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Pharmacological Interaction Between 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) and Paroxetine: Pharmacological effects and pharmacokinetics

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MDMA-paroxetine interaction

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Number of text pages: 30

Number of tables: 2

Number of figures: 3

Number of references: 40

Number of words in the Abstract: 221

Number of words in the Introduction: 516

Number of words in the Discussion: 1352

ABBREVIATIONS:

MDMA, 3,4-Methylenedioxymethamphetamine, SSRI, selective serotonin uptake inhibitors; 5-HT, serotonin, CYP2D6, cytochrome P-450 2D6 isoenzyme; HMMA, 3-methoxy-4-hydroxymethamphetamine, SERT, serotonin membrane reuptake transporter, 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, PCAG, pentobarbital-chlorpromazine-alcohol group, MBG, morphine-benzedrine group, LSD, lysergic acid diethylamine group, BG, benzedrine group, A, amphetamine group, SED, sedation
scale, ANX, psychosomatic anxiety scale, PER, changes in perception scale, SOC, pleasure and sociability scale, ACT, activity and energy scale, PSY, psychotic symptoms scale, HHMA, 3,4-dihydroxymethamphetamine, MDA, 3,4-methylenedioxyamphetamine, HMA, 4-hydroxy-3-methoxyamphetamine, ANOVA, analysis of variance, NET, norepinephrine membrane reuptake transporter, MDR1, multidrug resistance transporter; Pgp, P-glycoprotein
Abstract

3,4-Methylenedioxyamphetamine (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 SSRIs. A clinical trial was designed where subjects pre-treated 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 aim of the study was to evaluate the pharmacodynamic and pharmacokinetic interaction between paroxetine and MDMA in humans. A randomized, double-blind, cross-over, 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 of paroxetine (or placebo) orally for the three 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 HMMA plasma concentrations suggest a metabolic interaction of paroxetine and MDMA. These data shows 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.
Introduction

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; Hernandez-Lopez et al., 2002; Farré et al., 2004).

During the 1990’s the simultaneous use of MDMA and 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 the 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). Case reports of the interaction between MDMA and citalopram, paroxetine, or fluoxetine showed conflicting results with observed blockage or reinforcement of MDMA effects (Stein and Rink, 1999; McCann and Ricaurte 1993).

Experimental studies of the pharmacologic 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 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 appears to attenuate both MDMA-related physiologic effects (cardiovascular activity) and subjective effects of positive mood, increase extraversion, and self-confidence (Liechti et al., 2000; Liechti and Vollenweider 2000a).

One difference between the SSRIs is their potential to cause drug-drug interactions through inhibition of cytochrome-P450 (CYP) isoforms. While citalopram appears to have little effect on the major CYP isoforms, two drugs experimentally consumed by MDMA users, paroxetine and fluoxetine, are potent inhibitors of CYP2D6. As 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 worth to test if 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 pre-treated 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 units per day). Eligible subjects were interviewed by a psychiatrist (structured clinical interview...
for DSM-IV) in order 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 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 Ethical Committee of the Institut Municipal d’Assistència Sanitària (IMAS), Barcelona, and authorized by the Spanish Ministry of Health.

Study subjects had a mean age of 24 years (range 19–34), mean weight of 71.0 kg (range 56.5–84.0), and mean height of 177.0 cm (range 167.5–190). The group of participants included both current smokers (n = 8) and non-smokers (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 history of abuse or drug dependence according to DSM-IV criteria (except for nicotine dependence) and had never 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 thirteenth volunteer was withdrawn from the study due to the presence of paroxetine-related adverse effects. Following 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 08:00h after an
overnight fast and had an indwelling intravenous catheter inserted into a subcutaneous
vein in the forearm of the non-dominant 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 09:00h in fasting conditions.
Taking into account the average \( T_{\text{max}} \) of MDMA and paroxetine (2 h for MDMA and 5 h
for paroxetine) MDMA was administered 3 hours after paroxetine (12:00h) to obtain
maximum plasma concentrations of both drugs at the same time (14:00h).

