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A comprehensive assessment of the safety of intravenous methamphetamine administration during treatment with selegiline

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Abstract

Selegiline (L-deprenyl) is a selective irreversible monoamine oxidase B inhibitor shown to be effective in the treatment of Parkinson's and Alzheimer's diseases. Recent evidence suggests that selegiline may also be useful in treating specific aspects of cocaine and nicotine dependence, generating interest in this compound for the treatment of methamphetamine addiction. To investigate this, we performed a randomized, single-blind, placebo-controlled study to evaluate the safety of selegiline treatment (as compared to placebo), concurrent with intravenous methamphetamine (15 or 30 mg). Secondary study objectives included determinations of plasma levels of selegiline and its metabolites, evaluating whether selegiline administration altered the pharmacokinetics of methamphetamine or its metabolites, and evaluating whether selegiline treatment alters the subjective responses to methamphetamine. Twenty-four methamphetamine-dependent participants were randomized to treatment, and 9 of these ($N=5$ selegiline, $N=4$ placebo) completed the entire protocol. The principal finding from this study was that intravenous administration of moderate doses of methamphetamine was safely tolerated during treatment with selegiline. No participants had electrocardiogram changes, and there were no meaningful differences in any laboratory values either between groups at screening or as a result of the study procedures. In general, adverse events were mild or moderate, and no subjects were discontinued due to adverse events or serious adverse events. Selegiline treatment did not enhance any of the cardiovascular changes (heart rate, blood pressure) produced by methamphetamine administration. Selegiline treatment slightly increased methamphetamine associated "bad effects" but did not alter any other subjective effects. The elimination half-life of methamphetamine was ~12 h, and selegiline did not alter clearance of methamphetamine. The available data suggest that selegiline is likely to be safe if used as a pharmacotherapy for methamphetamine dependence.

Keywords: Selegiline; Deprenyl; MAO-B; Methamphetamine; Treatment; Addiction

1. Introduction

A variety of neuropharmacological strategies are being pursued in the search for an effective treatment for methamphetamine abuse. One approach has been to target the dopaminergic neurotransmitter system involved in reward in an effort to interrupt the reinforcing action of methamphetamine and thus reduce its use and prevent relapse (Di Chiara and Imperato, 1988; Ling and Shoptaw, 1997; Mendelson and Mello, 1996). Methamphetamine is known to produce its major effects through dopaminergic mechanisms in the midbrain. Acute exposure to methamphetamine causes dopamine (DA) release and blocks the reuptake of DA; the consequent excess of DA stimulates the midbrain reward centers. Chronic exposure to methamphetamine results in neuroadaptations in presynaptic DA neurons, leading to reductions in available DA (Volkow et al., 2001; Wilson et al., 1996). Deficient striatal DA has been shown to result in exaggerated response to exogenous agonists, suggesting how DA depletion may accentuate drug effects (Kim et al., 2000). One therapeutic strategy is to

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develop and test DA antagonists, to determine if blocking excess DA associated with acute methamphetamine exposure (or associated cues) can reduce methamphetamine abuse. A second, and diametrically opposed therapeutic strategy, is to develop and test DA agonists, to see if agents that normalize (increase) DA release or activity can reduce methamphetamine abuse.

Selegiline, a candidate compound for methamphetamine addiction, is a selective monoamine oxidase (MAO)-B inhibitor. MAO enzymes (A and B forms) are responsible for metabolizing DA, serotonin (5-HT), and norepinepherine (NE). The relative selectivity of selegiline for inhibiting MAO-B rather than MAO-A is a great advantage, because MAO-A inhibition carries the risk of hypertensive crisis following the ingestion of dietary tyramine (found in red wine, cheeses, beer, and other foods). In humans, selegiline is relatively selective for MAO-B at doses up to 10mg. At higher doses, selegiline non-selectively inhibits MAO and has other effects as well. In preclinical models, these other effects include substitution for cocaine (Colpaert et al., 1980; Yasar et al., 1996), suppression of self-administration at higher doses (McCann et al., 1999) but not at lower doses (Winger et al., 1994). These effects may be due to potentiation of cocaine-induced increases in nucleus accumbens DA (Schiffer et al., 2003).

