Addiction
RESEARCH REPORT
doi:10.1111/j.1360-0443.2011.03706.x

Comparison of intranasal methamphetamine and *d*-amphetamine self-administration by humans

Matthew G. Kirkpatrick[1,2]*, Erik W. Gunderson[2], Chris-Ellyn Johanson[3], Frances R. Levin[2], Richard W. Foltin[2] & Carl L. Hart[1,2]

Department of Psychology, Columbia University, New York, NY, USA,[1] Division on Substance Abuse, New York State Psychiatric Institute and Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, NY, USA[2] and Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI, USA[3]

ABSTRACT

Aims There are no studies directly comparing self-administration of methamphetamine and *d*-amphetamine by humans. This study compared intranasal methamphetamine- and *d*-amphetamine self-administration and characterized the mood, performance and physiological effects produced by the drugs. **Design** A randomized, double-blind, placebo-controlled, cross-over study. **Setting** An out-patient research unit at the New York State Psychiatric Institute. **Participants** Male recreational methamphetamine users ($n = 13$). **Measurements** Five 2-day blocks of sessions were conducted. On the first day of each block, participants 'sampled' a single methamphetamine or *d*-amphetamine dose (0, 12, 50 mg/70 kg) and a monetary reinforcer ($5 or $20). Amphetamine plasma levels, cardiovascular, mood, and psychomotor performance effects were assessed before drug administration and repeatedly thereafter. On the second day of each block, participants chose between the sampled reinforcers (drug or money). **Findings** There were no significant differences between the drugs on the majority of measures. Under the $5 condition, both amphetamines increased self-administration dose-dependently, with 41% drug choices overall. Under the $20 condition, only 17% drug options were selected. Both drugs increased cardiovascular activity and 'positive' mood, although methamphetamine produced more prominent effects on some measures (e.g. heart rate and ratings of 'high'). **Conclusions** Methamphetamine and *d*-amphetamines appear to produce a similar dose-related profile of effects in humans, which supports their equivalence for abuse potential.

Keywords Amphetamines, *d*-amphetamine, humans, methamphetamine, performance, self-administration, subjective effects.

Correspondence to: Carl L. Hart, New York State Psychiatric Institute, 1051 Riverside Drive, Unit 120, New York, NY 10032, USA.
E-mail: clh42@columbia.edu
Submitted 23 July 2011; initial review completed 25 August 2011; final version accepted 28 October 2011

INTRODUCTION

Methamphetamine and *d*-amphetamine have nearly identical chemical structures. Methamphetamine is the *N*-methylated analog of *d*-amphetamine and both are approved in several countries to treat similar medical conditions. Despite their structural similarities and medical sanctioning, *d*-amphetamine is one of the most frequently prescribed medications, whereas methamphetamine is rarely prescribed [1]. It is possible that methamphetamine is prescribed relatively less frequently because it is perceived to have a greater abuse potential. In fact, epidemiological evidence indicates that methamphetamine abuse rates are greater than those of *d*-amphetamine. According to the US Treatment Episode Data Set [2], in 2007 methamphetamine users comprised approximately 96% of all amphetamine treatment admissions. One possible explanation for the greater incidence of methamphetamine abuse is that illicit methamphetamine is more readily available due to its purported ease of synthesis.

Another explanation is that the addition of the *N*-methyl group to the basic amphetamine structure makes methamphetamine more lipophilic (and thus

*Current address: Department of Psychiatry and Behavioral Neurosciences, University of Chicago, Chicago, IL, USA.

more potent) compared to *d*-amphetamine [3,4]. Despite this structural modification, results from pre-clinical studies generally support the notion that methamphetamine and *d*-amphetamine are equipotent on a range of dependent variables. For example, Melega and colleagues [5] observed that the drugs had equivalent pharmacokinetic profiles and similarly increased striatal dopamine in rats. Findings from behavioral studies are also in line with this view. At equivalent doses, methamphetamine and *d*-amphetamine produced similar locomotor activation [6] and discriminative stimulus effects in rats [7]. Finally, both drugs—at comparable doses—are self-administered by rhesus monkeys and rats at similar rates [8,9].

Concordant with the literature obtained with laboratory animals, direct comparisons of the effects of oral methamphetamine and *d*-amphetamine in humans indicate that the drugs produce overlapping effects on measures of cardiovascular activity, mood and drug discrimination [10–12]. An important consideration of these studies, however, is that they compared relatively low oral doses (i.e. 2.5–30 mg). It is unclear to what degree these findings generalize to illicit methamphetamine use. Recreational methamphetamine use is purportedly used in larger doses via routes of administration that produce a more rapid onset of effects (e.g. intranasal, intravenous and smoked: [13]). The onset speed of drug-related effects is a critical determinant of the intensity of mood and behavioral effects of a drug [14,15]. Thus, it is possible that potential differences between methamphetamine and *d*-amphetamine may only be detected following a route of administration associated with a faster onset of effects. There have been no direct comparisons of these amphetamines using a route associated commonly with abuse.

It is also important to note that previous comparisons of oral methamphetamine and *d*-amphetamine primarily examined drug-related effects on mood and/or drug discrimination. Although these measures provide potentially useful information about the abuse potential of a given drug, they are related indirectly to actual drug-taking behavior and may not correspond with self-administration data. Results from studies indicating that drug-related subjective effects and self-administration can be dissociable highlight this point [16]. For example, using a choice procedure during which participants had several opportunities to self-administer oral *d*-amphetamine (5 mg) or placebo, Johanson & Uhlenhuth [17] reported that *d*-amphetamine-related subjective effects were comparable in all subjects but did not predict choice to self-administer the drug. These results underscore the importance of assessing drug-taking behavior in the human laboratory.