In order to prevent any possible anticipatory response, subjects were told that
they will receive two types of drugs. In the first study day, 1 capsule containing
paroxetine or placebo, in the second study day, 1 capsule containing paroxetine or
placebo, and in the third study day, 1 capsule containing paroxetine or placebo
followed 3 hours later by 2 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
(Mas et al., 1999; Brauer et al., 1995). Paroxetine was supplied as Seroxat®
(GlaxoSmithKline, Tres Cantos, Madrid, Spain) and 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 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 hours; on day 2 at 0 and 3 hours; 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, Tampa, FL).

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; de la Torre et al., 2000; Cami J et al., 2000; Hernández-Lopez et al., 2002; Farré et al., 2004). 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 seconds. 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 hours; on day 2 at 0 and 3 hours; 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: PCAG (pentobarbital-chlorpromazine-alcohol group, a measure of sedation); MBG (morphine-benzedrine group, a measure of euphoria); LSD (lysergic acid diethylamine group, a measure of dysphoria and somatic symptoms); BG (benzedrine group, a stimulant scale consisting mainly of items relating to intellectual efficiency and energy); and A (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 hours; on day 2 at 0 and 3 hours; 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 includes six scales: sedation (SED), psychosomatic anxiety (ANX), changes in perception (PER), pleasure and sociability (SOC), activity and energy (ACT), and psychotic symptoms (PSY). Each scale consists of six questions with a five-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 hours, on day 2 at 0 hours, 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 hours; on day 2 at 0 hours; 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 hours 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 hours after MDMA administration). Blood was collected in heparinized tubes and centrifuged at 1100 x g and 4°C for 10 minutes. 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 hours) and immediately acidified with 1mL 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 as 3,4-dihydroxymethamphetamine
(HHMA), 3,4-methylenedioxyamphetamine (MDA) and 4-hydroxy-3-methoxyamphetamine (HMA) were determined in blood and urine. In addition samples were collected to determine immunological parameters and hormones. These results have been previously published (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 x 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 x time interaction.

With regard to plasma concentrations of MDMA, the following experimental pharmacokinetic parameters were obtained: peak concentration ($C_{\text{max}}$), time taken to reach peak concentration ($t_{\text{max}}$), and area under the concentration-time curve (AUC) from 0 to 27 h. AUC values were calculated by the trapezoidal rule. The Student t test ($C_{\text{max}}, \ AUC$) and the Wilcoxon test ($t_{\text{max}}$) were used for statistical analysis. Pharmacokinetic parameters were obtained with use of specific functions of computer program (PK Functions for Microsoft Excel, Microsoft Corporation, USA).
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 $E_{\text{max}}$ measurements between placebo and paroxetine during the first two days of administration except a significant increase in systolic blood pressure during paroxetine administration (peak difference 8 mmHg). 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 Figure 1. MDMA alone 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 $E_{\text{max}}$ values, systolic blood pressure decreased by 12 mm Hg, diastolic blood pressure by 5 mmHg and heart rate by 14 bpm. MDMA induced mydriasis was reduced drastically by the paroxetine treatment from 3.33 mm to 1.23 mm (peak difference). A significant decrease in the rise of oral temperature produced by MDMA alone was observed after paroxetine pre-treatment (peak difference 0.3°C).

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

**Subjective Effects**

Subjective effects are shown in Figures 2 and 3. Pre-treatment 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-A 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 perception of lights”, “different or altered body sensation”, and “different or unreal surroundings”. Neither pretreatment with paroxetine nor MDMA alone produced significant changes in the scales of PER and PSY of VESSPA, as well as in the VAS scores for “bad effects”, “hallucinations”, “fear”, and “depression”. No differences were observed as a function of treatment condition in sedation scales (ARCI-PCAG, VESSPA-SED). 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 co-administered with paroxetine increased by 22% (AUC)
and 16% (C_max) while 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 elsewhere (Segura et al., 2005).