Prior work in humans has shown that MAO-B selective doses of transdermal (Houtsmuller et al., 2004) and orally (Newton et al., 1999) administered selegiline attenuated some subjective effects produced by cocaine. Selegiline also reduced glucose utilization in hippocampus and amygdala, suggestive of a relationship between cocaine-induced euphoria and limbic metabolism (Bartzokis et al., 1999). Based on these preclinical and clinical findings, the primary objective of this study was to determine the safety of a MAO-selective dose of selegiline concurrent with intravenous (IV) challenges with D-methamphetamine (15 and 30 mg), with a focus on safety and tolerability, including cardiovascular responses. Secondary study objectives included determinations of plasma levels of selegiline and its metabolites (desmethylselegiline, L-amphetamine, and L-methamphetamine), evaluating whether administration of selegiline altered the pharmacokinetics of D-methamphetamine or its metabolites, and evaluating whether selegiline treatment altered the subjective responses to methamphetamine.

2. Methods

2.1. Subjects

The study was approved by the UCLA Institutional Review Board and all participants gave informed consent. Twenty-four participants met inclusion criteria, were hospitalized, and completed randomization. Of these, 9 patients (5 selegiline and 4 placebo) completed the entire inpatient component of the study. Of the original 24 participants, 11 withdrew from the study on their own accord and in 4 cases participation was administratively terminated. Because the primary goal of this study was to evaluate the safety of methamphetamine administration during treatment with selegiline, data from all participants (including drop-outs) will be reported. In order to participate in the study, subjects were required to meet DSM-IV TR criteria for methamphetamine dependence, must have been non-treatment seeking at time of study, and must have been between 18 and 45 years of age. In addition, participants must have used methamphetamine by the smoked or IV route on average at least twice per week for at least 4 of the 6 weeks preceding entry, as assessed by self-report and a positive urine test within 2 weeks of entering the study.

2.2. Study design

The study utilized a randomized, single-blind, placebo-controlled design to evaluate the safety of IV methamphetamine administration during treatment with selegiline, as compared to placebo. The study assessed the subjective and physiological responses produced by methamphetamine administration, the pharmacokinetics of methamphetamine and its major metabolite, and blood levels of selegiline and its metabolites. Participants received repeated doses of IV methamphetamine (0, 15, 30 mg) in a single-blind fashion prior to and following randomization to study drug or placebo (Fig. 1). Participants randomized to receive selegiline ($N=5$) had FDG PET scans completed following treatment with saline and with 30 mg methamphetamine. PET data are not part of this report and this aspect of the study design is included here for completeness.

2.3. Drugs

Selegiline HCl (5 mg capsules for oral administration) and matched placebo were obtained from Somerset Pharmaceuticals and dispensed according to standard pharmacy and nursing procedures. Selegiline or placebo tablets were administered twice daily at 8 a.m. and 1 p.m. except on the last day of treatment (day 26) when selegiline was administered once only at 8 a.m.

Human use methamphetamine HCl (10 mg/ml in 1 ml ampules) was obtained from NIDA. Sterile IV methamphetamine preparation was performed according to UCLA pharmacy procedures. Aliquots of 0, 15 or 30 mg were drawn into a syringe for IV administration and methamphetamine was administered by IV infusion over 2 min by the study physician.

