Original Article

Influence of CYP2D6 activity on the pharmacokinetics and pharmacodynamics of a single 20 mg dose of ibogaine in healthy volunteers[†]

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Abstract:

Conversion of ibogaine to its active metabolite noribogaine appears to be mediated primarily by CYP2D6. We compared 168 h pharmacokinetic profiles of both analytes after a single oral 20 mg dose of ibogaine in 21 healthy subjects who had been pretreated for 6 days with placebo or the CYP2D6 inhibitor paroxetine. In placebo-pretreated subjects, ibogaine was rapidly converted to noribogaine. Median peak noribogaine concentrations occurred at 4 h. Compared with placebo-pretreated subjects, paroxetine-pretreated subjects had rapid (Tmax = 1.5 h) and substantial absorption of ibogaine, with detectable levels out to 72 h, and an elimination half-life of 10.2 h. In this group, ibogaine was also rapidly converted to noribogaine with a median Tmax of 3 h. Extent of noribogaine exposure was similar in both groups. CYP2D6 phenotype was robustly correlated with ibogaine AUC0-t (r = 0.82) and Cmax (r = 0.77). Active moiety (ibogaine plus noribogaine) exposure was ~2-fold higher in paroxetine-pretreated subjects. Single 20 mg ibogaine doses were safe and well tolerated in all subjects. The doubling of exposure to active moiety in subjects with reduced CYP2D6 activity suggests it may be prudent to genotype patients awaiting ibogaine treatment, and to at least halve the intended dose of ibogaine in CYP2D6 poor metabolizers.

Introduction: Ibogaine is a naturally occurring psychoactive chemical from the roots of the *Tabernanthe iboga* plant. It has been used for centuries in low doses to help combat hunger, thirst and fatigue, and in high doses to cause dream-like hallucinations for spiritual rituals[1,2]. Low-dose ibogaine (7 mg 3-4 times/day) was marketed as a pharmaceutical in France from ~1939 until ~1970[1]. Considerably higher doses of ibogaine have been used since the 1960's as a self-help treatment for opioid dependence, following the serendipitous discovery by a group of lay drug experimenters that single high doses of ibogaine prevented withdrawal symptoms in heroin-dependent subjects, and could facilitate abstinence in previously opioid-dependent subjects via reduced drug craving[3,4]. At present, provision of ibogaine to facilitate opioid withdrawal is mainly provided through non-medical groups[1].

Mash and colleagues at the University of Miami reported that ibogaine was metabolized by cytochrome P450 (CYP) 2D6, and identified its demethylated long-acting active metabolite noribogaine[5], which due to its long half-life might contribute to the drug's anti-withdrawal and anti-craving effects[5,6]. This group also characterized both molecules as having mu-opioid agonist effects[7], although this has been questioned recently[8]. In contrast to the extensive literature on ibogaine's use to assist with withdrawal in opioid dependent patients[1], published human pharmacokinetic data include mean pharmacokinetic parameters in 24 CYP2D6 extensive metabolizers (EMs) and 3 CYP2D6 poor metabolizers (PMs), and individual patients' 24-hour whole blood concentration-time profiles[4]. This showed higher noribogaine and lower ibogaine concentrations in CYP2D6 EMs and a reversed pattern in PMs. Published data on the safety and pharmacodynamics of ibogaine have almost exclusively focussed on opioid withdrawal symptoms[9-11], with no detailed vital sign or other physiological parameters reported.

The purpose of this study was to evaluate the influence of CYP2D6 activity on the pharmacokinetics of a single low (20 mg) dose of ibogaine in healthy volunteers, some of whom had intrinsic CYP2D6 activity reduced by prior administration of the CYP2D6 inhibitor paroxetine, a selective serotonin reuptake inhibitor (SSRI) antidepressant. We also evaluated the safety, tolerability and mu-opioid-related pharmacodynamic responses to ibogaine. The ibogaine dose was based on two considerations; subject safety, and being able to achieve

detectable concentrations in blood. The 20 mg dose was based on prior safe use of Lambarene in France from 1940-1970, where dosing ranged between 21-28 mg/day[1]. The use of higher doses (e.g. ~500-800 mg or higher, which might be used for treatment of opioid withdrawal or craving) was not considered acceptable, because of the population being tested (healthy volunteers), likely hallucinatory effects, and unknown ECG safety profile. An earlier noribogaine pharmacokinetic study[12] indicated acceptable assay sensitivity around this dose range.