In an effort to understand further the impact of modifications of the basic amphetamine structure on human behavior, the present investigation directly compared intranasal methamphetamine and *d*-amphetamine (0, 12 and 50 mg/70 kg) self-administration and documented the subjective, cardiovascular and psychomotor performance effects of the drugs. During a 'sample' session, participants were administered a single drug dose and given a monetary reinforcer (US$5 or $20). On the following day, participants had the opportunity to choose between the sampled reinforcers (drug or money). Data from several self-administration studies indicate that increasing the value of an alternative non-drug reinforcer decreases drug choice in laboratory animals [18,19] and humans [20,21]. Thus, we hypothesized that methamphetamine and *d*-amphetamine would similarly increase drug self-administration when $5 was the alternative reinforcer, but amphetamine-related self-administration would be attenuated when $20 was the alternative reinforcer. Furthermore, we predicted that both drugs would increase 'positive' subjective-effects ratings and cardiovascular values dose-dependently, and improve psychomotor performance.

METHODS AND MATERIALS

Participants

Male research volunteers ($n = 13$: one Asian, six black, two Hispanic, four white) completed this study. They were 37.4 ± 7.3 [mean ± standard deviation (SD)] years of age and had completed 14.8 ± 2.0 years of formal education. All passed comprehensive medical examinations and psychiatric interviews and were within normal weight ranges according to the 1983 Metropolitan Life Insurance Company height/weight table (body mass index: 24.9 ± 2.7). All participants reported current methamphetamine use (9.4 ± 4.7 days/month). Seven participants reported current alcohol use (four to 10 drinks/week), seven reported current cocaine use (1–8 days/month), three participants reported current marijuana use (4–12 days/month) and four smoked three to 20 tobacco cigarettes/day. Three met criteria for current methamphetamine dependence but none were seeking treatment for drug use and none met criteria for any other Axis I disorder.

All participants were solicited via word-of-mouth referral and newspaper and online advertisement in New York City. Before enrollment, each signed a consent form that was approved by the Institutional Review Board of The New York State Psychiatric Institute (NYSPI). Upon discharge, each participant was informed about experimental and drug conditions and paid for participation at a rate of $60 per day.

Pre-study training

Prior to starting the study, participants completed two training sessions (3–4 hours each) on the computerized psychomotor tasks that would be used during the study. Additionally, on a separate day, they received the largest active methamphetamine dose (50 mg/70 kg) to be administered during the study in order to monitor any adverse reactions and provide them with experience with a study drug. No untoward effects were noted.

Design

This 10-session out-patient study consisted of five 2-day blocks of sessions, during which physiological measures were assessed and participants completed visual analog mood scales and computerized psychomotor task batteries. Table 1 shows the study design. Briefly, the first day of each block was a sample session, during which participants received an intranasal amphetamine dose (0, 12, 50 mg/70 kg) and a monetary reinforcer. The monetary reinforcer was US$5 for seven participants and US$20 for six participants. The second day of each block was a choice session, during which participants could work for all or part of the drug and/or money they received on the previous day. Each block of sessions was separated by at least 48 hours and each participant experienced all dosing conditions, which were counterbalanced.

Procedure

Sample sessions

Each session began at approximately 09:00 hours and lasted for nearly 6 hours. Upon reporting to the laboratory, participants passed a field sobriety test and gave a urine sample that was negative for several drug metabolites, excluding amphetamines and tetrahydrocannabinol (THC). Following a light breakfast, they completed a visual analog sleep questionnaire and the baseline subjective-effects questionnaire and psychomotor task battery (described below). After baseline assessments, participants were given the monetary reinforcer and drug, which was insufflated immediately. Then, they completed four task batteries, took a 45-minute lunch break period and completed two additional task batteries. Subjective effects and cardiovascular measures were assessed at baseline and 5, 15, 30, 60, 90, 120, 180 and 240 minutes post-drug administration. Blood samples were collected at baseline and 15, 60, 90, 120, 180 and 240 minutes post-drug administration via an intravenous (i.v.) line, which was kept patent by a physiological saline solution drip.

Upon completion of a session, participants were evaluated for signs of intoxication, passed a field sobriety test, provided fare for public transportation and excused.

Choice (self-administration) sessions

The second day of each block was identical to the first with two exceptions: (i) blood samples were not collected; and (ii) after baseline assessment, participants completed a 50-minute computerized self-administration task. On this task, participants were given 10 opportunities to choose between 10% of the drug dose or 10% of the monetary reinforcer that they received on the previous day. Responses consisted of finger presses on a mouse manipulandum. The response requirements to choose drug or money increased independently as follows: 50, 100, 200, 400, 800, 1200, 1600, 2000, 2400 and 2800 responses. In order to receive 100% of either reinforcer, a participant had to select that reinforcer on all 10 trials and make a total of 11 550 responses. Following completion of the task, participants received the chosen amount of drug and/or money.

Subjective effects and psychomotor battery

The computerized visual analog questionnaire (VAS) consisted of a series of 100-mm lines labeled 'not at all' at one end and 'extremely' at the other end [22]. The lines were labeled with adjectives describing a mood (e.g. 'I feel . . .', 'irritable', 'talkative'), a drug effect (e.g. 'I feel . . .', 'stimulated', 'a good drug effect') or a physical symptom ('I feel nauseous', 'I have a headache'). Additionally, at 45 minutes post-drug administration participants completed a drug-effect questionnaire (DEQ), during which they were required to rate 'good effects' and 'bad effects' on a five-point scale: 0 = 'not at all' and 4 = 'very much'. They were also asked to rate the drug strength as well as their 'desire to take the drug again'.

