazolam; and 30, 50, and 80 mg of indiplon) and time (0.5 when applicable, 1, 2, 3, 4, 6, 8, and 10 h after administration) as factors. Planned comparisons between each drug condition and placebo were made.

Dose Comparisons (Peak Effects and Single Measurements). For the Balance, Circular Lights, DSST, and Digit Enter and Recall tasks, the peak effect was defined as the minimum value within 10 h after drug administration. For the observer ratings, Drug Effect Questionnaire, Subjective Effects Questionnaire, and the Visual Analog Scales, the peak effect was defined as the maximum value within 10 h after drug administration. The subscale scores of the ARCI and POMS were analyzed at the 2-h time point because this time point was within the period of drug effect. The Word Recognition and Recall tasks, Next Day Questionnaire, and Multiple Choice Questionnaire were completed once per session. Data from the Pharmacological Class Questionnaire were calculated as the percentage of participants and are presented descriptively only. Data from the peak effect calculations and from tasks that were completed once per session were analyzed using a repeated measures ANOVA with condition (placebo, 0.25, 0.5, and 0.75 mg of triazolam, and 30, 50, and 80 mg of indiplon) as the primary factor of interest. When the results of the ANOVA were significant, pairwise comparisons were made using Tukey’s honestly significant difference post hoc test with adjustments made for multiple comparisons.

Slope Comparisons. Slope comparisons were assessed using SAS Proc Mixed (SAS Institute) with drug as a categorical variable and the log of dose as a continuous variable, with the interaction of drug and dose providing a test of homogeneity of slopes.

Results
Time Course of Drug Effects
Both drugs produced dose- and time-related behavioral and subjective effects. Figure 1 shows the time course of triazolam (left column) and indiplon (right column) on a representative behavioral (DSST) and a representative subjective (participant-rated liking) measure of drug effect. In general, the maximal effects of both drugs occurred 1 to 2 h after administration. The onset of effects was rapid (i.e., within 30 min; Fig. 1, bottom), and it was similar for both drugs, although the duration of action of indiplon was shorter than that of triazolam. Both drugs produced equivalent participant ratings of strength and liking of the drug effect at the largest dose that was administered (Fig. 1, bottom; Table 1);
Behavioral Performance: Psychomotor and Cognitive Measures

Consistent with the time course data, Fig. 2 shows that triazolam and indiplon impaired psychomotor and cognitive performance in a dose-dependent manner. Both drugs significantly decreased performance on the Balance, Circular Lights, DSST, Word Recognition, and Word Recall tasks compared with placebo (Table 1; Fig. 2), although, the effects of indiplon on psychomotor and cognitive performance were generally less than those of triazolam (Fig. 2). Administration of 0.75 mg of triazolam resulted in a significantly greater impairment of performance on the Circular Lights task and DSST task (trials attempted) compared with 80 mg of indiplon and unlike triazolam, indiplon did not significantly decrease performance on the 10-s delay condition of the Digit Enter and Recall task at any dose studied (Fig. 2; Table 1). The trend for indiplon to have less of an effect than triazolam on psychomotor performance is also apparent from the significantly shallower dose-effect curves for indiplon compared with triazolam on the Circular Lights ($F_{(2,102)} = 11.74$; $p < 0.005$), DSST ($F_{(2,102)} = 5.27$; $p < 0.05$), and Digit Recall ($F_{(2,102)} = 10.19$; $p < 0.005$) tasks (Table 1).

Observer-Rated Measures

Both drugs significantly increased observer ratings of drug effect, including ratings of drug strength (Fig. 3, top left). Indiplon, unlike triazolam, did not significantly increase observer ratings of sedation/sleepiness at any dose (Fig. 3, bottom left). Furthermore, peak observer ratings of sleep time within the first 4 h were significantly greater after administration of 0.75 mg of triazolam compared with 80 mg of indiplon and the slope of the triazolam dose-effect curve for peak sleep time was significantly greater than that of indiplon ($F_{(2,102)} = 10.01$; $p < 0.005$; Table 1). The difference in slopes for triazolam and indiplon on observer-rated, sedation/sleepiness approached statistical significance ($F_{(2,102)} = 3.70$; $p = 0.057$).

Participant-Rated Measures

Ratings of Drug Effect and Drug Strength. Triazolam and indiplon significantly and dose-dependently increased same-day participant ratings of drug effect on the Visual Analog Scale and the Subjective Effects Questionnaire (Table 1). Likewise, same-day and next-day participant ratings of drug strength were also significantly increased by both drugs in a dose-dependent manner (Fig. 3, top right). Table 1 shows that neither the peak effects of the largest dose of triazolam and indiplon nor the slopes of the triazolam and indiplon dose-effect curves for participant ratings of drug effect and drug strength were significantly different from each other.