Methods: The protocol for this study was approved by the Southern Health and Disability Ethics Committee (NTY/12/040), and the study was registered with the Australian New Zealand Clinical Trial Registry (ACTRN12613000324718). Subjects were healthy male or sterilized female volunteers, aged between 20-40 years, and drug- and medication-free. All subjects provided signed informed consent prior to enrolment, and were assessed as suitable to participate based on review of medical history, physical examination, safety laboratory tests, vital signs and ECG.

The study design is shown in Figure 1. On day 1, subjects were given a single oral 30 mg dose of dextromethorphan, and urine was collected for the next five hours, for CYP2D6 phenotyping. No genotyping was performed. Subjects were randomized to receive double blind capsules containing paroxetine or placebo between days 2-15 (10 mg on days 2-3 and 20 mg/day on days 4-15, according to a computer-generated random code). On day 7 subjects were given a single 30 mg dose of dextromethorphan, and urine was collected for the next five hours, for repeated CYP2D6 phenotyping. On day 8, a single 20 mg dose of ibogaine was administered to all subjects, and 8 mL blood samples collected pre-dose and at 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144 and 168 h post-dose. All study medications were administered with 240 ml of water after an overnight fast. On days 1, 7 and 8, subjects did not receive any food until at least 4 hours post-dose. Blood samples were collected into light-protected heparinized containers, centrifuged, and plasma was stored at -70^{o}C until analysed. The volumes of the day 1 and 7 five-hour urine collections were recorded and aliquots were frozen at -20^{o}C until analysed.

Because of ibogaine and noribogaine's expected mu-opioid agonist pharmacology, pupillary miosis (a pharmacodynamic assessment sensitive to mu-opioid agonist effects) was assessed by pupillometry. Dark-adapted pupil diameter was measured in triplicate using a Neuroptics PLR-200 pupillometer under standardized light intensity (<5 lux) pre-dose and at 1, 2, 3, 4, 6, 12, 24 and 168 h. Self-ratings of feeling sleepy, energetic, nausea, anxious and calm were obtained pre-dose and at 2, 4, 12, 24, and then daily until 168 h, using 100 mm visual analog scales (VAS), where 0 mm represented "not at all…" and 100 mm "the most … ever". Safety evaluations included clinical monitoring, recording of adverse events (AEs) and vital signs.

Determination of ibogaine and noribogaine in human plasma by LC-MS/MS:
300 μL of plasma was pipetted into a 96 well plate along with 50 μL of 1 M NaOH and 50 μl of 32 ng/mL of the internal standard noribogaine-d4, into each well. Samples were extracted with 600 μL of tert-butyl methyl ether, and 480 μL of the supernatant of the extracted solvent was dried under a stream of nitrogen. Samples were reconstituted with 150 μL of acetonitrile: British Pharmacopoeia (B.P.) water (5:95, v/v) and 10 μL was injected into the LC-MS/MS system. Within- and between-day assay precision was <9% for ibogaine and <13% for noribogaine, and within- and between-day assay accuracy was <9% for ibogaine and <11% for noribogaine. Assay performance was not affected by paroxetine.

Determination of dextromethorphan (DM) and dextrorphan (DX) in human urine by LC-MS/MS: 100 μL of urine was pipetted into each well along with 100 μL of 2000 unit/mL beta-glucuronidase solution. The 96 well plate was placed in a 37°C water bat h for 18 hours. 100 μL of 0.1 M sodium acetate buffer (pH 5.0) was added to the samples, along with 50 μL of the internal standard (1.6 μg/mL levallorphan) and 40 μL of 1 M NaOH into each well. The samples were extracted with 600 μL hexane:ethyl acetate (60:40, v/v) and 480 μL of supernatant of the extracted solvent was dried under a stream of nitrogen. Samples were reconstituted with 600 μL of acetonitrile:B.P. water (5:95, v/v) containing 10 mM ammonium acetate (pH to 4.75 with formic acid) and 10 μL was injected into the LC-MS/MS system. Within- and between-day assay precision was <10% for DM and <11% for DX, and within- and between-day assay accuracy was < 8% for DM and <10% for DX. The detection limit for

dextromethorphan was 5 ng/ml and 50 ng/ml for dextrorphan. Assay performance was not affected by paroxetine.

Plasma ibogaine and noribogaine concentrations above the limit of quantification (LOQ) were used to calculate pharmacokinetic parameters using model-independent methods (non-compartmental analysis). The maximum plasma concentration (Cmax) and time to maximum plasma concentration (Tmax) were the observed values. The terminal elimination rate constant (Kel) was calculated from the slope of the log-transformed plasma concentration versus time data in the post-distribution phase. The half-life ($t_{1/2}$) was determined using the formula $t_{1/2} = 0.693/Kel$. The area under the concentration-time curve (AUC0-t) from time zero to the last determined concentration-time point in the post distribution phase was calculated using the trapezoidal rule. Active moiety concentrations and pharmacokinetic parameters were calculated as the sum of molar noribogaine and ibogaine values. The DM to DX metabolic ratio (MR) was calculated as the molar ratio of the concentrations of each analyte in the day 1 and day 7 urine collections. If the MR was above 0.3[13], the subject was classified as a PM.