Table 1 Study design.

Week		*Monday*	*Tuesday*	*Wednesday*	*Thursday*	*Friday*
1	MA (mg/70 kg)	S (50)	C (50)	Off	S (12)	C (12)
2	AMPH (mg/70 kg)	S (12)	C (12)	Off	S (50)	C (50)
3		S (placebo)	C (placebo)			

Sample administration and choice procedure occurred at 1000 hours. MA: methamphetamine; AMPH: *d*-amphetamine; S: sample session; C: choice session. All participants completed five 2-day blocks of sessions, one for each dosing condition. Dosing order was varied across participants.

Participants were also asked to rate how much they liked the drug effect on a nine-point scale: −4 = 'disliked very much' 0 = 'feel neutral, or feel no drug effect' and 4 = 'liked very much'.

The computerized psychomotor task battery consisted of two tasks: (i) the digit-symbol substitution task (DSST), designed to assess changes in visuospatial processing [23]; and (ii) the divided attention task (DAT), designed to assess changes in vigilance and inhibitory control [24].

Drug

Methamphetamine HCl [provided by the National Institute on Drug Addiction (NIDA)] and *d*-amphetamine sulfate (provided by Cambrex, Charles City, IA, USA) were prepared by the New York State Psychiatric Institute (NYSPI) Pharmacy. Lactose powder was used as a placebo and added to each active amphetamine dose (12 and 50 mg/70 kg) to achieve a final weight of 60 mg/70 kg. A research nurse placed each dose in a small medicine cup, along with a plastic straw (~7 cm). Participants were instructed to insufflate the entire dose within a 30-s period in either one or both nostrils. This procedure has been shown to produce dose-dependent changes in subjective-effects measures and cardiovascular activity [22]. All drugs were administered in a double-blind manner.

Data analysis

For each choice session, choice data were analyzed using a single-factor repeated-measures analysis of variance (ANOVA); the factor was drug condition (0, 12, 50 mg methamphetamine and *d*-amphetamine). Separate analyses were conducted for each group [i.e. those who received the $20 monetary reinforcer ($n = 6$) and those who received the $5 reinforcer ($n = 7$)]. For each sample session, cardiovascular effects, plasma levels and psychomotor performance data were analyzed using two-factor ANOVAs: the first factor was drug condition and the second factor was time (time and number of assessments varied depending on the measure). Subjective-effect ratings were summed across the session and analyzed using single-factor ANOVAs. The two groups did not differ on any physiological, subjective or performance measure; therefore, we combined these data for these analyses ($n = 13$). In order to assess the residual effects of the amphetamines, single-factor ANOVAs were conducted for subjective-effect ratings, cardiovascular measures and psychomotor performance data obtained 24 hours after drug administration (i.e. baseline measures on choice days). For all analyses, ANOVAs provided the error terms needed to calculate within-drug planned comparisons (0 mg versus all other doses, 12 mg versus 50 mg) and between-drug planned comparisons (methamphetamine versus *d*-amphetamine). Values were considered statistically significant at $P < 0.05$, using Huynh–Feldt corrections when appropriate.

RESULTS

Plasma methamphetamine and *d*-amphetamine levels

Acute effects

Figure 1 (top left panel) demonstrates that methamphetamine and *d*-amphetamine increased plasma concentrations dose-dependently. Peak concentrations for both drugs were observed 3–4 hours after drug administration. All amphetamine doses increased plasma concentrations significantly compared to placebo and the 50-mg doses produced larger increases than the 12-mg doses ($P < 0.0001$ for all comparisons).

Methamphetamine and *d*-amphetamine choice (self-administration)

Figure 2 (left panel) shows that, when $5 was the alternative reinforcer, participants selected a greater number of 50-mg methamphetamine and 50-mg *d*-amphetamine options compared to placebo ($P < 0.05$); there was no significant difference between methamphetamine and *d*-amphetamine. In contrast, when $20 was the alternative reinforcer, participants overwhelmingly chose the monetary option and no significant dose effects were noted (Fig. 2; right panel). Overall, participants chose 41% of drug options under the $5 condition but only 17% of this option under the $20 condition.

Cardiovascular effects

Acute effects

Figure 1 (top right and bottom panels) displays cardiovascular measures as a function of dosing condition and time. Relative to placebo and the 12-mg doses, both 50-mg doses increased heart rate (HR), systolic pressure (SP) and diastolic pressure (DP: $P < 0.01$ for all comparisons) significantly. Regarding HR, methamphetamine produced greater increases than *d*-amphetamine ($P < 0.05$). In contrast to peak drug plasma concentrations, which occurred hours after drug administration, peak cardiovascular effects occurred within 15 minutes.