Somatic Subjective Effects. Consistent with the deficits in psychomotor and cognitive performance and observer ratings of sedation and muscle relaxation, Table 1 shows that triazolam and indiplon significantly increased participant ratings of subjective effects suggestive of sedation (e.g., increased ratings of depressant or sedating, sleepy, tired or lazy, fatigued or weak, and drowsy), muscle relaxation (e.g., increased ratings of limpid or loose, unsteady, relaxed, and impaired), and cognitive impairment (e.g., increased ratings of confused or disoriented, difficulty concentrating, mentally slowed down, and forgetful). In general, the profile of subjective effects was similar for triazolam and indiplon, and the magnitude of participant ratings after administration of the largest dose of each drug was not significantly different from each other (Table 1).

Although the slopes of the triazolam and indiplon dose-effect curves were not significantly different from each other on most measures of subjective effects, including participant ratings of drug effect and drug strength, there were significant slope differences on some participant ratings suggestive of sedation. Figure 3 (bottom right) shows the peak participant ratings of sleepy. The slope of the triazolam dose-effect curve was significantly greater than that of indiplon for participant ratings of sleepy ($F_{(2,102)} = 7.86$; $p = 0.01$), drowsy ($F_{(2,102)} = 8.30$; $p = 0.01$), and sedated ($F_{(2,102)} = 8.25$; $p = 0.01$; Table 1).

Pharmacological Class Questionnaire. Table 2 shows drug class identification data from the Pharmacological Class Questionnaire during the period of peak drug effect (2 h) and approximately 24 h after drug administration (data from the 8-h time point are not shown because drug effects, when they occurred, typically subsided by this time). At 2 h after administration, 76% of participants correctly identified placebo as a blank or placebo and 81% of participants identified 0.75 mg of triazolam as a benzodiazepine or barbiturate. Like triazolam, higher doses of indiplon resulted in a
greater percentage of participants identifying indiplon as a benzodiazepine or barbiturate; however, the largest dose of indiplon that was studied (80 mg) was only identified as a benzodiazepine or barbiturate by 52% of participants during the period of drug effect (Table 2, top).

Data from the next-day retrospective Pharmacological
Class Questionnaire were similar to data obtained during the period of drug effect. On the next-day Pharmacological Class Questionnaire, 81% of participants correctly identified placebo as a blank or placebo and 76% of participants identified 0.75 mg of triazolam as a benzodiazepine or barbiturate; however, the largest dose of indiplon that was studied (80 mg) was only identified as a benzodiazepine or barbiturate by 48% of participants (Table 2, bottom panel).

**Positive and Negative Subjective Effects.** Triazolam and indiplon dose-dependently increased same-day and next-day participant ratings of like, liking, and good effects (Table 1; representative measures shown in Fig. 4). The magnitude of peak participant ratings of like, liking, and good effects after administration of 0.75 mg of triazolam or 80 mg of indiplon were not significantly different from each other (Fig. 4; Table 1). The slopes of the triazolam and indiplon dose-effect curves for positive subjective effects were also not significantly different from each other. On ratings of negative drug effects, triazolam, but not indiplon, significantly increased peak participant ratings of bad effects on the Subjective Effects Questionnaire (Table 1).

**ARCI and POMS.** Table 1 shows that the PCAG subscale of the ARCI was significantly increased by triazolam and indiplon 2 h after administration. Neither the peak effects of the largest dose of triazolam and indiplon nor the slopes of the triazolam and indiplon dose-effect curves were significantly different from each other (Table 1). There were no significant differences on any of the POMS subscales.

**Measures of Reinforcement.** Triazolam and indiplon increased measures of drug reinforcement on the Next Day Questionnaire (Table 1). The highest dose of triazolam and indiplon significantly increased next-day participant ratings of the degree to which they "would take the drug again" (compared with placebo; Fig. 4). On the Multiple Choice Procedure in which participants choose to receive drug or money, indiplon, but not triazolam, significantly increased the crossover point (i.e., the maximal amount of money at which participants chose to receive drug over money) at the highest dose that was administered (80 mg; Fig. 4). On each of these measures, neither the effects of the largest dose of triazolam and indiplon nor the slopes of the triazolam and indiplon dose-effect curves were significantly different from each other (Table 1).

**Discussion**

The aim of this study was to compare the abuse potential of indiplon with triazolam in human participants that use sedatives recreationally. Triazolam and indiplon were studied at doses that produced equivalent participant and observer ratings of drug strength (Table 1; Fig. 3); however, triazolam tended to result in greater psychomotor impairment at these doses (Table 1; Figs. 1 and 2). Neither the largest dose of indiplon nor the slope of the indiplon dose-effect curve was significantly different from triazolam on any of the next-day measures of reinforcing effects, same-day or next-day measures of positive drug effects, or the PCAG subscale of the ARCI (Table 1; Fig. 4). Together, these data suggest that the abuse potential of indiplon is not different from that of triazolam.