Summary statistics (means, standard deviations, and coefficients of variation) were determined for subjects randomized to placebo and paroxetine groups for pharmacokinetic and pupillometry parameters. Categorical variables were analysed using counts and percentages. Relationships between variables were assessed using regression methods.

Results: Twenty-one healthy male volunteers were enrolled in and completed the study. Mean age was 23.5 years (range 20-40), and mean BMI was 24.5 kg/m^2 (range 19.8-30.9). Sixteen subjects were Caucasian, two were Maori, two were Asian, and one was other.

Pharmacokinetics (i): urinary dextromethorphan:dextrorphan metabolic ratios (MRs): Subject 1 was phenotypically a poor metabolizer on day 1 (MR = 0.51; all other subjects had MRs <0.3[13]), therefore his ibogaine and noribogaine data were excluded from this analysis. Individual MRs on days 1 and 7 for the placebo- and paroxetine-pretreated groups are shown in Figure 2. Mean (SD) MR on day 1 were similar between groups (paroxetine: 0.015 (0.011); placebo: 0.019 (0.023); p = 0.64). By day 7, mean (SD) MR in the paroxetine group had

increased 11-fold to 0.160 (0.200), whereas that of the placebo group was unchanged (0.018 (0.023); $p<0.05$).

Pharmacokinetics (ii): plasma ibogaine and noribogaine (excluding subject 1): Mean plasma concentration-time plots of ibogaine and noribogaine are shown in Figure 3, and mean pharmacokinetic parameters are shown in Table 1. In subjects pre-treated with placebo, ibogaine concentrations were barely detectable, whereas there were substantial noribogaine exposures. In subjects pre-treated with paroxetine, there were substantial ibogaine and noribogaine exposures. Mean ibogaine peak concentration in paroxetine-pretreated subjects was 26-fold greater than that of placebo-pretreated subjects, mean AUC0-t was 66-fold greater, and mean half-life was longer (10.2 h vs 2.5 h; Table 1; $p<0.05$ for all). Although mean noribogaine AUC0-t values were similar in both groups, mean Cmax was lower (12.7 vs 18.7 ng/mL; $p = 0.05$) and t1/2 longer (20.1 vs 13.0 h; $p = 0.07$) in paroxetine-pretreated compared with placebo-pretreated subjects (Table 1). Mean active moiety AUC0-t was almost 2-fold greater in paroxetine-pretreated subjects compared with placebo-pretreated subjects ($p = 0.005$; Table 1).

Correlation of log day 7 urinary dextromethorphan:dextrorphan MRs with ibogaine AUC0-t and Cmax data from both groups (Figure 4) showed robust relationships, with Pearson r values of 0.82 and 0.77 respectively. Weaker relationships were noted between log day 7 urinary dextromethorphan:dextrorphan MRs and noribogaine AUC0-t and Cmax (Pearson r values of 0.14 and 0.47 respectively; data not shown).

Pharmacodynamics: Mean change in pupil diameter over 12 hours post-ibogaine dosing on day 8 is shown in Figure 5. Both paroxetine- and placebo-pretreated subjects had mean maximal decreases of 0.4-0.6 mm in pupil diameter at 4 hours post-dosing, and a return towards baseline diameter by 12 hours. Repeated measures ANOVA showed a significant effect of time ($F = 8.4$, $p<0.001$), no effect of treatment ($F = 1.1$, $p = 0.32$), and a significant treatment x time interaction ($F = 2.9$, $p = 0.01$). There were no correlations between ibogaine, noribogaine or active moiety exposures and changes in pupil diameter. Mean VAS scores for self-ratings of sleepy, calm, energetic, nausea and anxious for the 24 hours after ibogaine dosing are shown in Figure 6. There were trends for sleepy ratings to decrease over time, and

energetic self-ratings to increase, however there were no differences noted between subjects pretreated with placebo or paroxetine.

