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# Pharmacological Interaction between 3,4-Methylenedioxymethamphetamine (Ecstasy) and Paroxetine: Pharmacological Effects and Pharmacokinetics

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**ABSTRACT**

3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") is increasingly used by young people for its euphoric and empathic effects. MDMA can be used in combination with other drugs such as selective serotonin reuptake inhibitors. A clinical trial was designed where subjects pretreated with paroxetine, one of the most potent inhibitors of both 5-hydroxytryptamine reuptake and CYP2D6 activity, were challenged with a single dose of MDMA. The aim of the study was to evaluate the pharmacodynamic and pharmacokinetic interaction between paroxetine and MDMA in humans. A randomized, double-blind, crossover, placebo-controlled trial was conducted in 12 healthy male subjects. Variables included physiological parameters, psychomotor performance, subjective effects, and pharmacokinetics. Subjects received 20 mg/day paroxetine (or placebo) orally for the 3 days before MDMA challenge (100 mg oral). MDMA alone produced the prototypical effects of the drug. Pretreatment with paroxetine was associated with marked decreases of both physiological and subjective effects of MDMA, despite a 30% increase in MDMA plasma concentrations. The decreases of 3-methoxy-4-hydroxymethamphetamine plasma concentrations suggest a metabolic interaction of paroxetine and MDMA. These data show that pretreatment with paroxetine significantly attenuates MDMA-related physiological and psychological effects. It seems that paroxetine could interact with MDMA at pharmacodynamic (serotonin transporter) and pharmacokinetic (CYP2D6 metabolism) levels. Marked decrease in the effects of MDMA could lead users to take higher doses of MDMA and to produce potential life-threatening toxic effects.

3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") is a phenylethylamine derivative with a similar chemical structure to amphetamine and mescaline. MDMA acts as an indirect serotonin agonist, inducing serotonin release from neuronal endings and inhibiting reuptake through interaction with the membrane serotonin transporter (SERT). In addition, MDMA is a potent inducer of the release of dopamine and norepinephrine (Green et al., 2003). MDMA given at single recreational doses in experimental settings produces marked increases in blood pressure and heart rate, mydriasis, and modest increases in body temperature (Mas et al., 1999; de la Torre et al., 2000; Hernández-Lopez et al., 2002; Farré et al., 2004). Subjective effects of MDMA are characterized by feelings of euphoria, friendliness, and empathy. Mild changes in body perception, including visual and auditory alterations, are observed, but no hallucinogenic or psychotic episodes usually occur (Cami et al., 2000; Hernández-Lopez et al., 2002; Farré et al., 2004).

During the 1990s, the simultaneous use of MDMA and

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**ABBREVIATIONS:** MDMA, 3,4-methylenedioxymethamphetamine; SERT, serotonin membrane reuptake transporter; SSRI, selective serotonin uptake inhibitor; P450, cytochrome P450; 5-HT, 5-hydroxytryptamine; SBP, systolic blood pressure; DBP, diastolic blood pressure; DSST, digit symbol substitution task; ARCI, Addiction Research Center Inventory; VESSPA, Evaluation of the Subjective Effects of Substances with Abuse Potential questionnaire; VAS, visual analog scales; ANX, psychosomatic anxiety scale; SOC, pleasure and sociability scale; ACT, activity and energy scale; MBG, morphine-benzedrine group; LSD, lysergic acid diethylamine group; BG, benzedrine group; HMMA, 3-methoxy-4-hydroxymethamphetamine; AUC, area under the curve; ANOVA, analysis of variance; NE, norepinephrine; Pgp, P-glycoprotein.

selective serotonin reuptake inhibitors (SSRIs) was a matter of discussion in some Internet forums visited by ecstasy users. The concomitant consumption of these substances was justified in light of animal studies where SSRIs showed some neuroprotective effects against MDMA-induced neurotoxicity (Sanchez et al., 2001). It was postulated that SSRIs lengthened the desirable effects and alleviated the "come down" and undesirable residual effects of MDMA (Erowid et al., http://www.erowid.org/chemicals/mdma/mdma_info9.shtml). Case reports of the interaction between MDMA and citalopram, paroxetine, or fluoxetine showed conflicting results with observed blockage or reinforcement of MDMA effects (McCann and Ricaurte, 1993; Stein and Rink, 1999).

Experimental studies of the pharmacological interaction between MDMA and SSRIs in rat models provided evidence for the neuroprotective effects of SSRIs. Fluoxetine blocked the decrease of cortical serotonin concentration after MDMA administration (Schmidt, 1987), and it attenuated MDMA-induced increase of extracellular serotonin in hippocampus (Mechan et al., 2002), although MDMA-induced hyperthermia remained unaffected. A decrease of neurotoxic responses to MDMA was observed when animals received fluoxetine before MDMA administration or when fluvoxamine and MDMA were given concomitantly (Sanchez et al., 2001). In humans exposed to MDMA, the administration of intravenous citalopram seems to attenuate both MDMA-related physiological effects (cardiovascular activity) and subjective effects of positive mood, increase extraversion, and self-confidence (Liechti et al., 2000; Liechti and Vollenweider, 2000b).

One difference between the SSRIs is their potential to cause drug-drug interactions through inhibition of cytochrome P450 (P450) isoforms. Although citalopram seems to have little effect on the major P450 isoforms, two drugs experimentally consumed by MDMA users, paroxetine and fluoxetine, are potent inhibitors of CYP2D6. Because this isoenzyme of cytochrome P450 regulates the first metabolic step of MDMA disposition, a pharmacokinetic interaction with both drugs could be expected with accumulation of MDMA in the body. In this context, it would be worthwhile to test whether, despite higher MDMA plasma concentrations, the inhibition of serotonin reuptake due to SSRI pre-exposure prevails over MDMA subjective and physiological effects. A clinical trial was designed where subjects pretreated with paroxetine, one of the most potent inhibitors of both 5-HT reuptake and CYP2D6 activity, were challenged with a single dose of MDMA. The pharmacodynamic and pharmacokinetic interaction between both drugs is presented.

## Materials and Methods

**Subjects.** Male subjects were recruited by word of mouth. Eligibility criteria required the recreational use of MDMA on at least five occasions. Exclusion criteria included daily consumption of more than 20 cigarettes and more than 30 g of ethanol (3 U/day). Eligible subjects were interviewed by a psychiatrist (structured clinical interview for Diagnostic and Statistical Manual—Version IV) to exclude the presence of major psychiatric disorders, including schizophrenia, psychosis, and major affective disorders. Each participant underwent a general physical examination, routine laboratory tests, urinalysis, and a 12-lead electrocardiogram to confirm health status. Thirteen subjects gave written consent to participate in the study, and they were informed about the possible adverse effects during the study. They were financially compensated for the possible inconveniences derived from the procedures. The study was conducted in accordance with the Declaration of Helsinki, approved by the Ethics Committee of the Institut Municipal d'Assistència Sanitària (Barcelona, Spain), and authorized by the Spanish Ministry of Health.