**Discussion**

We studied the pharmacologic 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 3 subsequent days before MDMA administration with two purposes. Firstly, to achieve nearly steady-state paroxetine plasma concentrations promoting high SERT occupancy rates and consequently a possible pharmacodynamic interaction, and secondly, to inhibit CYP2D6 activity to a degree that would significantly impair MDMA metabolic disposition (Bertelsen at al., 2003; Kotzaialias et al., 2004). In fact, paroxetine increased MDMA plasma concentrations approximately 30% and 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 appears 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 (Farre 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, while MDMA must be transported into nerve terminals to promote neurotransmitter release, paroxetine binds to the carrier but 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 while MDMA binding properties are 300-fold lower ($K_i=0.34 \mu M$) (Sanchez and Hyttel, 1999; Battaglia et al., 1988). *In vitro* studies have shown that fluoxetine inhibits MDMA-induced release of serotonin into the synaptic space (Gudelsky and Nash, 1996) and there are some evidences that pretreatment with SSRIs reduces some MDMA-related effects (Liechti et al., 2000; Liechti and Vollenweider, 2000a, 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 previously described 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 to 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 prior to 1.5 mg/kg MDMA (Liechti and Vollenweider, 2000a; 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 (NET) with a similar IC₅₀ for NE than that observed for 5-HT and SERT (55.6 nM vs 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 NET (Cleary and Docherty, 2003), so that a reduction of these effects here observed may support a possible 5-HT-mediated release of NE. On the other hand, some reports link α₁ and possibly α₂ adrenoreceptors and 5-HT2 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. Since 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 completely 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 to 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, 2000b). On the other hand, 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, 2000a; 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-HT2 receptors (Battaglia et al., 1988; Koch and Galloway, 1997) and 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 their interaction with the MDR1 transporter, p-glycoprotein (Pgp). Paroxetine is a strong inhibitor of Pgp (Weiss et al., 2003) while MDMA appears to be a weak one (Ketabi-Kiyavash et al., 2003). On the other hand, neurotoxicity induced by MDMA is dependent on Pgp, as in mdr1a knockout mice alterations in the dopamine transporter are reduced when compared to 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 SSRIIs) with implications for the increase of potential life-threatening toxic effects of the drug.
Acknowledgments

The authors thank Esther Menoyo, RN, and Isabel Sánchez, RN, for technical assistance, and Marta Pulido, MD, for editing the manuscript and for editorial assistance.
References


Footnotes

This study was supported by Fondo de Investigación Sanitaria, Madrid, Spain (grants FIS 97/1198, FIS 98/0181, FIS 00/0777 and FIS 01/1336), Generalitat de Catalunya, Barcelona, Spain (GENCAT-CIRIT; grant 2001SGR00407), and “Area Progetto Droga”, Instituto Superiore di Sanità, Rome, Italy. S. Abanades is recipient the grant “Ayudas para contratos post Formación Sanitaria Especializada”, Instituto de Salud Carlos III, Spain.
Legends for figures

**Figure 1.** Physiological effects after administration of 100 mg MDMA following a three doses regimen of 20 mg paroxetine or placebo (n=12). Paroxetine or placebo were administered at 0h and MDMA at 3h. From left to right: time course, Emax3-9h and AUC3-9h (□ = paroxetine, ○ = placebo). The following symbols denote statistical significance: **/ □ = p<0.01, */ □ = p<0.05.

**Figure 2.** Subjective effects (ARCI subscales) after administration of 100 mg MDMA following a three doses regimen of 20 mg paroxetine or placebo (n=12). Paroxetine or placebo were administered at 0h and MDMA at 3h. From left to right: time course, Emax3-9h and AUC3-9h (□ = paroxetine, ○ = placebo). The following symbols denote significance: **/ □ = p<0.01, */ □ = p<0.05.