2.4. Experimental sessions

Methamphetamine administration sessions occurred at 9 am. Vital signs were monitored at frequent intervals during the first hour (every 2–5 min) following drug administration and less frequently thereafter (every 10–15 min). Preset stopping criteria were in place to address possible methamphetamine-related adverse events (AE's), though none occurred. To assess subjective effects, computerized visual analogue scales (VAS) were completed before drug administration, and 3, 6, 10, 15, 30, 45, and 60 min after each infusion. Thereafter, VAS scales were administered every 30 min for hours 1–4 and every 60

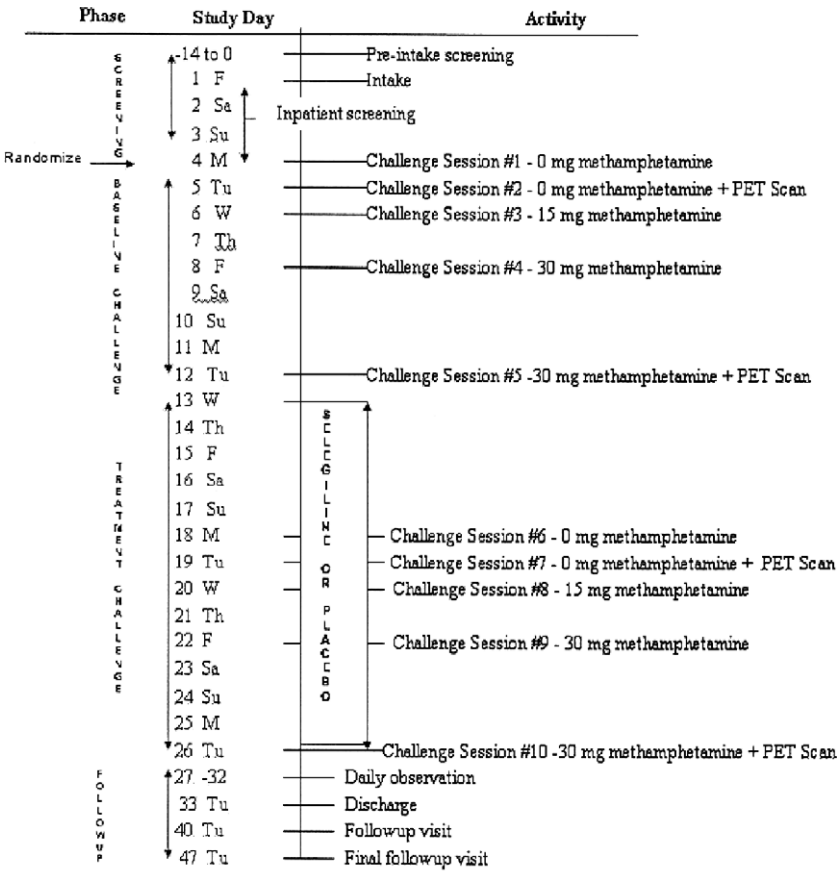

Fig. 1. Study scheme.

min for hours 4–8 after infusion. VAS data were collected for ratings of "any drug effect", "desire", "high", "good effect", "liking", "anxious", "bad effect", "depressed", "likely", and "stimulating". These 10 cm scales ranged from 0 (no effect) to 100 (greatest effect ever). Blood was drawn for methamphetamine and selegiline pharmacokinetic analysis prior to and at intervals following methamphetamine administration.

2.5. Daily measures

Qualitative urine drug toxicology was monitored once daily at 8 a.m. Beck Depression Inventory (BDI), Brief Psychiatric Rating Scale (BPRS), and Profile of Mood States (POMS) were collected every other day. Vital signs and AEs were monitored daily.

2.6. Pharmacokinetics

Plasma samples were analyzed for concentrations of selegiline, desmethylselegiline, L-methamphetamine, D-amphetamine, L-amphetamine, D-methamphetamine, L-methamphetamine, and phenethylamine (PEA) using liquid chromatographic/mass spectrometric/mass spectrometric methods at the University of California, San Francisco under the direction of Emil T. Lin, Ph.D.

All plasma concentrations were calculated from 0.025 ng/ml to 3.00 ng/ml selegiline, from 0.100 ng/ml to 12.0 ng/ml desmethylselegiline, from 0.500 ng/ml to 200 ng/ml D-, L-amphetamine and D-,L-methamphetamine, and from 0.100 ng/ml to 5.00 ng/ml PEA human plasma calibration curves. Clinical samples with concentrations above 3.00 ng/ml selegiline or above 200 ng/ml D-meth were repeated with appropriate dilution.