Safety: There were no changes of note in vital signs associated with ibogaine dosing. A total of 25 adverse events were reported by 16 participants; 18 of these were prior to dosing with ibogaine on day 8, and 7 of these after dosing with ibogaine. Seventeen (68%) adverse events were reported by subjects randomized to paroxetine pretreatment and 8 reported by subjects randomized to placebo pretreatment. The most common adverse events were nausea (5 reports, all paroxetine), gastrointestinal symptoms (3 reports, 2 paroxetine), and dizziness (3 reports, 2 paroxetine). Most adverse events were of mild severity, and all resolved without intervention prior to study completion. Of the 7 adverse events that occurred on or after day 8, there was one report of dizziness (day 8) in placebo-pretreated subjects, and 2 of dizziness (day 8), 2 of nausea (day 8), and single reports of cold symptoms (day 12) and conjunctivitis (day 14) in paroxetine-pretreated subjects. All three reports of dizziness were associated with cannulation, and occurred prior to ibogaine dosing. No subjects reported hallucinations or any perceptual changes.

Discussion: Although ibogaine has been extensively evaluated in medical and lay settings over the last 50 years, this appears to be the first comprehensive evaluation of its single low dose pharmacokinetics in humans, along with exploration of its pharmacodynamics and safety. This study has confirmed the important role of CYP2D6 in the metabolism of ibogaine to noribogaine, and showed that single 20 mg doses of ibogaine were safe and well tolerated in healthy male volunteers.

To alter CYP2D6 activity in half of our study population, we administered the antidepressant paroxetine. The M2 metabolite of paroxetine is a potent CYP2D6 inhibitor[14]. Subjects randomized to paroxetine had an 11-fold increase in DM:DX MR by day 7, whereas those receiving placebo had no change. This magnitude of increase falls within the range of those reported previously in healthy volunteers given paroxetine 20 mg/day (8.6[15] – 39[16] fold).

In placebo-pretreated subjects, ibogaine was rapidly converted to noribogaine, with undetectable ibogaine levels in all subjects by 4 hours post dose. Median peak noribogaine

concentrations occurred by 4 h. Compared with placebo-pretreated subjects, subjects who had reduced CYP2D6 activity from paroxetine pretreatment had rapid (median Tmax = 1.5 h) and substantial absorption of ibogaine, with detectable levels out to 72 h, and an elimination half-life of 10.2 h. In this group, ibogaine was also rapidly converted to noribogaine, with a median Tmax of 3 h. The extent of noribogaine exposure was similar in both groups. Both CYP2C19 and CYP3A4 appear to be involved in demethylation of ibogaine[5], however these enzymes appear to be less efficient than CYP2D6, given the much longer time ibogaine was present in paroxetine-treated subjects. Further confirmation of the importance of CYP2D6 in the metabolism of ibogaine to noribogaine is shown in the very robust correlations of ibogaine AUC0-t and Cmax with the day 7 CYP2D6 phenotyping measure, the DM:DX metabolic ratio (Figure 4). Because noribogaine clearance is primarily by phase 2 reactions (glucuronidation)[12], the lack of correlation correction between CYP2D6 phenotyping measures and noribogaine PK parameters is therefore not unexpected.

These pharmacokinetic results differ from those reported by Mash[4]. In comparing genotyped CYP2D6 PMs with EMs, she reported equivalent ibogaine Cmax, lower noribogaine Cmax, and equivalent active moiety AUC0-24 h values. Direct comparison of her data with ours is complicated by the different matrices assayed (whole blood vs plasma), different assay methods, and different doses (20 mg vs 10 mg/kg). Mash[4] tested genotyped CYP2D6 PMs, whereas in this study we used paroxetine as a CYP2D6 inhibitor in phenotyped EMs. It is clear that paroxetine reduced CYP2D6 activity (Figure 2), however only 2/11 subjects became phenotypically PMs (i.e. MRs of >0.3[13]), so in the present study there might still be a small contribution of CYP2D6 to ibogaine demethylation in some paroxetine-treated subjects. Subject 1, a phenotypic PM on day 1, had almost 7 fold-higher Cmax for ibogaine compared with noribogaine (47.5 vs 6.9 ng/mL) and a 2.6 fold higher AUC0-t (580.3 vs 220.8 ng.h/mL); the ibogaine/noribogaine Cmax and AUC ratios for paroxetine-treated subjects were smaller, at 2.3 and 0.8 respectively (Table 1).

Because ibogaine and noribogaine appear to have common pharmacological activities[2,4], we calculated extent of active moiety exposure and compared this between groups. In paroxetine-pretreated subjects active moiety AUC0-t was almost double that of placebo-pretreated subjects (Table 1). The greater exposure to active moiety in CYP2D6 PMs might

explain individual differences in tolerability or response to ibogaine[10,11], and might suggest that CYP2D6 genotyping or phenotyping be advised prior to use of ibogaine.