**Figure 3.** Subjective effects (VAS scales) after administration of 100 mg MDMA following a three doses regimen of 20 mg paroxetine or placebo (n=12). Paroxetine or placebo were administered at 0h and MDMA at 3h. From left to right: time course, Emax3-9h and AUC3-9h (□ = paroxetine, ○ = placebo). The following symbols denote significance: **/ □ = p<0.01, */ □ = p<0.05.
Table 1. Results of statistical analysis of variables that presented significant differences after MDMA 100 mg administration between placebo and paroxetine conditions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MDMA-Placebo vs. MDMA-Paroxetine, day 3</th>
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<tr>
<td></td>
<td></td>
<td>AUC Emax Time x Condition</td>
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<tr>
<td></td>
<td></td>
<td>F p</td>
<td>F p</td>
<td>F p</td>
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<tr>
<td></td>
<td></td>
<td>(d.f.: 1, 11)</td>
<td>(d.f.: 1, 11)</td>
<td>(d.f.: 10, 110*)</td>
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<tr>
<td><strong>Physiological Parameters</strong></td>
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<tr>
<td>Systolic Blood Pressure</td>
<td>5.94 0.033 22.20 0.001 4.13 &lt;0.001</td>
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<tr>
<td>Diastolic Blood Pressure</td>
<td>0.27 0.613 1.75 0.213 3.97 &lt;0.001</td>
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<tr>
<td>Heart Rate</td>
<td>3.39 0.093 7.64 0.018 3.11 0.002</td>
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<tr>
<td>Oral Temperature</td>
<td>2.01 0.184 5.33 0.041 2.04 0.036</td>
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<tr>
<td>Pupil Diameter</td>
<td>39.02 &lt;0.001 70.35 &lt;0.001 31.14 &lt;0.001</td>
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<tr>
<td><strong>Psychomotor performance</strong></td>
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<td>DSST correct</td>
<td>0.15 0.702 0.15 0.705 2.21 0.034</td>
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<tr>
<td>Reaction time errors</td>
<td>4.00 0.071 5.65 0.037 1.63 0.129</td>
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<tr>
<td>Pauli total</td>
<td>0.03 0.877 0.88 0.367 4.18 0.013</td>
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<tr>
<td>Pauli correct</td>
<td>0.13 0.723 1.38 0.265 4.62 0.008</td>
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<td>Pauli errors</td>
<td>0.25 0.626 0.17 0.872 3.41 0.029</td>
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<td>Maddox wing</td>
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<td><strong>Subjective effects</strong></td>
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<td>VAS</td>
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<tr>
<td>Stimulated</td>
<td>27.04 &lt;0.001 14.39 0.003 7.50 &lt;0.001</td>
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<tr>
<td>High</td>
<td>41.66 &lt;0.001 34.16 &lt;0.001 10.88 &lt;0.001</td>
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<tr>
<td>Any effects</td>
<td>38.17 &lt;0.001 26.18 &lt;0.001 8.74 &lt;0.001</td>
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<td>Good Effects</td>
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<td>Liking</td>
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<td>Drowsiness</td>
<td>4.87 0.049 2.48 0.144 1.15 0.330</td>
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<tr>
<td>Changes in lights</td>
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<td>Dizziness</td>
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<td>Different body sensation</td>
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<td>Different surroundings</td>
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<tr>
<td><strong>ARCI</strong></td>
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<td>ARCI-MBG</td>
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<tr>
<td>ARCI-LSD</td>
<td>6.85 0.024 1.121 0.312 2.13 0.028</td>
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<tr>
<td>ARCI-BG</td>
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<td>ARCI-A</td>
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<td><strong>VESSPA</strong></td>
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<td>VESSPA-ANX</td>
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<tr>
<td>VESSPA-SOC</td>
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<td>VESSPA-ACT</td>
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</table>

Abbreviations: AUC: area under the curve from 3 to 9 hours; Emax: peak effects from 3 to 9 hours; F = ANOVA F value; p = statistical significance level; d.f.: degrees of freedom.

*For Psychomotor performance tasks d.f. were 8, 88; For VESSPA questionnaire d.f. were 3, 33
Table 2. Pharmacokinetics of MDMA and HMMA after administration of 100 mg MDMA following a three doses regimen of 20 mg paroxetine or placebo (n=12). Values are mean and standard deviation (SD). ** Significant difference between placebo and paroxetine conditions, paired Student t-test or Wilcoxon test (p<0.01)

<table>
<thead>
<tr>
<th></th>
<th>C$_{\text{max}}$ (µg/L)</th>
<th>t$_{\text{max}}$ (h)</th>
<th>K$_{\varepsilon}$ (h$^{-1}$)</th>
<th>AUC$_{0-21}$ (µg/L*h)</th>
<th>t$_{1/2}$ (h)</th>
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<td><strong>MDMA</strong></td>
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<td>paroxetine</td>
<td>246.62**</td>
<td>1.75</td>
<td>0.0853</td>
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<td>0.66</td>
<td>0.0143</td>
<td>661.68</td>
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</table>
Figure 1.
Figure 2.
Figure 3.