Pharmacokinetic parameters were determined by non-compartmental methods (Gibaldi and Perrier, 1982) using the WinNonlin Pro computer program, version 4 (Pharsight Corporation, Mountain View, CA). Areas were determined by a combination of the linear and logarithmic trapezoidal rules, where the linear trapezoidal rule was used for increasing values, and the log trapezoidal rule for decreasing values. Area to the last measurable data point [$(AUC_{(0\text{-}t)}]$f was determined directly. Area from the last measurable data point to infinity was determined by extrapolation, taking the last measurable plasma concentration and dividing by the terminal exponential rate constant (λz, see beyond). The terminal exponential rate constant (λz) was determined by linear regression analysis of data points occurring during the terminal linear phase of the semilogarithmic plasma concentration-time profile. The terminal exponential half-life ($T_{1/2}$) was calculated by dividing ln2 by λz. Clearance (CL) was calculated as dose divided by $AUC_{(0-\infty)}$. Terminal exponential volume of distribution (Vz) was calculated from the relationship $Vz = CL/\lambda z$. Steady-state volume of distribution was calculated as $[AUMC_{(0-\infty)}/AUC_{(0-\infty)}] - (0.0333)$, where $AUMC_{(0-\infty)}$ is the area under

the first moment plasma curve from zero to infinity, and the 0.0333 value is a correction factor, accounting for the 2 minute IV infusion (2 min = 0.0333 h). Mean residence time (MRT) was calculated as Vss/CL.

2.7. Statistical analysis

For analysis of the effects of methamphetamine administration on cardiovascular indices, the difference between the pre-infusion baseline observation and the maximum post-infusion observation was calculated for systolic blood pressure, diastolic blood pressure, and heart rate, for each subject and for each methamphetamine dose. 95% confidence intervals were calculated for the difference in average maximum change from pre-infusion baseline between placebo and selegiline arms for each methamphetamine dose during the treatment phase, as well as the average difference in maximum post-dose change from pre-infusion baseline between the pre-treatment and treatment phases of the experiment for each group and methamphetamine dosage. *t*-tests were calculated for each of these comparisons.

The main effects of methamphetamine dosage, study arm (i.e. placebo or selegiline), and treatment phase (i.e. before or after treatment with study drug) upon the mean post-methamphetamine maximum subjective effects ratings were tested using generalized estimating equations (GEE).

Differences between selegiline and placebo groups in C_{max}, $AUC_{(0-8)}$, $T_{1/2}$, and λz for baseline challenge and treatment challenge were assessed by using an ANOVA model with treatment factor in the model. The group comparisons during treatment challenge were also performed by using an ANCOVA model, with treatment as the main factor and the baseline value as the covariate.

3. Results

3.1. Patient characteristics

The data did not reveal differences between selegiline or placebo treatment groups along any demographic variable (Table 1). All participants met criteria for methamphetamine dependence. Cannabis dependence and alcohol dependence were each reported by one subject in the selegiline group. One subject in the placebo group reported alcohol abuse. There was no pattern of other drug abuse across or within the treatment groups and no major psychiatric disorders were identified.

For all subjects, medical history, physical examination, and standard laboratory studies (ECG, electrolytes, CBC, renal and hepatic testing) were normal. No participants had a previous adverse reaction to methamphetamine and none were taking prescription or over the counter medications. Female volunteers had a negative urine pregnancy test.