Study subjects had a mean age of 24 years (range 19–34 years), mean weight of 71.0 kg (range 56.5–84.0 kg), and mean height of 177.0 cm (range 167.5–190 cm). The group of participants included both current smokers ($n = 8$) and nonsmokers ($n = 4$). Average alcohol consumption was 12 units per week. All subjects had previous experience with the consumption of cannabis, cocaine, and methamphetamine. None had a history of abuse or drug dependence according to Diagnostic and Statistical Manual—Version IV criteria (except for nicotine dependence), and none had ever experienced any medical or psychiatric adverse reaction after MDMA consumption. All participants were classified as extensive metabolizers for CYP2D6 using dextromethorphan as probe drug. A 13th volunteer was withdrawn from the study due to the presence of paroxetine-related adverse effects. After two doses of paroxetine, he arrived on the morning of the third study day presenting insomnia, restlessness, and anxiety (consequently, MDMA was not given to this subject). Therefore, results of the remaining 12 participants are described.

**Study Design.** The study design was double-blind, randomized, crossover, and controlled. Treatment conditions (paroxetine/MDMA and placebo/MDMA) were randomly assigned. Each subject participated in two, 3-day study sessions, with a washout period of 15 days. In each session, subjects arrived at the laboratory at 8:00 AM after an overnight fast, and they had an indwelling intravenous catheter inserted into a subcutaneous vein in the forearm of the nondominant arm. Thereafter, they remained seated in a quiet room throughout the session. Subjects received either paroxetine (20 mg/day on days 1, 2, and 3) or placebo (on days 1, 2, and 3) and MDMA (100 mg on day 3). Paroxetine or placebo was administered at approximately 9:00 AM in fasting conditions. Taking into account the average $T_{max}$ of MDMA and paroxetine (2 h for MDMA and 5 h for paroxetine), MDMA was administered 3 h after paroxetine (12:00 PM) to obtain maximum plasma concentrations of both drugs at the same time (2:00 PM).

To prevent any possible anticipatory response, subjects were told that they would receive two types of drugs. On the first study day, they would receive one capsule containing paroxetine or placebo; on the second study day, one capsule containing paroxetine or placebo; and on the third study day, one capsule containing paroxetine or placebo followed 3 h later by two capsules containing different doses of MDMA or placebo.

Volunteers were requested to abstain from consumption of any drug of abuse during the study period. Urine drug testing was performed for opiates, cocaine, cannabis, and amphetamines before each experimental session. Negative results were a requisite condition for participation.

**Drugs.** The doses of paroxetine and MDMA were chosen according to data of previous studies (Brauer et al., 1995; Mas et al., 1999). Paroxetine was supplied as Seroxat (GlaxoSmithKline, Tres Cantos, Madrid, Spain), and it was prepared by the Service of Pharmacy of Hospital del Mar (Barcelona, Spain) as white, soft gelatin capsules indistinguishable from placebo. MDMA was supplied by the Spanish Ministry of Health, and it was prepared by Service of Pharmacy as soft gelatin capsules.

**Physiological Measures.** Noninvasive systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, oral temperature, and pupil diameter were recorded at −15 min and immediately before drug administration (time 0, baseline) and on day 1 at 1, 3, 5, and 8 h; on day 2 at 0 and 3 h; and on day 3 at 0, 1, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 11, and 24 h after paroxetine administration. SBP, DBP, heart rate, and oral temperature were recorded using a Dinamap 8100-T vital signs monitor (Critikon, Tampa, FL). Pupil diameter was recorded using a pupil gauge (Haab scale). For safety

reasons, ECG was continuously monitored during the session with a Dinamap Plus vital signs monitor (Critikon).

**Psychomotor Performance Measures.** The psychomotor performance battery included the digit symbol substitution test (DSST), the simple reaction time, the Pauli test, and the Maddox-wing device. This battery has been used previously in the evaluation of psychostimulants and MDMA effects (Farré et al., 1993, 2004; Cami et al., 2000; de la Torre et al., 2000; Hernández-Lopez et al., 2002). The DSST is a subtest of the Wechsler Adult Intelligence Scale-Revised. A computerized version was used, and scores were based on the number of correct patterns keyed in 90 s (correct responses). The simple reaction time and the Pauli test were assessed using the Vienna Reaction Unit (PC/Vienna System, Schufried, Austria). For reaction time, results were expressed in milliseconds as the mean of the response time to 20 stimuli (simple reaction time). In the Pauli test, the respondent is required to add as fast as possible two numbers at a time, results were based on the total and corrects number of additions, and number of errors during 90 s. The Maddox-wing device measures the balance of extraocular muscles and quantifies exophoria, as an indicator of extraocular musculature relax, and esophoria. Results were expressed in transformed diopters along the horizontal scale of the device (Mas et al., 1999). The psychomotor performance battery was performed on day 1 at 1, 3, 5, and 8 h; on day 2 at 0 and 3 h; and on day 3 at 0, 1, 3 (immediately before MDMA), 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 11, and 24 h after paroxetine administration.

**Subjective Effects Rating Scales.** Subjective effects were measured using the Addiction Research Center Inventory (ARCI), the Evaluation of the Subjective Effects of Substances with Abuse Potential (VESSPA) questionnaire, and a set of a variety of visual analog scales (VAS; 100 mm). ARCI is a true-false questionnaire with empirically derived scales sensitive to the effect of different classes of drugs of abuse. A Spanish validated version of a 49-item short form of ARCI was used (Lamas et al., 1994). The questionnaire included five scales: pentobarbital-chlorpromazine-alcohol group, a measure of sedation; morphine-benzedrine group (MBG), a measure of euphoria; lysergic acid diethylamine group (LSD), a measure of dysphoria and somatic symptoms; benzedrine group (BG), a stimulant scale consisting mainly of items relating to intellectual efficiency and energy); and amphetamine, an empirically derived scale sensitive to the effects of *d*-amphetamine). ARCI was administered at 0 h (immediately before drug administration) and on day 1 at 1, 3, 5, and 8 h; on day 2 at 0 and 3 h; and on day 3 at 0, 1, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 11, and 24 h after paroxetine administration. VESSPA is an in-house-developed and validated questionnaire to measure MDMA-induced changes in subjective variables (Poudevida et al., 2003), and it includes six scales: sedation, psychosomatic anxiety (ANX), changes in perception, pleasure and sociability (SOC), activity and energy (ACT), and psychotic symptoms. Each scale consists of six questions with a 5-point Likert response (0 to 4 depending on the intensity of the effect). VESSPA scales were administered at 0 h (before drug administration) and on day 1 at 3 and 8 h; on day 2 at 0 h; and on day 3 at 0, 3, 5, 6, 8, 11, and 24 h after paroxetine administration. Twenty-one 100-mm VAS labeled with different adjectives marked at opposite ends with "not at all" and "extremely" were used (Cami et al., 2000). Subjects were asked to rate effects of "stimulated", "high", "drunken", "any effect", "good effects", "bad effects", "liking", "content", "drowsiness", "changes in distances", "changes in colors", "changes in shapes", "changes in lights", "hallucinations-seeing of lights or spots", "changes in hearing", "hallucinations-hearing sounds or voices", "dizziness", "hallucinations-seeing animals, things, insects, or people", "confusion", "fear", "depression or sadness", "different, changed or unreal body feeling", and "different or unreal surroundings". Scales were administered at 0 h (before drug administration) and on day 1 at 1, 3, 5, and 8 h; on day 2 at 0 h; and on day 3 at 0, 1, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 11, and 24 h after paroxetine administration.