Consistent with its benzodiazepine-like profile of effects in rodents (Foster et al., 2004), indiplon decreased psychomotor and cognitive performance in human participants (Fig. 2). The effects of indiplon on psychomotor and cognitive performance, however, were generally less than those of triazolam at these doses (Table 1; Figs. 1 and 2). When comparing the highest doses tested, triazolam produced significantly greater impairment than indiplon on two of the seven psychomotor and cognitive performance measures, and the slopes of the triazolam dose-effect curves were significantly steeper than...
those of indiplon on more than half (four of seven) of the psychomotor and cognitive measures (Table 1).

Although doses of triazolam tended to produce greater psychomotor impairment than indiplon at these doses, observer and participant ratings of the magnitude of drug effects and the strength of the drug effects were not significantly different between the two drugs. Most observer ratings of drug effects, including drug strength, were not

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**TABLE 2**

Results of pharmacological class identification questionnaire

<table>
<thead>
<tr>
<th>Time Point/Category</th>
<th>Placebo</th>
<th>Triazolam</th>
<th>Indiplon</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.25 mg</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>0.25 mg</td>
<td>76</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td>0.5 mg</td>
<td>5</td>
<td>29</td>
<td>52</td>
</tr>
<tr>
<td>0.75 mg</td>
<td>14</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>30 mg</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>50 mg</td>
<td>19</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>80 mg</td>
<td>76</td>
<td>43</td>
<td>76</td>
</tr>
</tbody>
</table>

Twenty-four hours after administration (next day retrospective)

| Blank or placebo            | 81      | 29        | 14       | 0       | 38    | 29    | 19    |
| Benzodiazepine              | 0       | 19        | 38       | 33      | 29    | 38    | 19    |
| Barbiturate                 | 5       | 24        | 29       | 43      | 14    | 10    | 29    |
| Muscle relaxant             | 5       | 14        | 10       | 5       | 5     | 10    | 10    |
| Opiate                      | 0       | 0         | 0        | 0       | 0     | 0     | 0     |
| Stimulant                   | 5       | 0         | 5        | 0       | 5     | 0     | 5     |
| Antidepressant              | 5       | 0         | 0        | 0       | 0     | 5     | 0     |
| Hallucinogen                | 0       | 0         | 0        | 0       | 0     | 0     | 0     |
| Alcohol                     | 0       | 5         | 0        | 0       | 5     | 0     | 0     |
| Marijuana                   | 0       | 5         | 0        | 0       | 5     | 0     | 0     |
| Other                       | 0       | 10        | 5        | 0       | 0     | 0     | 10    |
| Benzodiazepine/barbiturate  | 10      | 43        | 76       | 81      | 38    | 38    | 52    |
significantly different after the highest doses of triazolam and indiplon (Table 1; Fig. 3). Likewise, the magnitude of peak effects and the slope of the dose-effect curves of same-day and next-day participant ratings of drug effect and drug strength were not significantly different after triazolam and indiplon (Table 1; Fig. 3). In general, the profile and magnitude of participant-rated subjective effects on the Subjective Effects Questionnaire, Visual Analog Scales, and ARCI were very similar after administration of triazolam and indiplon.

Despite the similar profile of subjective effects of indiplon and triazolam, the percentage of participants that identified the highest dose of indiplon as a benzodiazepine or barbiturate (52%) tended to be lower than that after the highest dose of triazolam (81%). This suggests that the subjective effects of these doses of indiplon might differ from those of triazolam in a discriminable way. Although no single subjective effect measure differentiated the two drugs at the highest doses of indiplon and triazolam that were studied, the slopes of the triazolam dose-effect curves were significantly steeper than the indiplon dose-effect curves for four participant-rated subjective effects relevant to sedation: sleepy, fatigued or weak, drowsy, and sedated (Table 1; Fig. 3). Moreover, the relatively greater participant-rated sedative effects of triazolam were substantiated by steeper dose-effect curves for observer-rated measures of peak sedation/sleepiness ($p = 0.057$) and peak sleep time (in an hour) across the first 4 h after drug administration ($p < 0.05$) after administration of triazolam (Table 1). Observer-rated total sleep time across the first 4 h was similar to peak sleep time, but it was not included as a primary measure of sleep due to the possible confound from differences in duration of action between the two drugs. Collectively, these data show that the slope of the triazolam dose-effect curve is steeper than that of the indiplon dose-effect curve for subjective and objective measures of sedation.