Table 1
Participant demographics

	Selegiline	Placebo	Randomized
Gender *N* (%)			
Male	12 (100)	11 (92)	23 (96)
Female	0 (0)	1 (8)	1 (4)
Single major race *N* (%)			
White, not Hispanic	8 (67)	7 (58)	15 (63)
Hispanic or Latino	2 (17)	2 (17)	4 (17)
African American or Black	1 (8)	1 (8)	2 (8)
Asian Pacific Islander	0 (0)	1 (8)	1 (4)
Other	1 (8)	1 (8)	2 (8)
Age (years)			
Mean	32.3	27.1	29.7

3.2. Cardiovascular measures

The maximal effects for each dose of methamphetamine (0, 15 and 30 mg) are shown for each study arm (selegiline versus placebo) and each treatment phase (pre-treatment versus treatment). Data for heart rate (Fig. 2A, B), diastolic (Fig. 2C, D) and systolic (Fig. 2E, F) blood pressure are shown. Selegiline treatment did not significantly alter the cardiovascular effects produced by methamphetamine. There was a trend ($p = 0.06$) for maximum heart rate to be greater during treatment with placebo as compared to selegiline (Table 2).

3.3. Subjective measures

3.3.1. Effects of methamphetamine treatment

On average, post-infusion maximum "any drug" score was significantly higher following administration of 15 mg and 30 mg methamphetamine as compared to placebo ($p < 0.0005$). For "stimulating", the mean maximum score following administration of 15 mg and 30 mg methamphetamine was higher compared to placebo ($p < 0.0005$). Mean maximum scores for "any drug", "desire", "high", "good effect", "liking", "likely to use" and "stimulating" were also significantly higher for 15 mg and 30 mg methamphetamine infusions compared to 0 mg ($p < 0.040$). For "likely to use", the average score was higher for the 15 mg dosage of methamphetamine as compared to placebo ($p < 0.036$), and average score was higher for 30 mg dosage of methamphetamine as compared to placebo ($p < 0.008$). For "anxious", mean maximum scores for methamphetamine at 30 mg, but not 15 mg, were significantly higher than placebo ($p < 0.030$). For "bad effect", mean maximum was significantly higher for the 30 mg dosage of methamphetamine than for placebo ($p < 0.007$).

3.3.2. Effects of selegiline treatment

For "bad effect" only, a study arm by treatment phase interaction emerged, demonstrating that post-methamphetamine ratings were higher during selegiline treatment compared to placebo treatment ($p < 0.018$).

3.4. Measures of mood

Baseline scores on the BDI were low in both placebo (5.02 ± 7.8) and selegiline (5.50 ± 7.1) groups ($p > 0.05$). Inspection of daily BDI scores revealed that scores tended to