**Determination of MDMA and HMMA in Plasma.** Blood samples were collected on day 3 only before dose administration, and at 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 11, 24, and 30 h after paroxetine or placebo administration [or 0, 0.33 (20 min), 0.67 (40 min), 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 21, and 27 h after MDMA administration]. Blood was collected in heparinized tubes, and then it was centrifuged at 1100*g* at 4°C for 10 min. Plasma was stored at −20°C until analysis. Urine samples were collected on day 3 only at different time periods after MDMA administration (predose, 0–3, 3–6, 6–9, 9–21, 21–33, and 33–45 h), and they were immediately acidified with 1 ml of 0.1 mol/l HCl and stored at −20°C until analysis. MDMA and 3-methoxy-4-hydroxymethamphetamine (HMMA) were analyzed in plasma samples following a previously reported method based on a solid-liquid extraction with Bond Elut Certify columns and gas chromatography coupled to mass spectrometry (Pizarro et al., 2002). In a subset of participants ($n = 7$), paroxetine and 4-hydroxy-3-methoxyparoxetine, and other MDMA metabolites such as 3,4-dihydroxymethamphetamine, 3,4-methylenedioxyamphetamine, and 4-hydroxy-3-methoxyamphetamine, were determined in blood and urine. In addition, samples were collected to determine immunological parameters and hormones. These results have been published previously (Pacifici et al., 2004; Segura et al., 2005).

**Statistical Analysis.** Values from physiological, psychomotor performance measures, and subjective variables were transformed to differences from baseline. The peak effect in the first 6 h following MDMA or matched placebo administration (maximum absolute change from baseline values) and the 6-h area under the curve (AUC) of effects versus time calculated by the trapezoidal rule were determined for each variable. These transformations were analyzed by one-way repeated measures analysis of variance (ANOVA) with drug conditions as factor. When ANOVA results showed significant differences between treatment conditions, post hoc multiple comparisons were performed using the Tukey test. Furthermore, a detailed comparison of time course of effects was conducted using repeated measures two-way ANOVA, with treatment condition and time as factors. When treatment condition or the treatment condition × time interaction was statistically significant, multiple Tukey post hoc comparisons were performed at each time point using the mean square error term of the treatment condition × time interaction.

With regard to plasma concentrations of MDMA, the following experimental pharmacokinetic parameters were obtained: peak concentration ($C_{max}$), time taken to reach peak concentration ($T_{max}$), and AUC from 0 to 27 h. AUC values were calculated by the trapezoidal rule. The Student's $t$ test ($C_{max}$ and AUC) and the Wilcoxon test ($T_{max}$) were used for statistical analysis. Pharmacokinetic parameters were obtained with use of specific functions of computer program (PK Functions for Microsoft Excel; Microsoft, Redmond, WA).

All statistical tests were performed using SPSS (SPSS Inc., Chicago, IL), and differences associated with $p$ values lower than 0.05 were considered to be statistically significant.

## Results

A summary of results for physiological and subjective effects showing a statistical significant difference between treatments are presented in Table 1. There were no differences in AUC and $E_{max}$ measurements between placebo and paroxetine during the first 2 days of administration except a significant increase in systolic blood pressure during paroxetine administration (peak difference 8 mm Hg). Paroxetine alone improved some psychomotor performance variables (DSST correct response), but no changes on subjective variables during its administration were observed.

**Physiological Effects.** Physiological effects versus time curves for the third day are shown in Fig. 1. MDMA alone

TABLE 1
Results of statistical analysis of variables that presented significant differences after 100-mg MDMA administration between placebo and paroxetine conditions

| Variable | MDMA-Placebo vs. MDMA-Paroxetine, Day 3 | | | | | |
|---|---|---|---|---|---|---|
| | AUC[a] (df = 1, 11) | | $E_{max}$[b] (df = 1, 11) | | Time × Condition (df = 10, 110[c]) | |
| | *F* | *p* | *F* | *p* | *F* | *p* |
| Physiological parameter | | | | | | |
| Systolic blood pressure | 5.94 | 0.033 | 22.20 | 0.001 | 4.13 | <0.001 |
| Diastolic blood pressure | 0.27 | 0.613 | 1.75 | 0.213 | 3.97 | <0.001 |
| Heart rate | 3.39 | 0.093 | 7.64 | 0.018 | 3.11 | 0.002 |
| Oral temperature | 2.01 | 0.184 | 5.33 | 0.041 | 2.04 | 0.036 |
| Pupil diameter | 39.02 | <0.001 | 70.35 | <0.001 | 31.14 | <0.001 |
| Psychomotor performance | | | | | | |
| DSST correct | 0.15 | 0.702 | 0.15 | 0.705 | 2.21 | 0.034 |
| Reaction time errors | 4.00 | 0.071 | 5.65 | 0.037 | 1.63 | 0.129 |
| Pauli total | 0.03 | 0.877 | 0.88 | 0.367 | 4.18 | 0.013 |
| Pauli correct | 0.13 | 0.723 | 1.38 | 0.265 | 4.62 | 0.008 |
| Pauli errors | 0.25 | 0.626 | 0.17 | 0.872 | 3.41 | 0.029 |
| Maddox-wing | 8.79 | 0.013 | 9.03 | 0.012 | 3.81 | <0.001 |
| Subjective effects | | | | | | |
| VAS | | | | | | |
| Stimulated | 27.04 | <0.001 | 14.39 | 0.003 | 7.50 | <0.001 |
| High | 41.66 | <0.001 | 34.16 | <0.001 | 10.88 | <0.001 |
| Any effects | 38.17 | <0.001 | 26.18 | <0.001 | 8.74 | <0.001 |
| Good effects | 27.12 | <0.001 | 25.87 | <0.001 | 8.31 | <0.001 |
| Liking | 15.52 | 0.002 | 22.98 | 0.001 | 6.52 | <0.001 |
| Drowsiness | 4.87 | 0.049 | 2.48 | 0.144 | 1.15 | 0.330 |
| Changes in lights | 8.75 | 0.013 | 6.41 | 0.028 | 6.36 | <0.001 |
| Dizziness | 2.36 | 0.153 | 2.91 | 0.116 | 2.12 | 0.029 |
| Different body sensation | 14.32 | 0.003 | 13.09 | 0.004 | 4.72 | <0.001 |
| Different surroundings | 5.35 | 0.041 | 5.38 | 0.042 | 1.68 | 0.095 |
| ARCI | | | | | | |
| ARCI-MBG | 22.88 | 0.001 | 11.98 | 0.005 | 6.10 | <0.001 |
| ARCI-LSD | 6.85 | 0.024 | 1.121 | 0.312 | 2.13 | 0.028 |
| ARCI-BG | 5.68 | 0.036 | 1.421 | 0.258 | 1.47 | 0.159 |
| ARCI-A | 53.99 | <0.001 | 13.36 | 0.004 | 3.78 | <0.001 |
| VESSPA | | | | | | |
| VESSPA-ANX | 9.24 | 0.011 | 13.88 | 0.003 | 8.53 | <0.001 |
| VESSPA-SOC | 8.51 | 0.014 | 6.920 | 0.023 | 5.92 | 0.002 |
| VESSPA-ACT | 14.20 | 0.003 | 10.89 | 0.007 | 7.19 | 0.001 |