Residual effects

Both methamphetamine doses and the large *d*-amphetamine dose caused baseline HR on choice days to remain increased significantly 24 hours after their administration compared to placebo (0 mg: 76.8 ± 2.3 versus 12 mg MA: 86.1 ± 1.9; 50 mg *d*-amphetamine: 90.5 ± 3.4; and 50 mg MA: 87.8 ± 2.3, $P < 0.01$ for all comparisons). In addition, relative to placebo, 50 mg methamphetamine produced significantly elevated DP

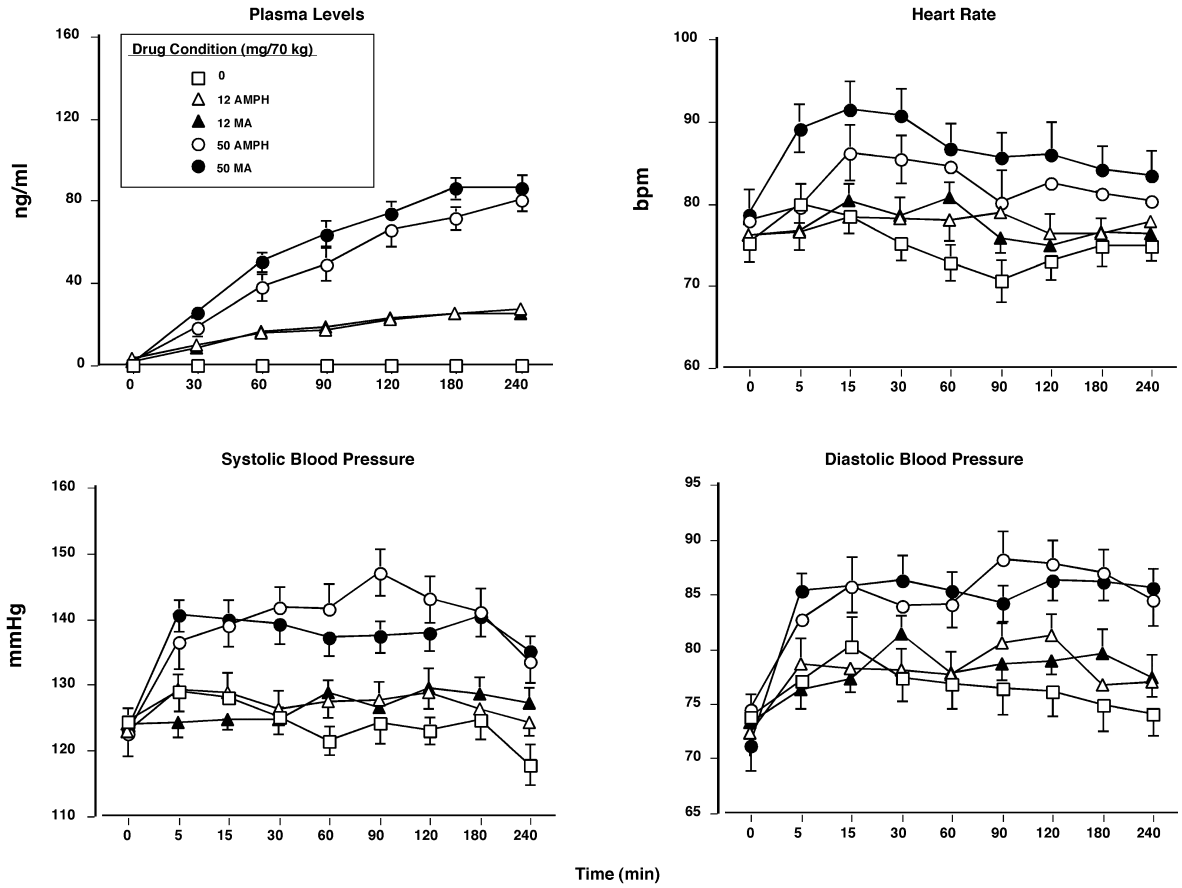

Figure 1 Upper panel (left): drug plasma levels as a function of drug dose and time ($n = 13$). Upper panel (right): heart rate as a function of drug dose and time. Lower panels: systolic and diastolic pressure as a function of drug dose and time. Error bars represent 1 standard error of the mean. Overlapping error bars were omitted for clarity. MA: methamphetamine; AMPH: d-amphetamine

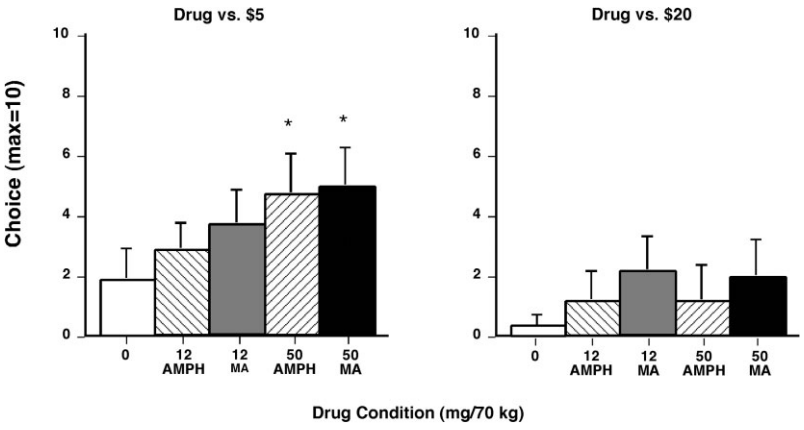

Figure 2 Number of selected drug options during the choice session as a function of drug dose ($5 group: $n = 7$; $20 group: $n = 6$). Error bars represent 1 standard error of the mean. *Significantly different from placebo ($P < 0.05$); significantly different from 12 mg ($P < 0.05$); significantly different from 50 mg *d*-amphetamine ($P < 0.05$). MA: methamphetamine; AMPH: d-amphetamine

24 hours post-drug administration (0 mg: 74.4 ± 2.2 versus 50 mg MA: 78.4 ± 2.4 $P < 0.05$).

