ADMINISTRATION OF 3,4 METHYLENDIOXY-METHAMPHETAMINE (MDMA) TO WOMEN WITH CHRONIC POST TRAUMATIC STRESS DISORDER (PTSD) AS A CONSEQUENCE OF SEXUAL ASSAULT. A DOSE FINDING PILOT STUDY.

PROTOCOL FOR A CLINICAL STUDY

Spanish Drug Agency Code # 99-0309

PROTOCOL CODE:DPBS/HPM/MDMA/1 (Amendment # 2, 27-12-99)

Biological Psychology and Health Department
Faculty of Psychology. Universidad Aut noma de Madrid
Hospital Psiqui trico de Madrid

SPONSOR:
Biological Psychology and Health Department
Faculty of Psychology. Universidad Aut noma de Madrid
28049 Cantoblanco
Madrid, Spain

1. ABSTRACT

0. Type of application

Pilot Clinical Study of a therapeutic type on physically healthy women diagnosed with chronic posttraumatic stress disorder according to the DSM-IV criteria as a consequence of a sexual assault. The medication is not sold legally. It is included in Schedule I of the United Nations Convention on Psychotropic Substances. Its therapeutic use is not authorized. First clinical study of a new indication.

1. Identification of the sponsor

Departamento de Psicolog a Biol gica y de la Salud
Facultad de Psicolog a, Universidad Aut noma de Madrid
28049 Cantoblanco. Madrid, Espa a

2. Title of the Clinical Trial

Administration of 3,4-methylendioxy-methamphetamine (MDMA) to women suffering from chronic posttraumatic stress disorder (PTSD) as a consequence of a sexual assault. Dose finding pilot study.

3. Protocol Code

DPBS/HPM/MDMA/1 (Third version, 27-12-99)

4. Main researchers: Work address

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5. Centers where the study is expected to be carried out

Hospital Psiqui trico de Madrid
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6. Clinical Research Ethical Committees that have approved the study

Approved by the CEIC of the Hospital Universitario "La Paz", on July 6th 1999.
Code of the CEIC protocol: HULP 99-1007.

7. Name and qualification of the person responsible for the monitoring

Dr. Gregorio G mez-Jarabo, Doctor in Biology
Departamento de Psicolog a Biol gica y de la Salud
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8. Experimental drug and control: dose, pharmaceutical form, mode of administration, therapeutic group

Experimental drug:

a) 3,4-methylendioxy-methamphetamine (MDMA), in capsule form containing 50, 75, 100, 125 and 150 mg of active principle. Oral administration. Phenylethylamine by-product (psychostimulant).

Control drug:

b) Placebo, in capsule form containing 100 mg lactose prepared by the Chemist Service at the Hospital Psiqui trico de Madrid.

All the medications will be presented in capsules of identical size and color, as means of disguising their content for the participants and researchers alike.

The MDMA will be obtained from police cache through the mediation of the Drugs Security General Sub-department, Narcotics Division of the Spanish Drugs Agency. The purity of the product will be tested. This analysis will take place at the Pharmacology Department of

the IMIM (Institut Municipal d Investigaci M dica) in Barcelona.

9. Stage of the Clinical Trial

Pilot Clinical Trial with healthy women who suffer from chronic posttraumatic stress disorder (PTSD) following a sexual assault.

10. Aims

Aims:

1. To determine the most effective therapeutic dose of MDMA in a psychotherapeutic context for women with chronic PTSD following a sexual assault.

2. To evaluate the therapeutic effectiveness of MDMA in a psychotherapeutic context for women with chronic PTSD following a sexual assault.

11. Design

Placebos and single doses of MDMA (50, 75, 100, 125 and 150 mg), will be administered to several limited groups of patients. The design will be double-blind, randomized and controlled with a placebo. Each of the groups will undergo an experimental stage. The doses will be studied on an incremental basis and shall be increased only if tolerance is satisfactory.