Both ibogaine and noribogaine interact most potently with the serotonin transporter, with lower affinities for mu- and kappa- opioid receptors and NMDA glutamatergic receptors[2,4]. Lambarene, a marketed tablet containing root extract which contained ~8 mg of ibogaine, was reported to be "a neuromuscular stimulant"[17]. In the absence of published data on the tolerability of single low-doses of ibogaine, we anticipated possible side effects might include nausea, anxiety and/or increased alertness, and assessed these side effects using VAS. The VAS data were included to provide the first evaluation of the subjective behavioural effects of single dose ibogaine, which has not been reported in a controlled clinical setting. There appeared to be modest trends for self-ratings of sleepy to decrease, and for self-ratings of energetic to increase. Whether these changes represent a drug effect, or simply a time-of-day effect is unclear, and cannot be determined further as a placebo-ibogaine arm was not included in the study.

Ibogaine and noribogaine have low micromolar affinity for mu-opioid receptors[2]. Originally these interactions were reported to be agonist activity[7] however this has been recently questioned[8]. We found a maximum 0.4-0.6 mm reduction in pupil diameter at 4 hours, with no correlations between blood levels and change in pupil diameter. In contrast, pupillometry after single doses of noribogaine between 3 and 60 mg showed no change in pupil diameter[12]. Further work is needed to clarify the mu-opioid pharmacodynamic profile of ibogaine.

Single 20 mg doses of ibogaine were well tolerated. Two-thirds of reported adverse events were from subjects randomized to paroxetine, and these were characteristic of SSRIs (nausea, gastrointestinal disturbance, impotence). There were no changes noted in vital signs.

The potential shortcomings of this study must be acknowledged. The use of paroxetine to reduce CYP2D6 activity did have a substantial effect on DM:DX MRs, however only 2 of 11 subjects became PMs. It is possible that if this study had used only CYP2D6 PMs, the EM:PM pharmacokinetic differences might have been greater, and this is suggested by the correlations between ibogaine pharmacokinetic parameters and MRs (Figure 4). The

pupillometry results from this study conflict with those of a larger single dose noribogaine study[12], and thus further work is need to characterize the mu-opioid pharmacodynamic profile of ibogaine. Patients were not genotyped for CYP3A or CYP2C19, so it is possible that PM polymorphisms for these enzymes could have influenced pharmacokinetic data in paroxetine-treated patients. There were no safety or tolerability problems identified in this study, however because of the low single doses used, our findings may not be applicable to future studies using higher doses or multiple doses of ibogaine.

In conclusion, single 20 mg doses of ibogaine were safe and well tolerated in healthy male volunteers. Compared with placebo-pretreated subjects, reduced CYP2D6 activity in paroxetine-pretreated subjects produced large increases in ibogaine AUC0-t and Cmax and equivalent noribogaine AUC0-t values, effectively providing a doubling in exposure to active moiety AUC0-t. Because of this doubling of exposure, it may be prudent to characterize the CYP2D6 genotype or phenotype of patients awaiting ibogaine treatment, and to at least halve the intended dose of ibogaine in CYP2D6 PMs. It is difficult to predict potential changes in ibogaine exposure in CYP2D6 PMs who might also have reduced CYP3A and/or CYP2C19 activity, and this should be studied prospectively.

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Conflict of Interest/Disclosure: In last 2 years PG has been PI on 3 clinical trials sponsored by Demerx Inc. HW is an employee of Genentech Inc. CTH is Director of Zenith Technology Ltd, a Phase I CRO.

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Table 1: Influence of placebo or paroxetine pretreatment on mean (SD) plasma ibogaine and noribogaine pharmacokinetic parameters, and mean active moiety AUC0-t, following a single 20 mg oral dose of ibogaine.

		Pretreatment		
Analyte	Parameter	Placebo (n = 9)	Paroxetine (n = 11)	p
Ibogaine	AUC0-t (ng.h/mL)	3.6 (7.2)	238.2 (202.1)	0.0028
	Cmax (ng/mL)	1.1 (1.8)	29.5 (16.8)	<0.0001
	Tmax (h)*	1.0 (0-3)	1.5 (0-3)	0.17
	t1/2 (h)	2.5 (0.9)	10.2 (7.8)	0.009
Noribogaine	AUC0-t (ng.h/mL)	277.4(116.9)	304.1 (127.9)	0.64
	Cmax (ng/mL)	18.7 (7.3)	12.7 (5.3)	0.05
	Tmax (h)*	4.0 (2-4)	3.0 (1.5-8)	0.63
	t1/2 (h)	13.0 (4.7)	20.1 (10.2)	0.07
Active Moiety	AUC0-t (nM.h/mL)	948 (407)	1793 (695)	0.005
*median (range)				