[a] AUC is from 3 to 9 h.
[b] $E_{max}$ is peak effects from 3 to 9 h.
[c] For psychomotor performance tasks, df = 8, 88; for VESSPA questionnaire, df = 3, 33.

produced the prototypical effects of the drug as has been previous published: increases in systolic and diastolic blood pressure, heart rate, oral temperature, and pupil diameter. Paroxetine significantly reduced many of the physiological alterations induced by MDMA. SBP and DBP as well as heart rate were decreased significantly. Upon comparing $E_{max}$ values, systolic blood pressure decreased by 12 mm Hg, diastolic blood pressure by 5 mm Hg and heart rate by 14 beats/min. MDMA induced mydriasis was reduced drastically by the paroxetine treatment from 3.33 to 1.23 mm (peak difference). A significant decrease in the rise of oral temperature produced by MDMA alone was observed after paroxetine pretreatment (peak difference 0.3°C).

**Psychomotor Performance.** Paroxetine reduced the slight deterioration of psychomotor performance caused by MDMA but without reaching significance, except for $E_{max}$ in reaction time errors (0.1 versus 0.9 errors), and a few time points in DSST correct responses and Pauli test (total and correct responses, and errors). Alternatively, esophoria measured by the Maddox-wing device was almost abolished ($E_{max}$ increases from −2.73 to −1.23 diopters; Fig. 1).

**Subjective Effects.** Subjective effects are shown in Figs. 2 and 3. Pretreatment with paroxetine significantly decreased many of the subjective effects observed after MDMA alone. Significant decreases were found in ARCI (ARCI-MBG peak effects from 7.27 to 4, ARCI-LSD from 3.27 to 2.58, ARCI-BG from 2.73 to 1.92, and ARCI-amphetamine from 5.27 to 3.67) and VESSPA scales (VESSPA-ANX from 5.55 to 2.7, VESSPA-SOC from 3.0 to 0.58, and VESSPA-ACT from 5.91 to 1.21). Paroxetine also significantly reduced the scores in the following VAS: stimulated; high; any effect; good effects; liking; changes in lights; different, changed or unreal body feeling; and different or unreal surroundings. Neither pretreatment with paroxetine nor MDMA alone produced significant changes in the scales of changes in perception and psychotic symptoms of VESSPA, as well as in the VAS scores for bad effects, hallucinations-seeing of flights or spots, fear, and depression or sadness. No differences were observed as a function of treatment condition in sedation scales (ARCI-pentobarbital-chlorpromazine-alcohol group, VESSPA-sedation). No hallucinations or psychotic symptoms were observed during the experimental sessions. None of the participants required specific therapy or special care during the study. Serious adverse events were not observed.

**Plasma Concentrations of MDMA and HMMA.** Pharmacokinetics parameters of MDMA and HMMA are shown in Table 2. MDMA plasma concentrations when coadmin-