Subjective effects

Acute effects

Figure 3 shows the effects of dosing condition on selected subjective-effect ratings summed across the entire sample session. Relative to placebo and the 12-mg amphetamine doses, both large doses increased visual analog questionnaire (VAS) ratings of 'good drug effect' and 'high' significantly, as well as DEQ ratings of 'desire to take drug again' ($P < 0.05$ for all comparisons). Ratings between the two amphetamines on several subjective-effect items did not differ significantly, but some differences were observed. For example, the large methamphetamine dose elevated

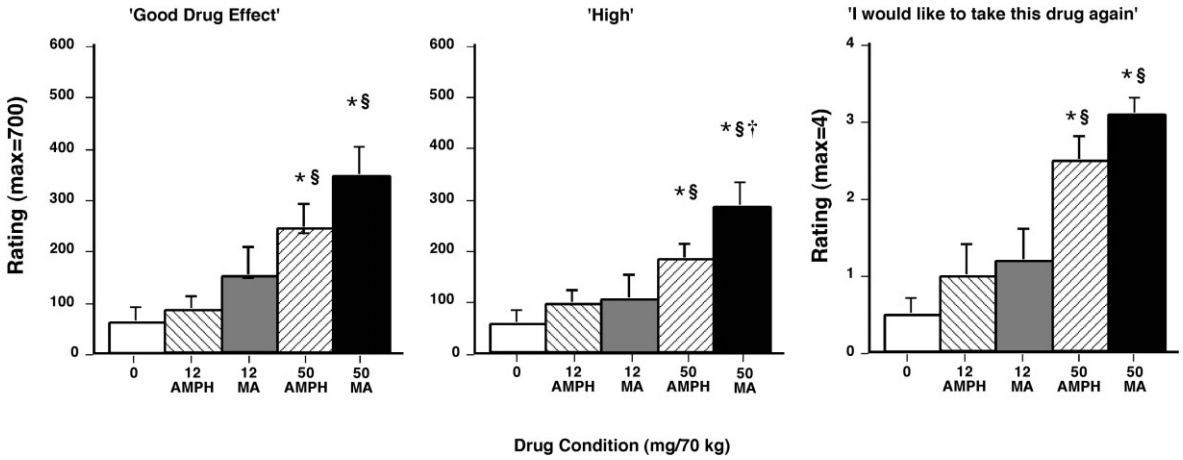

Figure 3 Selected subjective-effect ratings (summed across the session) as a function of drug dose ($n = 13$). Error bars represent 1 standard error of the mean. *Significantly different from placebo ($P < 0.05$); §significantly different from 12 mg ($P < 0.05$); †significantly different from 50 mg *d*-amphetamine ($P < 0.05$). MA: methamphetamine; AMPH: d-amphetamine

Table 2 Sum of acute amphetamine-related effects on subjective-effect ratings.

	Drug conditions				
	Placebo	*12 mg AMPH*	*12 mg MA*	*50 mg AMPH*	*50 mg MA*
	Mean (SEM)	*Mean (SEM)*	*Mean (SEM)*	*Mean (SEM)*	*Mean (SEM)*
VAS ratings (max = 700)					
Alert	274 (64)	353 (75)	389 (74)*	419 (81)*	446 (69)*
Energetic	271 (57)	319 (59)	361 (63)*	414 (59)*§	468 (65)*§
Friendly	324 (58)	359 (64)	375 (70)	434 (66)*§	463 (70)*§
Heart pounding	26 (8)	24 (8)	19 (7)	29 (12)	66 (23)*§†
Nose burning	37 (10)	48 (19)	41 (12)	102 (19)*§	107 (25)*§
Sleepy	205 (70)	163 (72)	88 (56)*	67 (41)*	47 (30)*
Social	314 (54)	346 (59)	367 (64)	448 (46)*§	454 (64)*§
Stimulated	111 (49)	160 (49)	172 (53)	226 (50)*§	320 (47)*§†
Talkative	271 (53)	282 (49)	338 (56)	411 (49)*§	419 (65)*§
Tired	224 (74)	176 (71)	127 (63)	68 (39)*	56 (21)*
DEQ ratings (max = 4)					
Good drug effect	0.7 (0.2)	0.8 (0.3)	1.6 (0.4)*	2.3 (0.3)*§	3.1 (0.2)*§†
Like drug	–0.1 (0.4)	0.7 (0.4)	1.1 (0.4)*	2.1 (0.4)*§	2.8 (0.3)*§
Drug strength	1.1 (0.3)	1.0 (0.2)	1.7 (0.4)	2.5 (0.3)*§	3.1 (0.2)*§†

*$P < 0.05$, significantly different from placebo. §$P < 0.05$, significantly different from 12 mg. †$P < 0.05$, significantly different from 50 mg *d*-amphetamine (AMPH). DEQ: drug-effect questionnaire; MA: methamphetamine; SEM: standard error of the mean; VAS: visual analog questionnaire.

ratings of 'high' significantly compared to the large *d*-amphetamine dose ($P < 0.05$). Additional statistically significant VAS and DEQ effects are summarized in Table 2.

Residual effects

Relative to placebo and all other active drug conditions, under the 50-mg methamphetamine dose condition ratings of 'content' were significantly lower approximately 24 hours after drug administration (0 mg = 54.6 ± 8.6; 12 mg *d*-amphetamine = 51.6 ± 9.6; 12 mg MA = 52.6 ± 10.3; 50 mg *d*-amphetamine = 54.7 ± 10.8; and 50 mg MA = 40.7 ± 10.0, $P < 0.05$ for all comparisons). No other significant subjective effects were observed.