Figure 1: Study Design Diagram

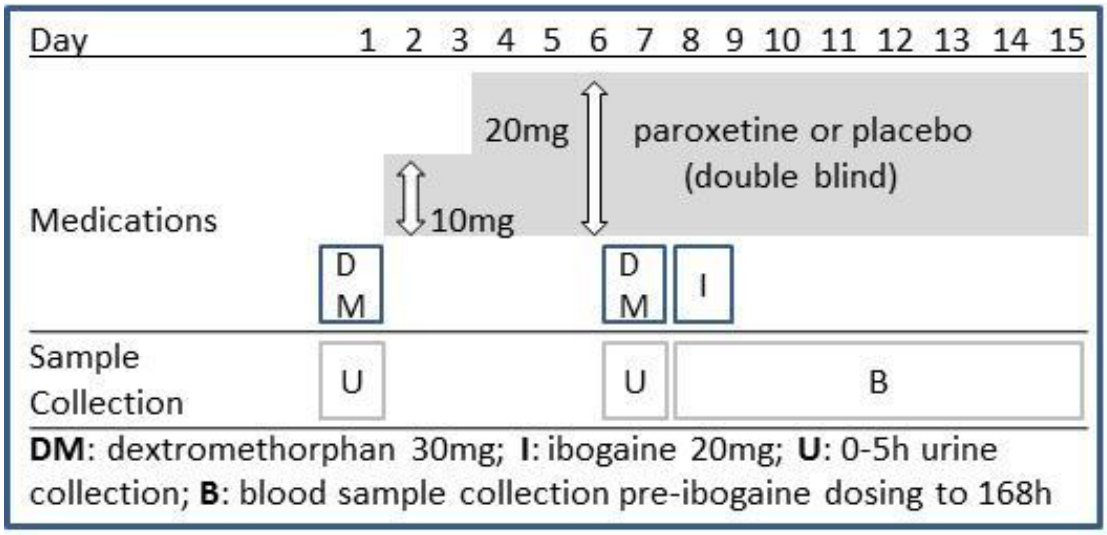

Figure 2: Effect of paroxetine or placebo pretreatment (days 2-7) on individual urinary dextromethorphan:dextrorphan (DM/DX) ratios. Note that Subject 1 was phenotypically a PM on Day 1 (MR = 0.51) and his data are not displayed.

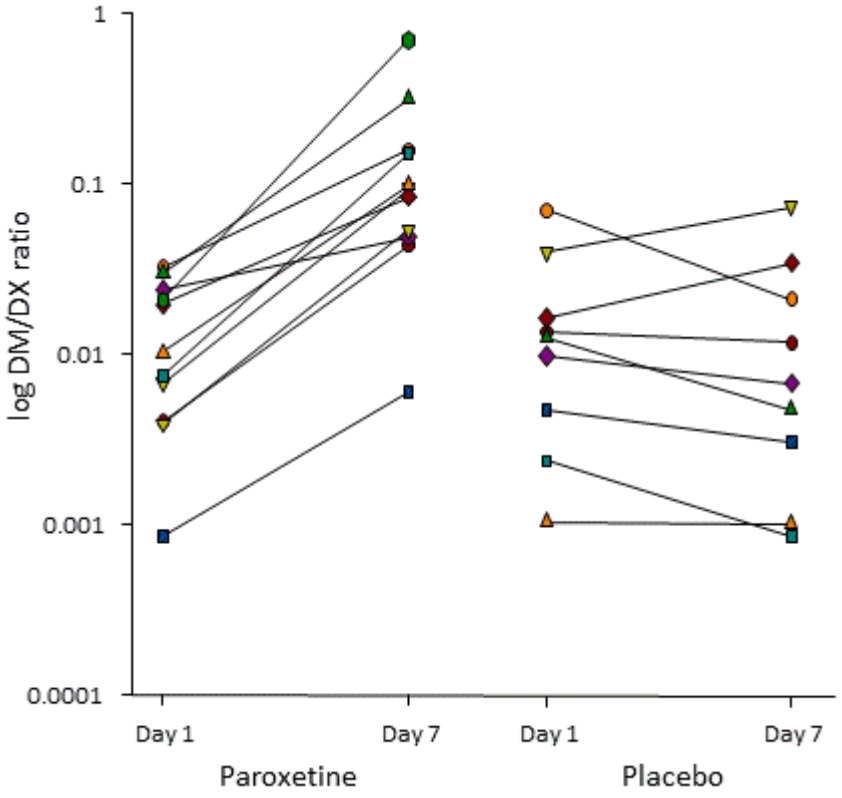

Figure 3: Mean ibogaine and noribogaine concentration-time profiles after a single 20 mg oral dose of ibogaine in subjects pretreated with placebo (n = 9) or paroxetine (n = 11). Inset: log concentration-time profiles, 0-6 h