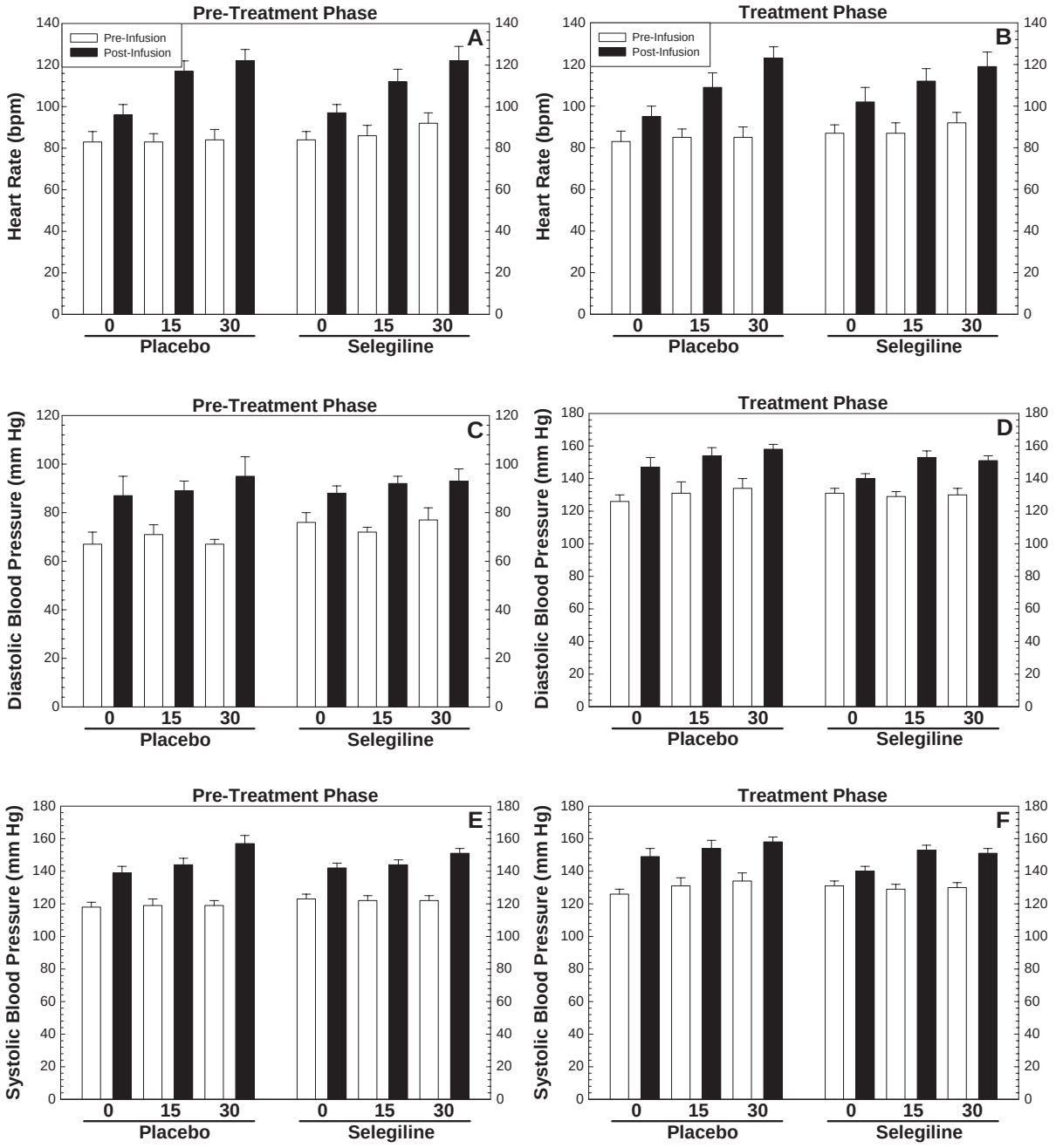

Fig. 2. Effects of methamphetamine administration on mean (±S.D.), maximal heart rate (A,B), diastolic blood pressure (C,D), and systolic blood pressure (E,F) prior to and during treatment with placebo or selegiline.

remain low and comparable between the groups. BPRS total average score summarized over time was similar for the placebo (29.8±4.7) and selegiline (30.1±4.8) groups ($p>0.05$). For the POMS, scores for "arousal", "tension–anxiety", "depression/dejection", "anger/hostility", "vigor", "fatigue", "confusion/bewilderment", and "friendly" were also similar between placebo and selegiline groups ($p>0.05$; data not shown).

3.5. Pharmacokinetic analysis

Pharmacokinetic data collected following administration of 30 mg methamphetamine are shown in Table 3. A similar analysis was performed for D-amphetamine (data not shown). For both analytes, D-meth and D-amp, no significant differences between selegiline and placebo groups were observed before the treatment with respect to C_{max}, $AUC_{(0-8)}$, $T_{1/2}$, and λz. After the treatment, there were still no detectable differences in C_{max}, $AUC_{(0-8)}$, $T_{1/2}$, and λz between the two treatment groups. This analysis was repeated using baseline values as covariates without changing the result.