Psychomotor performance effects

Acute effects

Figure 4 shows that both amphetamines improved performance on the DAT. Compared to placebo, all active doses increased maximum tracking speed, while the

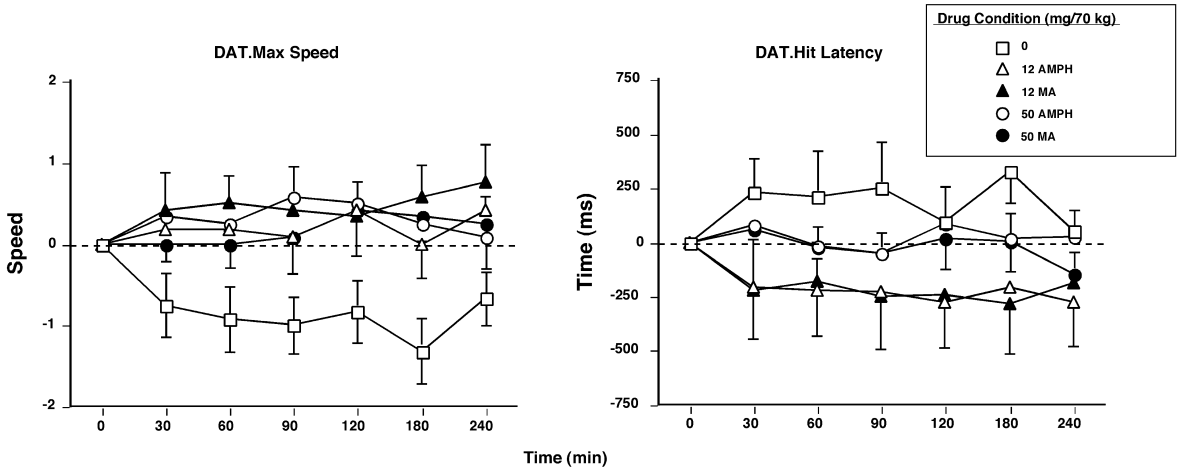

Figure 4 Divided attention task (DAT) task performance (change from baseline) as a function of drug dose and time ($n = 13$). Error bars represent 1 standard error of the mean. Overlapping error bars were omitted for clarity. MA: methamphetamine; AMPH: d-amphetamine

smaller methamphetamine and *d*-amphetamine doses decreased mean hit latency ($P < 0.05$ for all comparisons). No other significant drug effects on performance were noted.

Residual effects

No significant residual performance effects were observed.

DISCUSSION

The present findings show that when participants had the choice between the larger dose of drug and $5, methamphetamine and *d*-amphetamine (50 mg/70 kg) increased the number of selected drug options similarly. By contrast, when a higher magnitude monetary reinforcer ($20) was available, drug self-administration was diminished significantly. Consistent with these results, methamphetamine and *d*-amphetamine produced similar effects on the majority of subjective, physiological and behavioral measures. Both drugs enhanced ratings of euphoria and mood, increased cardiovascular activity and improved psychomotor performance. Methamphetamine did, however, engender greater effects on some measures (e.g. heart rate and ratings of 'high'). These data generally agree with previous studies that have compared low doses of oral methamphetamine and *d*-amphetamine [10–12]; they extend earlier findings by providing the first data directly comparing intranasal self-administration of the two stimulants.

As predicted, methamphetamine and *d*-amphetamine (50 mg/70 kg) similarly increased drug self-administration; regardless of amphetamine, participants chose approximately 47–50% drug. This is consistent with results from the pre-clinical literature indicating that rats and rhesus monkeys self-administer both amphetamines at equivalent rates [8,9]. Conversely, when $20 was the alternative reinforcer, both amphetamines were self-administered no more than placebo. Thus, amphetamine self-administration is malleable in the presence of higher and lower magnitude reinforcers and provides further evidence that monetary incentives may be particularly efficacious in substance abuse treatment programs that rely on alternative reinforcers to reduce problematic stimulant use (see ref. [25] for review). It is important to note, however, that it is unclear whether the current self-administration data would generalize to illicit methamphetamine use in the natural ecology. During the current study participants were given the opportunity to self-administer amphetamines in the morning and were then required to complete a 4-hour work period consisting of computerized tasks. This procedure is quite different from recreational amphetamine-taking outside the laboratory [13,26,27]. It is possible that we would have observed a different pattern of self-administration had the drugs been made available during the evening, in a social setting with fewer work requirements. Nevertheless, the current choice data do not support the view that methamphetamine is a more potent reinforcer in humans compared with *d*-amphetamine.

We hypothesized that the drugs would produce equipotent mood effects. For many subjective-effects measures, this prediction was borne out. The larger methamphetamine and *d*-amphetamine dose increased ratings of 'energetic' 'good drug effect' and 'social' and decreased ratings of 'sleepy' and 'tired' to the same extent. Conversely, high-dose methamphetamine effects were significantly greater for DEQ ratings of good effects and drug strength as well as VAS ratings of 'high',

'stimulated' and 'heart pounding'. Furthermore, at the smaller doses only methamphetamine increased several mood ratings including 'alert', 'energetic' and 'good drug effect'. These observations appear to be inconsistent with data from previous studies indicating that the drugs produced equipotent subjective effects [12]. One explanation for this discrepancy is that the previous studies administered low oral doses (e.g. 10 mg). In this study, the drugs were given via the intranasal route, which is associated with a relatively faster onset of effects [22,28]. It is possible that some amphetamine-related effects are subtle and can only be detected following drug administration via a route associated with a rapid onset of effects. An alternative explanation is that the previous studies employed participants with no methamphetamine experience. By contrast, participants in the present study were current illicit methamphetamine users who used the drug regularly. Considering that acute drug effects can be influenced by use experience and learned associations [29,30], it is possible that the more prominent subjective responses caused by methamphetamine were due partially to a learned response to potentially subtle methamphetamine-related interoceptive cues.