The finding that the slope of the triazolam dose-effect curve for sedative effects was steeper than that of indiplon was somewhat unexpected in light of the previous preclinical studies that have reported that the sedative effects of benzodiazepines are mediated by GABA$_A$ receptors that contain an $\alpha_1$ subunit (Löw et al., 2000; McKernan et al., 2000). However, previous studies in nonhuman primates and human volunteers have repeatedly shown that the sleep-related and sedative subjective effects of compounds with selective affinity for GABA$_A$ receptors containing an $\alpha_1$ subunit tend to be less than those of triazolam when matched on other behavioral effects. In squirrel monkeys, triazolam, but not zolpidem, increased observer-rated measures of rest posture, which is associated with sleep in that species (Platt et al., 2002). In human drug abusers, participant ratings of sleepy and observer ratings of sedated and minutes slept were significantly increased after triazolam but not zaleplon at doses of these drugs that were equated on participant ratings of drug strength (Rush et al., 1999b). Likewise, in another study, participant ratings of sleepy and observer ratings of sedation/sleepiness and minutes asleep were significantly increased after triazolam and not zolpidem at doses of zolpidem that were rated as equal to or greater than those of triazolam on participant-rated measures of drug strength (Evans et al., 1990). In a human drug discrimination study in which volunteers were trained to discriminate between a dose of triazolam and a dose of zolpidem that were equated...
on participant ratings of drug strength, every participant reported feeling tired (sleepy, tired, exhausted, fatigued, or drowsy) on a greater percentage of sessions after administration of triazolam than zolpidem (Mintzer et al., 1998). Thus, data from this study showing that the slope of the triazolam dose-effect curve is steeper than the indiplon dose-effect curve for subjective and objective measures of sedation is consistent with previous reports in nonhuman primates and human volunteers that the sedative effects of compounds with preferential affinity for GABAA receptors containing an α1 subunit are comparably less than those of the nonselective benzodiazepine triazolam when the doses are equated on other measures of drug strength.

Arguably, the most face-valid measure of sedation is the subjective report from an individual stating that he or she feels sedated, sleepy, drowsy, etc. Because of the difficulty of measuring such a response in nonhuman subjects, previous preclinical studies have typically used behavioral measures such as locomotor activity, operant responding, or rotarod performance as proxies for sedation (e.g., Rudolph et al., 1999; Löw et al., 2000; McKernan et al., 2000). As a result, drug effects such as ataxia or muscle relaxation that might occur independently of subjective sedative effects could be responsible for a general decrease in activity, behavior, or performance and could subsequently be interpreted as sedation in preclinical studies where subjective sedative effects cannot be verified. Specifically, it has been suggested that the ataxic effects of benzodiazepine-like drugs are predominantly mediated by GABAA receptors that contain an α1 subunit (Platt et al., 2002; Licata et al., 2005; Rowlett et al., 2005). Thus, the “selective sedative effects” (decreases in locomotor activity and behavioral performance) of compounds that bind preferentially to GABAA receptors containing an α1 subunit that have been reported in preclinical studies (e.g., McKernan et al., 2000) could be a result of an impairment of motor function (ataxia). However, in the human participants with histories of drug abuse in this study, indiplon clearly did not impair psychomotor performance any more than triazolam (Fig. 2), and in many cases, the impairment was less.

The aim of this study was to compare the abuse potential of indiplon with triazolam in human participants with histories of drug abuse. At doses that produced equivalent participant and observer ratings of drug strength, both triazolam and indiplon increased scores on the PCAG and sedation/euphoria subscales of the ARCI, same-day and next-day measures of positive drug effects, and next-day measures of reinforcing effects. However, neither the magnitude of the effects of the largest dose of triazolam or indiplon nor the slope of the triazolam or indiplon dose-effect curves was significantly different from each other on any of the measures related to the likelihood of abuse of these drugs. Together, these data suggest that the abuse potential of indiplon is not different from that of triazolam.

Some of the results of the present study, particularly when considered with respect to the marketed or intended to be marketed acute doses of triazolam (0.125 and 0.25 mg) and immediate-release indiplon (5 and 10 mg), suggest that high doses of indiplon might produce less behavioral and cognitive impairment and less subjective sedation compared with triazolam. The highest dose of indiplon examined in the present study (80 mg) is 8 times greater than the proposed high-marketed dose, whereas the highest dose of triazolam (0.75 mg) is only 3 times greater than the highest marketed dose. Yet, the high dose of triazolam generally produced numerically and, in a few instances, statistically, greater psychomotor impairment, cognitive impairment, and subjective sedation than the high dose of indiplon (compare Table 1 with Figs. 2 and 3). Furthermore, the indiplon dose-effect curve was significantly less steep than the triazolam dose-effect curve on most of these measures. Thus, although the results of this study indicate that triazolam and indiplon do not differ in their potential for abuse, these results suggest that indiplon might produce less impairment after intentional or accidental overdose.

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References

Relative Abuse Liability of Indiplon in Humans

Address correspondence to: Dr. John D. Roache, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr., MC7793, San Antonio, TX 78229. E-mail: roache@uthscsa.edu