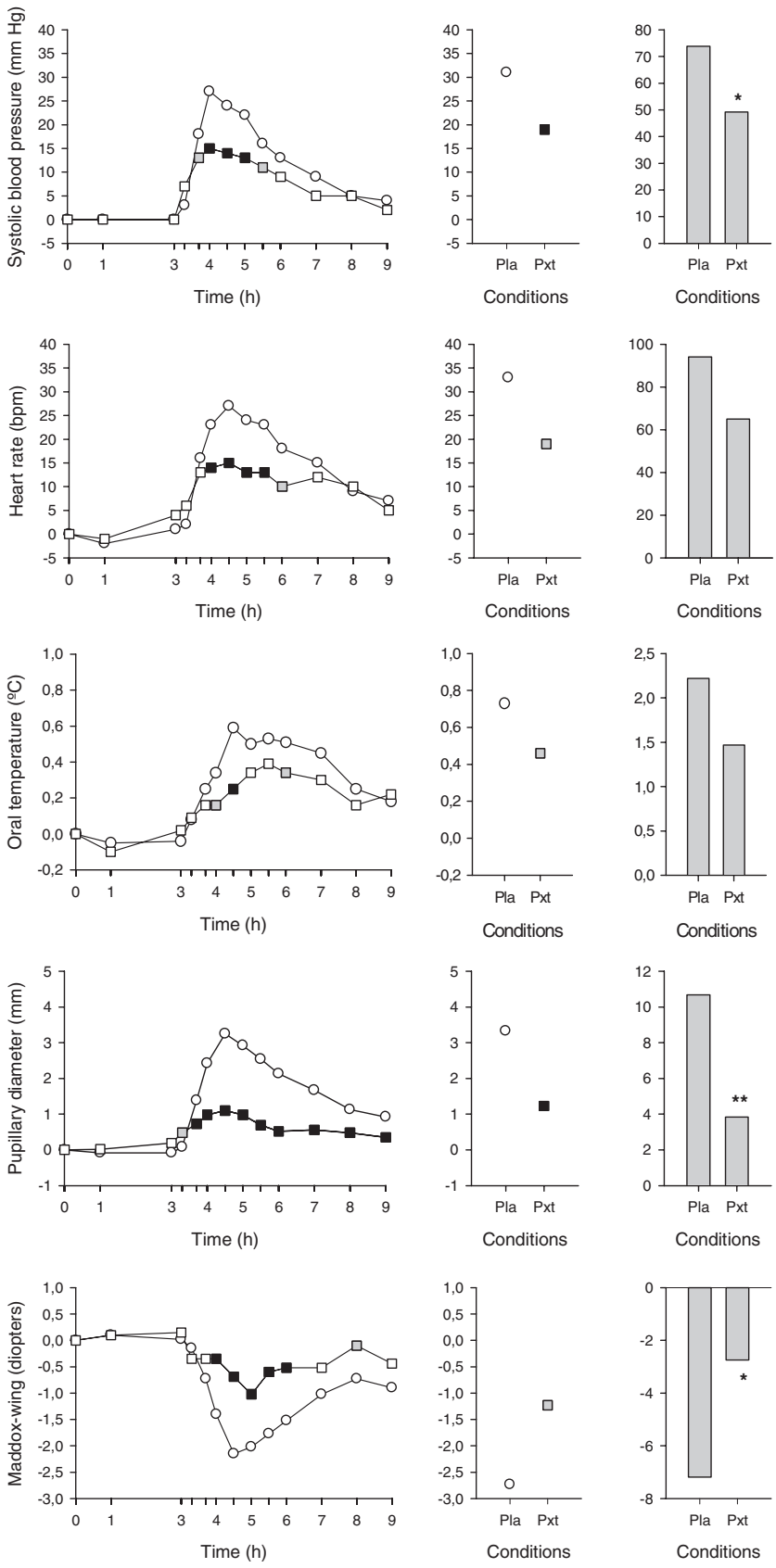


**Fig. 1.** Physiological effects after administration of 100 mg of MDMA following a three-dose regimen of 20 mg of paroxetine or placebo ($n = 12$). Paroxetine or placebo was administered at 0 h and MDMA at 3 h. From left to right, time course, $E_{max}$ 3 to 9 h, and AUC 3 to 9 h (□, paroxetine; ○, placebo). The following symbols denote statistical significance: **/■ = $p < 0.01$; */▨ = $p < 0.05$.

istered with paroxetine increased by 22 (AUC) and 16% ($C_{max}$), whereas those of HMMA were reduced by 39 (AUC) and 49% ($C_{max}$). Other details on the pharmacokinetic interaction between paroxetine and MDMA in a subset of subjects ($n = 7$) have been described in part previously (Segura et al., 2005).

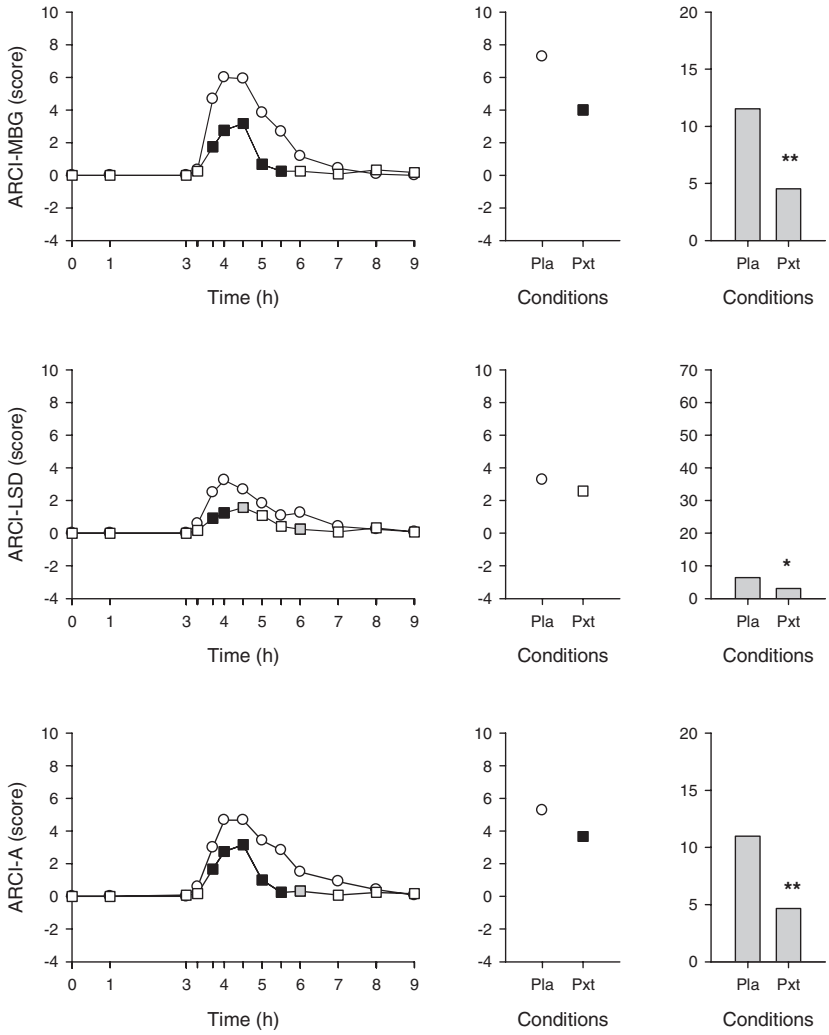


**Fig. 2.** Subjective effects (ARCI subscales) after administration of 100 mg of MDMA following a three-dose regimen of 20 mg of paroxetine or placebo ($n = 12$). Paroxetine or placebo was administered at 0 h and MDMA at 3 h. From left to right, time course, $E_{max}$ 3 to 9 h, and AUC 3 to 9 h (□, paroxetine; ○, placebo). The following symbols denote significance: **/■ = $p < 0.01$; */▨ = $p < 0.05$.

## Discussion

We studied the pharmacological interaction of MDMA with an SSRI, taking into account both pharmacokinetic and pharmacodynamic aspects in the framework of a randomized controlled clinical trial. The main result is that pretreatment with paroxetine was associated with marked decreases of both physiological and subjective effects following the administration of MDMA, despite a 30% increase in MDMA plasma concentration resulting from the metabolic interaction of paroxetine and MDMA.

Paroxetine was administered during three subsequent days before MDMA administration with two purposes. First, to achieve nearly steady-state paroxetine plasma concentrations promoting high SERT occupancy rates and consequently a possible pharmacodynamic interaction; and second, to inhibit CYP2D6 activity to a degree that would significantly impair MDMA metabolic disposition (Bertelsen at al., 2003; Kotzailias et al., 2004). In fact, paroxetine increased MDMA plasma concentrations approximately 30% and it decreased plasma concentrations of HMMA (the main metabolite of MDMA) approximately 40% (Segura et al., 2005). Considering that the reduction of HMMA concentrations is greater than the increase in MDMA concentrations, it seems that CYP2D6 contributes less to the metabolism of MDMA than the previously reported 60% based on in vitro studies (Tucker et al., 1994). The present results are also consistent with data from a repeated dose study of MDMA (Farré et al., 2004) in which a dose of 100 mg was able to inhibit by the same proportion the metabolism of a subsequent dose 24 h later. The comparison between the present study and the MDMA repeated doses study is possible because both paroxetine and MDMA share the same mechanism-based inhibition of CYP2D6 (Bertelsen et al., 2003; Heydari et al., 2004).