Concordant with the subjective effects findings, both amphetamines enhanced cardiovascular activity. The larger dose (50 mg) produced equivalent increases on blood pressure. Although both drugs increased heart rate, methamphetamine engendered greater sustained increases than *d*-amphetamine. Furthermore, approximately 24 hours after drug administration, heart rate remained elevated under both large amphetamine conditions and the 12-mg methamphetamine condition. In general, these results are consistent with previous findings from separate investigations of the acute cardiovascular effects of intranasal *d*-amphetamine [31] and the acute and residual effects of intranasal methamphetamine [22,32]. However, the current cardiovascular data should be interpreted within the context of a potential limitation: this study was conducted in an out-patient setting. Thus, several uncontrolled factors may have potentially influenced amphetamine-related residual cardiovascular effects. For instance, it is possible that participants may have consumed drugs outside of the laboratory that were undetected by standard urine toxicology. Future studies might investigate the relative residual effects of methamphetamine and *d*-amphetamine in an in-patient setting.

None the less, these data highlight the importance of distinguishing between pharmacological profile and dose potency when comparing drug effects. That is, even though the 50-mg methamphetamine dose produced greater increases on some subjective measures and heart rate than the identical *d*-amphetamine dose (dose potency), the totality of the data suggest that a slightly larger dose of *d*-amphetamine would have produced an identical profile of effects. Findings from a human drug discrimination study provide partial support for this view [11]. In that study, lower oral methamphetamine doses (10 and 20 mg) produced identical discriminative stimulus effects as the larger training *d*-amphetamine dose (30 mg) in two of four participants.

In conclusion, these results show that: (i) intranasal methamphetamine and *d*-amphetamine were self-administered by experienced methamphetamine users at similar rates; and (ii) amphetamine self-administration was malleable in the presence of an alternative monetary reinforcer. The effects of these amphetamines on mood, cardiovascular activity and psychomotor performance were nearly identical with a few exceptions (i.e. methamphetamine produced greater effects on some measures of mood and heart rate). Thus, the current data also provide additional evidence demonstrating the dissociation between drug self-administration and drug-related subjective effects. While the self-administration data lend support to the idea that the two amphetamines have an identical abuse potential, some subjective-effect ratings were more sensitive in differentiating between the drugs. This emphasizes the importance of also assessing subjective effects measures when determining the abuse potential of a drug. Finally, because the present data show that these amphetamines produced predominately similar effects, studies using *d*-amphetamine are germane to understanding the behavioral and pharmacological variables that contribute to the abuse of methamphetamine.

Declarations of interest

This research was funded by a grant awarded to Dr Hart from the National Institute on Drug Abuse. The authors declare that except for the income received from our primary employer no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest. There are no constraints on publishing these data.

Acknowledgements

The medical and nursing assistance of Drs Elias Dakwar, Soteri Polydorou and Audrey Perez RN and the technical assistance of Drew Thurmond, Michaela Bamdad, Maris Schwartz and Marc Scullin are gratefully acknowledged. This research was supported by grant number DA-19559 awarded to Dr Hart from the National Institute on Drug Abuse.