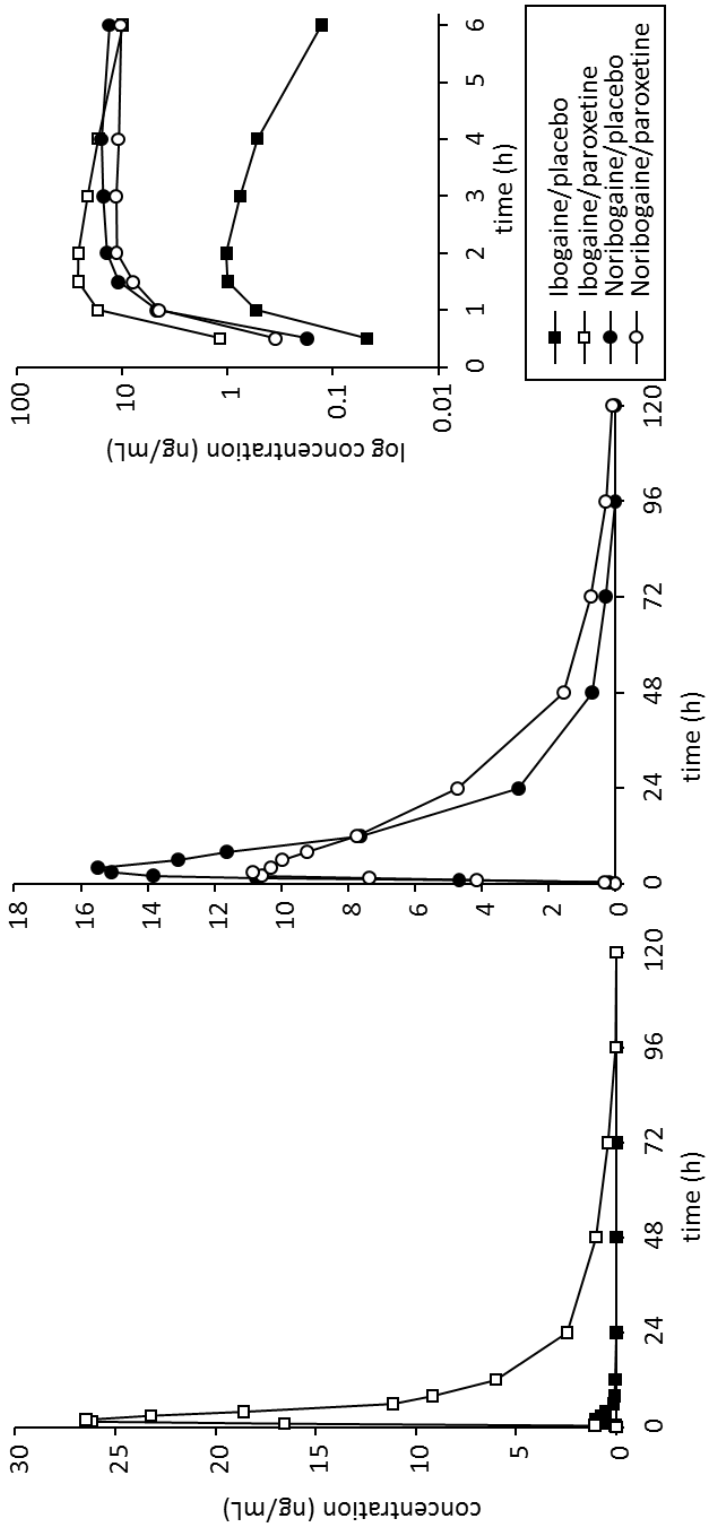

Figure 4: Relationship between log day 7 DM/DX Metabolic Ratio and log ibogaine Cmax (left panel; r = 0.77) and AUC0-t (right panel; r = 0.82). N = 15 for both graphs; 5 patients had ibogaine levels <LOQ.