Even though plasma concentrations of MDMA were increased, a boost in pharmacological and subjective effects was not observed. On the contrary, a clear decrease was observed, which indicates a pharmacodynamic interaction. MDMA and paroxetine can inhibit the reuptake of serotonin by interacting with SERT. However, although MDMA must be transported into nerve terminals to promote neurotransmitter release, paroxetine binds to the carrier, but it is not itself transported (Rothman and Baumann, 2002). Paroxetine binds competitively to the 5-HT uptake site, with a $K_i$ of 1.1 nM, whereas MDMA binding properties are 300-fold lower ($K_i = 0.34$ $\mu$M) (Battaglia et al., 1988; Sánchez and Hyttel, 1999). In vitro studies have shown that fluoxetine inhibits MDMA-induced release of serotonin into the synaptic space (Gudelsky and Nash, 1996), and there is some evidence that pretreatment with SSRIs reduces some

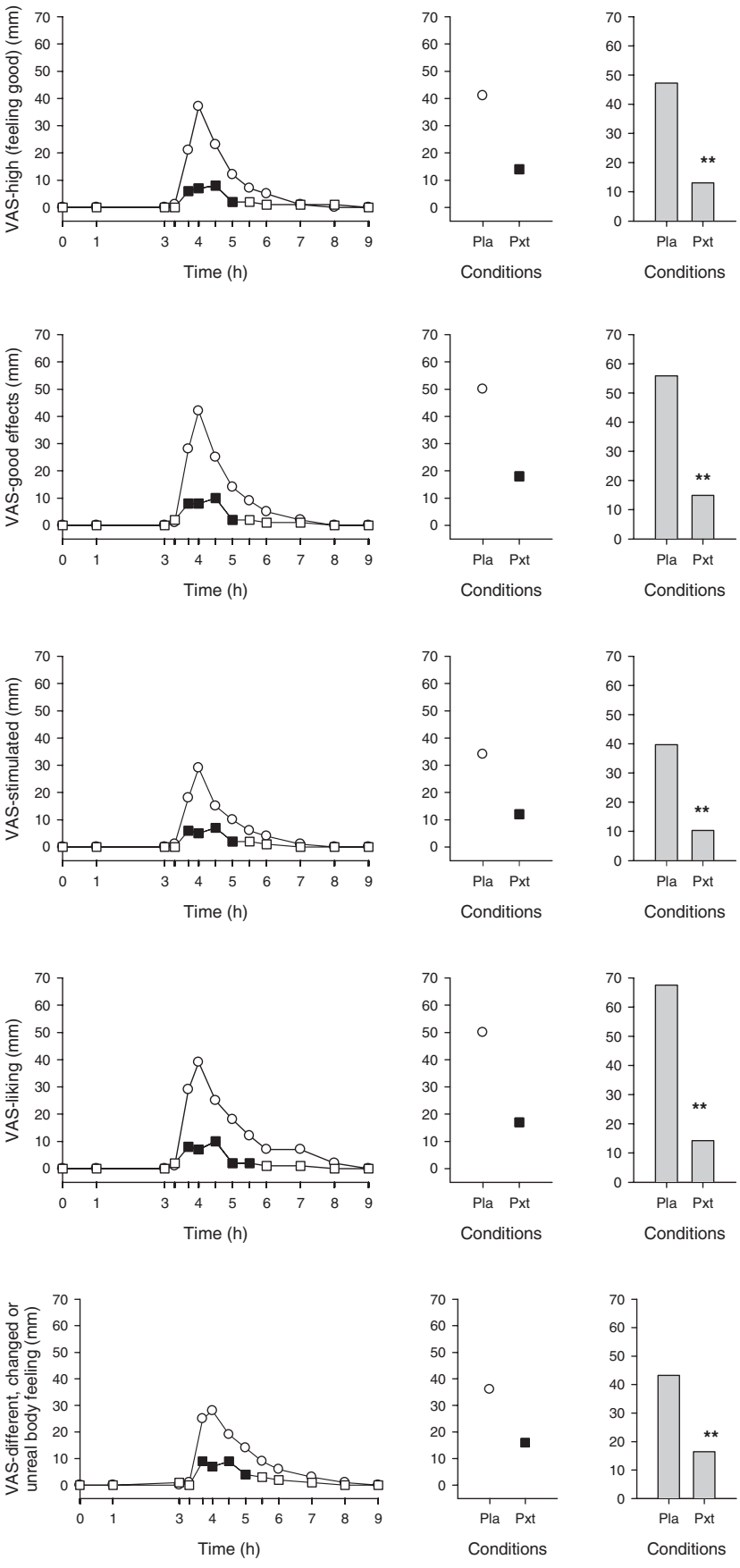


**Fig. 3.** Subjective effects (VAS scales) after administration of 100 mg of MDMA following a three-dose regimen of 20 mg of paroxetine or placebo ($n = 12$). Paroxetine or placebo was administered at 0 h and MDMA at 3 h. From left to right: time course, $E_{max}$ 3 to 9 h, and AUC 3 to 9 h (□, paroxetine; ○, placebo). The following symbols denote significance: **/■ = $p < 0.01$; */▨ = $p < 0.05$.

TABLE 2
Pharmacokinetics of MDMA and HMMA after administration of 100 mg of MDMA following a three-dose regimen of 20 mg of paroxetine or placebo ($n = 12$)
Values are mean and S.D.

| | $C_{max}$ | $T_{max}$ | $K_e$ | $AUC_{0-21}$ | $t_{1/2}$ |
|---|---|---|---|---|---|
| | $\mu g/l$ | $h$ | $h^{-1}$ | $\mu g/l \cdot h$ | $h$ |
| MDMA | | | | | |
| Placebo | 212.72 | 1.50 | 0.0903 | 2115.26 | 7.88 |
| S.D. | 46.74 | 0.62 | 0.0167 | 470.26 | 1.21 |
| Paroxetine | 246.62** | 1.75 | 0.0853 | 2572.21** | 8.34 |
| S.D. | 55.80 | 0.66 | 0.0143 | 661.68 | 1.41 |
| HMMA | | | | | |
| Placebo | 193.14 | 2.25 | 0.0740 | 1923.32 | 9.54 |
| S.D. | 77.50 | 0.66 | 0.0111 | 736.35 | 1.32 |
| Paroxetine | 97.88** | 3.00 | 0.0541** | 1189.47** | 13.10** |
| S.D. | 33.83 | 0.33 | 0.0092 | 388.78 | 2.09 |

** Significant difference between placebo and paroxetine conditions, paired Student's $t$ test or Wilcoxon test ($p < 0.01$).

MDMA-related effects (Liechti et al., 2000; Liechti and Vollenweider, 2000b; Tancer and Johanson, 2007). SSRIs, such as paroxetine, antagonize MDMA activity either by preventing its interaction with the 5-HT uptake site or alternatively by blocking the efflux of 5-HT through the carrier. The fact that paroxetine is not able to fully counteract MDMA effects further supports the contribution of other neurotransmission systems in the pharmacology of MDMA.