References

1. Bartholow M. Top 200 prescription drugs of 2009. *Pharm Times* website 2010. Available at: http://www.pharmacytimes.com/publications/issue/2010/May2010/RxFocusTopDrugs-0510 Accessed 28 November 2011. (Archived at http://www.webcitation.org/63XGy1uw9).
2. Substance Abuse and Mental Health Services Administration (SAMHSA), Office of Applied Studies. Treatment Episode Data Set (TEDS) highlights—2007 national admissions to substance abuse treatment services. OAS Series #S-45, HHS Publication no. (SMA) 09-4360. Rockville, MD: SAMHSA; 2009.
3. Gulaboski R., Cordeiro M. N., Milhazes N., Garrido J., Borges F., Jorge M. *et al*. Evaluation of the lipophilic properties of opioids, amphetamine-like drugs, and metabolites through electrochemical studies at the interface between two immiscible solutions. *Anal Biochem* 2007; **361**: 236–43.
4. Nichols D. E. Medicinal chemistry and structure–activity relationships. In: Cho A. K., Segal D. S., editors. *Amphetamine and its Analogs*. San Diego, CA: Academic Press; 1994, p. 3–41.
5. Melega W. P., Williams A. E., Schmitz D. A., DiStefano E. W., Cho A. K. Pharmacokinetic and pharmacodynamic analysis of the actions of d-amphetamine and d-methamphetamine on the dopamine terminal. *J Pharmacol Exp Ther* 1995; **274**: 90–6.
6. Hall D. A., Stanis J. J., Marquez Avila H., Gulley J. M. A comparison of amphetamine- and methamphetamine-induced locomotor activity in rats: evidence for qualitative differences in behavior. *Psychopharmacology* 2008; **195**: 469–78.
7. Kuhn D. M., Appel J. B., Greenberg I. An analysis of some discriminative properties of *d*-amphetamine. *Psychopharmacologia* 1974; **39**: 57–66.
8. Balster R. L., Schuster C. R. A comparison of d-amphetamine, l-amphetamine, and methamphetamine self-administration in rhesus monkeys. *Pharmacol Biochem Behav* 1973; **1**: 67–71.
9. Yokel R. A., Pickens R. Self-administration of optical isomers of amphetamine and methylamphetamine by rats. *J Pharmacol Exp Ther* 1973; **187**: 27–33.
10. Martin W. R., Sloan J. W., Sapira J. D., Jasinski D. R. Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clin Pharmacol Ther* 1971; **12**: 245–58.
11. Lamb R. J., Henningfield J. E. Human d-amphetamine drug discrimination: methamphetamine and hydromorphone. *J Exp Anal Behav* 1994; **61**: 169–80.
12. Sevak R. J., Stoops W. W., Hays L. R., Rush C. R. Discriminative stimulus and subject-rated effects of methamphetamine, d-amphetamine, methylphenidate, and triazolam in methamphetamine-trained humans. *J Pharmacol Exp Ther* 2009; **328**: 1007–18.
13. Simon S. L., Richardson K., Dacey J., Glynn S., Domier C. P., Rawson R. A. *et al*. A comparison of patterns of methamphetamine and cocaine use. *J Addict Dis* 2002; **21**: 35–44.
14. de Wit H., Dudish S., Ambre J. Subjective and behavioral effects of diazepam depend on its rate of onset. *Psychopharmacology* 1993; **112**: 324–30.
15. Hatsukami D. K., Fischman M. W. Crack cocaine and cocaine hydrochloride. Are the differences myth or reality? *JAMA* 1996; **276**: 1580–8.
16. Fischman M. W., Foltin R. W., Nestadt G., Pearlson G. D. Effects of desipramine maintenance on cocaine self-administration by humans. *J Pharmacol Exp Ther* 1990; **253**: 760–70.
17. Johanson C. E., Uhlenhuth E. H. Drug preference and mood in humans: d-amphetamine. *Psychopharmacology* 1980; **71**: 275–9.
18. Nader M. A., Woolverton W. L. Effects of increasing response requirement on choice between cocaine and food in rhesus monkeys. *Psychopharmacology* 1992; **108**: 295–300.
19. Campbell U. C., Carroll M. E. Reduction of drug self-administration by an alternative non-drug reinforcer in rhesus monkeys: magnitude and temporal effects. *Psychopharmacology* 2000; **147**: 418–25.
20. Hatsukami D. K., Pentel P. R., Glass J., Nelson R., Brauer L. H., Crosby R. *et al*. Methodological issues in the administration of multiple doses of smoked cocaine-base in humans. *Pharmacol Biochem Behav* 1994; **47**: 531–40.
21. Higgins S. T., Bickel W. K., Hughes J. R. Influence of an alternative reinforcer on human cocaine self-administration. *Life Sci* 1994; **55**: 179–87.
22. Hart C. L., Gunderson E. W., Perez A., Kirkpatrick M. G., Thurmond A., Comer S. D. *et al*. Acute physiological and behavioral effects of intranasal methamphetamine in humans. *Neuropsychopharmacology* 2008; **33**: 1847–55.
23. McLeod D. R., Griffiths R. R., Bigelow G. E., Yingling J. An automated version of the digit symbol substitution test (DSST). *Behav Res Methods* 1982; **14**: 463–6.
24. Miller T. P., Taylor J. L., Tinklenberg J. R. A comparison of assessment techniques measuring the effects of methylphenidate, secobarbital, diazepam and diphenhydramine in abstinent alcoholics. *Neuropsychobiology* 1988; **19**: 90–6.
25. Higgins S. T. The influence of alternative reinforcers on cocaine use and abuse: a brief review. *Pharmacol Biochem Behav* 1997; **57**: 419–27.
26. Halkitis P. N., Green K. A., Mourgues P. Longitudinal investigation of methamphetamine use among gay and bisexual men in New York City: findings from Project BUMPS. *J Urban Health* 2005; **82**: 18–25.
27. Kelly B. C., Parsons J. T., Wells B. E. Prevalence and predictors of club drug use among club-going young adults in New York City. *J Urban Health* 2006; **83**: 884–95.
28. Hart C. L., Ward A. S., Haney M., Foltin R. W., Fischman M. W. Methamphetamine self-administration by humans. *Psychopharmacology* 2001; **157**: 75–81.
29. Alessi S. M., Roll J. M., Reilly M. P., Johanson C. E. Establishment of a diazepam preference in human volunteers following a differential-conditioning history of placebo versus diazepam choice. *Exp Clin Psychopharmacol* 2002; **10**: 77–83.
30. Kirk J. M., de Wit H. Responses to oral delta9-tetrahydrocannabinol in frequent and infrequent marijuana users. *Pharmacol Biochem Behav* 1999; **63**: 137–42.
31. Lile J. A., Babalonis S., Emurian C., Martin C. A., Wermeling D., Kelly T. H. Comparison of the behavioral and cardiovascular effects of intranasal and oral d-amphetamine in healthy human subjects. *J Clin Pharmacol* 2011; **51**: 888–98.
32. Perez A. Y., Kirkpatrick M. G., Gunderson E. W., Marrone G., Silver R., Foltin R. W. *et al*. Residual effects of intranasal methamphetamine on sleep, mood, and performance. *Drug Alcohol Depend* 2008; **94**: 258–62.