Peak and trough levels of selegiline and its metabolites are shown in Table 4. Plasma concentrations of selegiline's primary active metabolite, desmethylselegiline, were greater that that of the parent compound. Moderate levels of

Table 2
95% Confidence limits on mean maximum change from pre-infusion baseline during treatment phase: placebo-selegiline

MA dose (mg)	CV Measure	Lower CL	Mean	Upper CL	*p*-value
0	Heart Rate	−12.2	0.3	11.6	0.96
	Diastolic BP	−16.1	−3.3	9.5	0.58
	Systolic BP	−8.7	8.4	25.4	0.43
15	Heart Rate	−8.9	2.5	13.9	0.64
	Diastolic BP	−2.5	8	18.5	0.12
	Systolic BP	−12.1	−1.4	9.3	0.78
30	Heart Rate	−0.6	8.8	18.2	0.06
	Diastolic BP	−8.1	1.2	10.5	0.78
	Systolic BP	−9.7	2.4	14.5	0.67

L-methamphetamine were observed. Inhibition of MAO-B by selegiline was associated with the appearance of low, but measurable levels of PEA.

4. Discussion

The principal finding from this study was that intravenous administration of moderate doses of methamphetamine was safely tolerated during treatment with selegiline. Of importance, selegiline did not enhance any of the cardiovascular effects produced by methamphetamine, and there was a non-significant trend for selegiline treatment to dampen the methamphetamine-associated increases in heart rate.

There was substantial drop out of subjects over the first several weeks of the protocol. Importantly, all study withdrawals occurred prior to the first session involving methamphetamine administration during selegiline treatment, so the attrition rate does not reflect any adverse interactions between methamphetamine and selegiline. Nevertheless, the rate of attrition was higher than we observed previously in studies involving cocaine users (Newton et al., 1999). It is likely that symptoms referable to methamphetamine abstinence contributed to attrition (McGregor et al., 2005; Newton et al., 2004). Symptoms associated with abstinence from methamphetamine include irritability, depression, and fatigue. These resolve fairly rapidly in most participants. We have since developed improved procedures for dealing with this population and attrition rates have diminished (Newton et al., 2005b, in press).

As expected, methamphetamine administration was associated with increased ratings on most subjective effects, including positive (e.g., "high" and "liking") and negative effects (e.g., "anxious" and "bad effects"). Methamphetamine also produced increased self-reported desire to use methamphetamine, which may be reflective of the priming effects produced by this stimulant. Of interest, ratings of "high," and "stimulating," as well as "bad effects" and "depressed" decreased over time during the inpatient stay in the hospital (data not shown). Selegiline treatment did not alter most effects produced by methamphetamine, but was associated with greater ratings on methamphetamine-induced "bad effects", as compared to placebo treatment.

The elimination half-life of methamphetamine was about 12 h in this methamphetamine-dependent population, which is similar to values reported previously for non-dependent methamphetamine abusing groups (Cook et al., 1993; Mendelson et al., 1995). As expected, selegiline did not alter clearance of methamphetamine.

At odds with previously reported findings for cocaine, selegiline had minimal impact on the subjective effects produced by methamphetamine (Houtsmuller et al., 2004; Newton et al., 1999). One interpretation of these results is that L-methamphetamine, a metabolite of selegiline, produces tolerance to the effects of subsequently administered cocaine, whereas chronic methamphetamine exposure itself produces tolerance, limiting the impact of selegiline treatment. However, we recently compared the effects of experimentally administered cocaine and methamphetamine, and found that the drugs

Table 3
Pharmacokinetic parameters collected following administration of 30 mg D-methamphetamine during the active phase of the study are shown