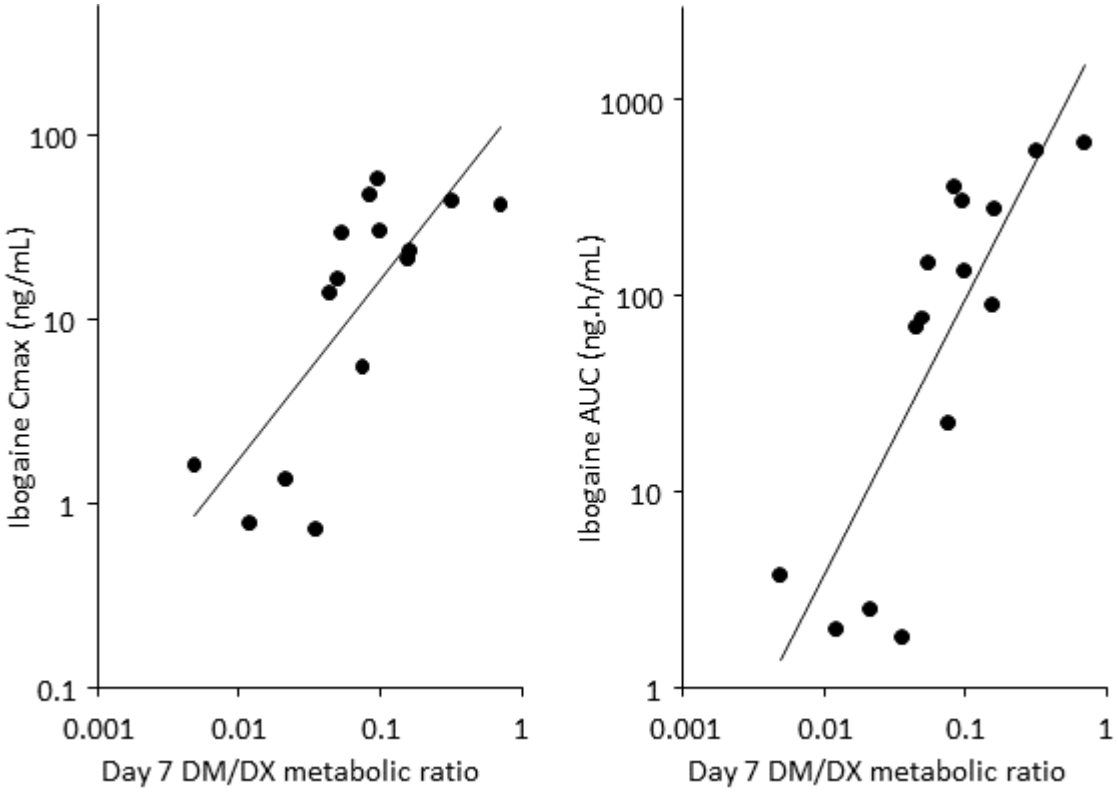

Figure 5: Mean (SD) change in pupil diameter over 12 h after a single 20 mg oral dose of ibogaine in subjects pretreated with placebo (●) or paroxetine (○).

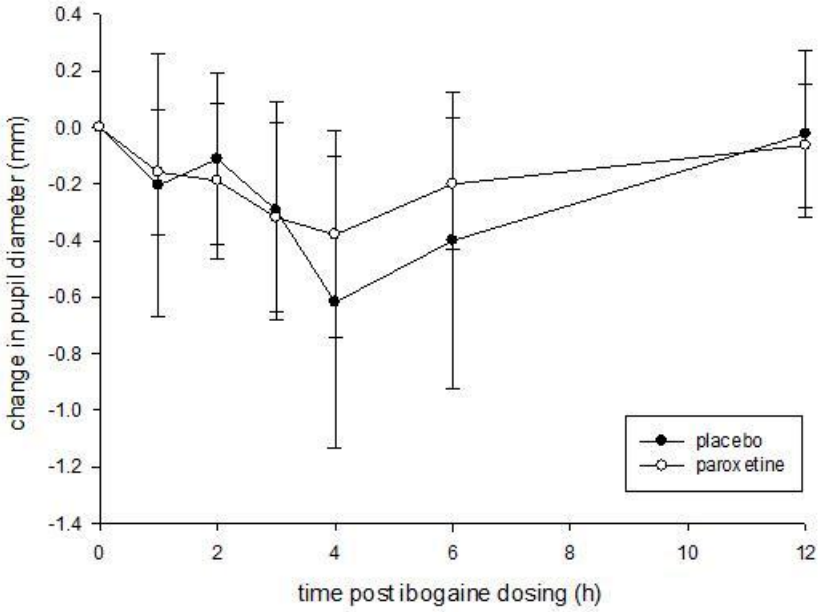

Figure 6: Mean visual analog scales (VAS) ratings after a single 20 mg oral dose of ibogaine in subjects pretreated with placebo (●) or paroxetine (○).