The physiological and subjective effects observed following MDMA administration are in the range described previously in an experimental laboratory setting where similar doses were administered (Hernández-López et al., 2002; Farré et al., 2004). Paroxetine reduced the cardiovascular effects produced by MDMA by approximately 50%. The reduction in SBP, DBP, and heart rate is in agreement with a previous study in which citalopram was administered intravenously 90 min before a 1.5-mg/kg oral dose of MDMA or fluoxetine was given daily for at least 5 days before 1.5 mg/kg MDMA (Liechti and Vollenweider, 2000b; Tancer and Johanson, 2007). The partial reduction in cardiovascular response indicates other receptors and neurotransmitters in addition to serotonin further contribute to the MDMA effects. MDMA releases norepinephrine through an interaction with the norepinephrine transporter, with a similar $IC_{50}$ for NE than that observed for 5-HT and SERT (55.6 versus 77.4 nM) (Battaglia et al., 1988). It is well known that NE system produces sympathomimetic effects resulting in increases in SBP, DBP, and heart rate. It has been recently postulated that myocardial MDMA effects are partially mediated by a competitive blockade of norepinephrine transporter (Cleary and Docherty, 2003), so that a reduction of these effects observed here may support a possible 5-HT-mediated release of NE. In contrast, some reports link $\alpha 1$ and possibly $\alpha 2$ adrenoreceptors and $5\text{-HT}_2$ receptors with blood pressure response to MDMA in animals (McDaid and Docherty, 2001).

The interaction with paroxetine reduces the increase in pupil diameter mediated by MDMA by approximately 70%. Interestingly, this variable shows the most prominent reduction after pretreatment with paroxetine. Pupil diameter depends on sympathetic-parasympathetic regulation. Because NE is the neurotransmitter of the postganglionic sympathetic neurons, it can be postulated that MDMA-mediated NE release is partially related to serotonin.

During the paroxetine condition, the increase in temperature shown during the administration of MDMA alone decreased by approximately 50%. Previous observations in rats showed that fluoxetine was not capable of reducing the increase in temperature seen following the administration of MDMA, even though serotonin release was decreased (Mechan et al., 2002). On the contrary, in mice, a pretreatment with fluoxetine abolished the hyperthermia induced by MDMA administration (O'Shea et al., 2001). Results from the present study, however, indicate a partial role of serotonin.

The concomitant administration of paroxetine produced a marked and significant reduction in the euphoric and pleasurable effects of MDMA and some feelings of dysphoria. MDMA-mediated euphoria and feelings of well being have been associated with dopamine and serotonin release. However, the relative contribution of the dopaminergic and serotonergic pathways in the production of MDMA-associated pleasurable affects is unknown. It has been shown that euphoria associated with the use of MDMA is partially reduced by pretreatment with the dopaminergic D2 antagonist haloperidol (Liechti and Vollenweider, 2000a). In contrast, depressive patients who were on chronic treatment with SSRIs exhibited a decrease in MDMA euphoric effects (Stein and Rink, 1999). Similar findings were obtained in other experimental studies with the coadministration of MDMA and citalopram or fluoxetine (Liechti and Vollenweider, 2000b; Tancer and Johanson, 2007). In the present study, pretreatment with paroxetine also reduced MDMA subjective effects even with simultaneous higher MDMA plasma concentrations. These findings may indicate that MDMA dopamine release mediated by dopamine reuptake inhibition is also amplified through the activation of postsynaptic $5\text{-HT}_2$ receptors (Battaglia et al., 1988; Koch and Galloway, 1997), and they do not exclude the hypothesis of the potential contribution of NE on the subjective effects elicited by stimulants such as MDMA (Rothman et al., 2001).

In addition to the pharmacokinetic interaction between MDMA and paroxetine discussed previously, it could be speculated that an interaction might occur in the distribution of drugs because of their interaction with the multidrug resistance transporter 1 transporter p-glycoprotein (Pgp). Paroxetine is a strong inhibitor of Pgp (Weiss et al., 2003), whereas MDMA seems to be a weak inhibitor (Ketabi-Kiyanvash et al., 2003). Alternatively, neurotoxicity induced by MDMA is dependent on Pgp, because in *mdr1a* knockout mice alterations in the dopamine transporter are reduced compared with wild-type mice (Mann et al., 1997). Some preliminary studies have suggested that paroxetine as well as other amines bearing a methylenedioxy group alter MDMA disposition into the brain (Hashimoto et al., 1993). Nevertheless, when considering in vitro results and concentrations needed to reach an inhibitory effect of paroxetine on Pgp, with the plasma concentrations reached for both paroxetine and MDMA in this study (Segura et al., 2005), a drug interaction seems unlikely (Hashimoto et al., 1993).

Furthermore, we reported previously that paroxetine decreased to approximately one half the MDMA-induced stimulation of cortisol and prolactin and that MDMA-induced immune dysfunction was mostly counteracted by paroxetine (Pacifici et al., 2004).

In summary, this controlled trial shows that pretreatment with paroxetine significantly attenuates MDMA-related physiological and psychological effects, further supporting

the involvement of SERT in the pharmacological actions of MDMA. An MDMA and paroxetine interaction causing important decreases in the euphoric and stimulatory effects of MDMA would make this drug combination less desirable for users. However, marked decrease in the positive effects of MDMA, which in turn are being sought by users, may be responsible for consumption of higher doses of MDMA (e.g., depressive MDMA users under treatment with SSRIs), with implications for the increase of potential life-threatening toxic effects of the drug.

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**References**

Battaglia G, Brooks BP, Kulsakdinun C, and De Souza EB (1988) Pharmacologic profile of MDMA (3,4-methylenedioxymethamphetamine) at various brain recognition sites. *Eur J Pharmacol* **149:**159–563.

Bertelsen KM, Venkatakrishnan K, Von Moltke LL, Obach RS, and Greenblatt DJ (2003) Apparent mechanism-based inhibition of human CYP2D6 in vitro by paroxetine: comparison with fluoxetine and quinidine. *Drug Metab Dispos* **31:**289–293.

Brauer LH, Rukstalis MR, and de Wit H (1995) Acute subjective responses to paroxetine in normal volunteers. *Drug Alcohol Depend* **39:**223–230.

Cami J, Farre M, Mas M, Roset PN, Poudevida S, Mas A, San L, and de la Torre R (2000) Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. *J Clin Psychopharmacol* **20:**455–466.

Cleary L and Docherty JR (2003) Actions of amphetamine derivatives and cathinone at the noradrenaline transporter. *Eur J Pharmacol* **476:**31–34.

de la Torre R, Farre M, Roset PN, Lopez CH, Mas M, Ortuno J, Menoyo E, Pizarro N, Segura J, and Cami J (2000) Pharmacology of MDMA in humans. *Ann NY Acad Sci* **914:**225–237.

Farré M, de la Torre R, Llorente M, Lamas X, Ugena B, Segura J, and Camí J (1993) Alcohol and cocaine interactions in humans. *J Pharmacol Exp Ther* **266:**1364–1373.

Farre M, de la Torre R, Mathuna BO, Roset PN, Peiro AM, Torrens M, Ortuno J, Pujadas M, and Cami J (2004) Repeated doses administration of MDMA in humans: pharmacological effects and pharmacokinetics. *Psychopharmacology (Berl)* **173:**364–375.

Green AR, Mechan AO, Elliott JM, O'Shea E, and Colado MI (2003) The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacol Rev* **55:**463–508.