	C_{max} (ng/ml)	T_{max} (h)	AUC (0–t) (ng h/ml)	AUC (0–∞) (ng h/ml)	%Ext AUC (0–∞)	λz (1/h)	T–1/2 (h)	MRT (l)	CL (ml/h)	Vz (l)	Vss (l)
Treatment group: selegiline											
N	8	8	8	8	8	8	8	8	8	8	8
Mean	95.1	0.6188	742	894	17.49	0.0680	10.8	15.0	36,972	543	523
Median	83.4	0.1252	693	816	7.30	0.0722	9.6	13.7	36,781	516	488
Geo Mean	90.7	0.2244	673	849	8.41	0.0662	10.5	14.6	35,334	533	516
SD	33.6	0.8649	347	324	22.12	0.0154	2.9	3.9	11,225	114	95
%CV	35.3	139.8	46.8	36.3	126.5	22.6	27.1	26.1	30.4	21.0	18.2
Minimum	63.8	0.0333	332	570	2.17	0.0444	7.9	11.3	19,621	430	426
Maximum	164.0	2.0000	1353	1529	56.10	0.0874	15.6	22.1	52,598	757	705
Treatment group: placebo											
N	5	5	5	5	5	5	5	5	5	5	5
Mean	108.4	0.2867	965	997	2.88	0.0779	9.1	13.4	31,058	399	407
Median	96.6	0.0833	938	949	2.63	0.0778	8.9	13.2	31,619	415	409
Geo Mean	101.2	0.1068	953	981	2.36	0.0769	9.0	13.3	30,571	398	406
SD	48.9	0.4146	171	193	1.88	0.0143	1.7	2.1	6237	31	25
%CV	45.1	144.6	17.7	19.4	65.2	18.3	18.5	15.9	20.1	7.8	6.2
Minimum	65.7	0.0167	740	748	1.08	0.0615	7.3	10.2	24,859	358	367
Maximum	192.0	1.0000	1156	1207	5.32	0.0954	11.3	15.8	40,104	427	435

Table 4
Peak and trough analysis of selegiline, its metabolites, and phenylethylamine

Timepoint (h)		Selegiline (ng/ml)	Desmethylselegiline (ng/ml)	L-Methamphetamine (ng/ml)	L-amphetamine (ng/ml)	Phenylethylamine (ng/ml)
Prior	Day 18 (0 mg)	0.13±0.04	0.55±0.19	6.04±2.51	2.33±0.74	
	Day 20 (15 mg)	0.11±0.07	0.66±0.27	6.55±2.36	2.62±0.71	
	Day 22 (30 mg)	0.13±0.08	0.57±0.28	5.98±1.84	2.41±0.61	
0.92 h	Day 18 (0 mg)	0.95±0.62	3.56±2.11	6.93±3.12	2.48±0.82	0.16±0.04
	Day 20 (15 mg)	1.62±1.78	2.46±1.80	6.55±1.76	2.56±0.72	
	Day 22 (30 mg)	0.83±0.58	2.77±1.58	5.88±2.67	2.36±0.89	0.15±0.05
3 h	Day 18 (0 mg)	0.51±0.29	3.19±0.82	9.17±2.94	2.92±0.81	0.26±0.13
	Day 20 (15 mg)	0.76±0.40	3.11±0.58	8.98±2.65	2.82±0.69	
	Day 22 (30 mg)	0.59±0.35	3.29±1.02	10.04±3.40	2.99±1.02	0.26±0.14

Timepoints reflect post-selegiline dosing.

produce similar peak effects in chronic users (Newton et al., 2005a). This suggests that differential tolerance does not explain the observed differences in the effects of selegiline on effects produced by cocaine and methamphetamine. Another possible explanation is that methamphetamine produces MAO inhibition, obviating effects of treatment with MAO inhibitors, whereas cocaine is not thought to affect MAO (Egashira et al., 1987). Finally, although no trends were evident, statistical power was limited, and this could contribute to null findings.

Limitations of the study include a small sample size and relatively high dropout rate. The sample size is typical of many inpatient studies, but a larger sample would have facilitated more extensive analysis. Although the preponderance of male participants was not planned (only one female participated), this constitutes a further limitation of the study.

Preclinical research supports further assessment of selegiline for the treatment of stimulant dependence (Colpaert et al., 1980), though higher doses (on the order of 4 mg/kg) of selegiline were required to alter self-administration. Data from this study show that administering methamphetamine during treatment with low doses of selegiline is safe, and assessment of effects produced by treatment with higher doses of selegiline may be indicated. Further study of the effects of selegiline treatment (at a range of doses) on methamphetamine self-administration in the laboratory would complement these safety data and may provide additional support for determining the effects of selegiline treatment on methamphetamine use in a clinical trial.

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