Gudelsky GA and Nash JF (1996) Carrier-mediated release of serotonin by 3,4-methylenedioxymethamphetamine: implications for serotonin-dopamine interactions. *J Neurochem* **66:**243–249.

Hashimoto K, Maeda H, Hirai K, and Goromaru T (1993) Drug effects on distribution of [3H]3,4-methylenedioxymethamphetamine in mice. *Eur J Pharmacol* **228:**247–256.

Hernández-López C, Farré M, Roset PN, Menoyo E, Pizarro N, Ortuño J, Torrens M, Camí J, and de la Torre R (2002) 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) and alcohol interactions in humans: psychomotor performance, subjective effects, and pharmacokinetics. *J Pharmacology Exp Ther* **300:**236–244.

Heydari A, Yeo KR, Lennard MS, Ellis SW, Tucker GT, and Rostami-Hodjegan A (2004) Mechanism-based inactivation of CYP2D6 by methylenedioxymethamphetamine. *Drug Metab Dispos* **32:**1213–1217.

Ketabi-Kiyanvash N, Weiss J, Haefeli WE, and Mikus G (2003) P-glycoprotein modulation by the designer drugs methylendioxymethamphetamine and parametho xyamphetamine. *Addict Biol* **8:**413–418.

Koch S and Galloway MP (1997) MDMA induced dopamine release in vivo: role of endogenous serotonin. *J Neural Transm* **104:**135–146.

Kotzailias N, Marker M, and Jilma B (2004) Early effects of paroxetine on serotonin storage, plasma levels, and urinary excretion: a randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol* **24:**536–539.

Lamas X, Farré M, Llorente M, and Cami J (1994) Spanish version of the 49-item short version of the Addiction Research Center Inventory (ARCI). *Drug Alcohol Depend* **35:**203–209.

Liechti ME, Baumann C, Gamma A, and Vollenweider FX (2000) Acute psychological effects of 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy") are attenuated by the serotonin uptake inhibitor citalopram. *Neuropsychopharmacology* **22:**513–521.

Liechti ME and Vollenweider FX (2000a) Acute psychological and physiological effects of MDMA ("Ecstasy") after haloperidol pretreatment in healthy humans. *Eur Neuropsychopharmacol* **10:**289–295.

Liechti ME and Vollenweider FX (2000b) The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') in healthy volunteers. *J Psychopharmacol* **14:**269–274.

Mann H, Ladenheim B, Hirata H, Moran TH, and Cadet JL (1997) Differential toxic effects of methamphetamine (METH) and methylenedioxymethamphetamine (MDMA) in multidrug-resistant (mdr1a) knockout mice. *Brain Res* **769:**340–346.

Mas M, Farre M, de la Torre R, Roset PN, Ortuno J, Segura J, and Cami J (1999) Cardiovascular and neuroendocrine effects and pharmacokinetics of 3,4-methylenedioxymethamphetamine in humans. *J Pharmacol Exp Ther* **290:**136–145.

McCann UD and Ricaurte GA (1993) Reinforcing subjective effects of (+/−) 3,4-Methylenedioxymethamphetamine ("ecstasy") may be separable from its neurotoxic actions: clinical evidence. *J Clin Psychopharmacol* **13:**214–217.

McDaid J and Docherty JR (2001) Vascular actions of MDMA involve alpha1 and alpha2-adrenoceptors in the anaesthetized rat. *Br J Pharmacol* **133:**429–437.

Mechan AO, Esteban B, O'Shea E, Elliott JM, Colado MI, and Green AR (2002) The pharmacology of the acute hyperthermic response that follows administration of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') to rats. *Br J Pharmacol* **135:**170–180.

O'Shea E, Esteban B, Camarero J, Green AR, and Colado MI (2001) Effect of GBR 12909 and fluoxetine on the acute and long term changes induced by MDMA ('ecstasy') on the 5-HT and dopamine concentrations in mouse brain. *Neuropharmacology* **40:**65–74.

Pacifici R, Pichini S, Zuccaro P, Farre M, Segura M, Ortuno J, Di Carlo S, Bacosi A, Roset PN, Segura J, et al. (2004) Paroxetine inhibits acute effects of 3,4-methylenedioxymethamphetamine on the immune system in humans. *J Pharmacol Exp Ther* **309:**285–292.

Pizarro N, Ortuno J, Farre M, Hernández-Lopez C, Pujadas M, Llebaria A, Joglar J, Roset PN, Mas M, Segura J, et al. (2002) Determination of MDMA and its metabolites in blood and urine by gas chromatography-mass spectrometry and analysis of enantiomers by capillary electrophoresis. *J Anal Toxicol* **26:**157–165.

Poudevida S, Farré M, Roset PN, and Camí J (2003) Construcción de un cuestionario para la Valoración de los Efectos Subjetivos de Sustancias con Potencial de Abuso (VESSPA): evaluación del éxtasis. *Adicciones* **15:**115–126.

Rothman RB, Baumann MH, Dersch CM, Romero DV, Rice KC, Carroll FI, and Partilla JS (2001) Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse* **39:**32–41.

Rothman RB and Baumann MH (2002) Therapeutic and adverse actions of serotonin transporter substrates. *Pharmacol Ther* **95:**73–88.

Sánchez C and Hyttel J (1999) Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding. *Cell Mol Neurobiol* **19:**467–489.

Sanchez V, Camarero J, Esteban B, Peter MJ, Green AR, and Colado MI (2001) The mechanisms involved in the long-lasting neuroprotective effect of fluoxetine against MDMA ('ecstasy')-induced degeneration of 5-HT nerve endings in rat brain. *Br J Pharmacol* **134:**46–57.

Schmidt CJ (1987) Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine. *J Pharmacol Exp Ther* **240:**1–7.

Segura M, Farre M, Pichini, S Peiro AM, Roset PN, Ramirez A, Ortuno J, Pacifici R, Zuccaro P, Segura J, et al. (2005) Contribution of cytochrome P450 2D6 to 3,4-methylenedioxymethamphetamine disposition in humans: use of paroxetine as a metabolic inhibitor probe. *Clin Pharmacokinet* **44:**649–660.

Stein DJ and Rink J (1999) Effects of "Ecstasy" blocked by serotonin reuptake inhibitors. *J Clin Psychiatry* **60:**485.

Tancer M and Johanson CE (2007) The effects of fluoxetine on the subjective and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology (Berl)* **189:**565–573.

Tucker GT, Lennard MS, Ellis SW, Woods HF, Cho AK, Lin LY, Hiratsuka A, Schmitz DA, and Chu TY (1994) The demethylenation of methylenedioxymethamphetamine ("ecstasy") by debrisoquine hydroxylase (CYP2D6). *Biochem Pharmacol* **47:**1151–1156.

Weiss J, Dormann S-M G, Martin-Facklam M, Dormann SM, and Haefeli WE (2003) Inhibition of P-glycoprotein by newer antidepressants. *J Pharmacol Exp Ther* **305:**197–204.

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