12. Disorder or syndrome under study

The object of the study will be chronic posttraumatic stress disorder suffered by physically healthy women following a sexual assault.

13. Main variable for assessment

- Posttraumatic stress disorder: Scale of Severity of the Symptoms of Posttraumatic Stress disorder.

Other variables:

- Personal and socio-demographic data: semi-structured interview regarding sexual aggression.
- Anxiety: The State Trait Anxiety Inventory (STAI). State version.

- Depression: The Beck Depression Inventory (BDI) and self-applied scale for the assessment of depression (HRS).
- Phobias: MFS III The Modified Fear Scale by Veronen and Kilpatrick. Subscale of fears related to rape.
- Maladjustment: Maladjustment Scale.
- Self Esteem: The Rosenberg Self Esteem Scale (SE/R).
- Side-effects: The UKU Side-Effects Rating Scale.
- Subjective Effects: Hallucinogen Subjective Effects Rating Scale (HRS-S).
- Therapeutic Alliance: Helping Alliance questionnaire (HAq).

14. Population under study and total number of patients

A total of 29 physically healthy women suffering from chronic PTSD will be included.

15. Duration of the treatment

The dose-finding pilot study consists of a single one day session. In each session (experimental day), one of the possible treatments (MDMA o placebo), will be administered in the form of 1 capsule to be taken orally.

16. Schedule and expected finishing date

The study is expected to take place throughout a one and a half year period.

2. INDEX

APPENDIX

3. GENERAL INFORMATION

A. IDENTIFICATION OF THE TRIAL

B.

A.1. Code of the protocol: DPBS/HPM/MDMA/1 (First version, 1-2-99; First modification, 19-11-99; second modification, 27-12-99)

A.2. Title: Administration of 3,4-methylendioxy-metanphetamine (MDMA) to women suffering from chronic posttraumatic stress disorder (PTSD) following a sexual assault. Dose-finding pilot study.

B. TYPE OF CLINICAL STUDY

Dose-finding pilot study. The drug is not commercialized. It is included in Schedule I of the United Nations Convention on Psychotropic Substances. Its therapeutic use is not authorized. The MDMA will be obtained from the police premises through the mediation of the Drug Security General Sub-department, Narcotics Division of the Spanish Drug Agency. First clinical study for a new indication.

C. DESCRIPTION OF PRODUCTS UNDER STUDY (EXPERIMENTAL AND CONTROL)

C.1. GENERIC NAME, COMMERCIAL NAME AND COUNTRIES WHERE IT IS MARKETED

Experimental drug:

3,4-methylendioxy-metamphetamine (MDMA), capsules containing 50, 75, 100, 125 and 150 mg of active principle.

Control drug:

Placebo, in capsule form containing lactose (100 mg) prepared by the Chemist Service at the Hospital Psiqui trico de Madrid.

All drugs will be presented in identical size and color capsules as means to disguise their contents from both researchers and participants.

C.2. QUANTITATIVE AND QUALITATIVE COMPOSITION AND CHEMICAL

STRUCTURE.

Experimental drug:

3,4-methylendioxy-metamphetamine (MDMA), capsules containing 50, 75, 100, 125 and 150 mg of active principle.

Control drug:

Placebo, in capsule form containing lactose (100 mg) prepared by the Chemist Service at the Hospital Psiqui trico de Madrid.

C.3. MATERIALS SUBJECT TO THE COMPULSORY DECLARATION

Experimental drug:

MDMA, taken from seized cache, confirmed by chemical analysis.

Control drug:

Lactose 100 mg.

C.4. PHARMACEUTICAL FORM

Capsules.

C.5. ORGANOLEPTIC CHARACTERISTICS

Not applicable.

C.6. ENTITIES PROVIDING THE SAMPLES

Experimental drug:

MDMA, packaged by the Chemist Service at the Hospital Psiqui trico of Madrid. Seized cache provided by the Drug Security General Subdepartment, Narcotic Division of the Spanish Drug Agency.

Control drug:

Placebo, Chemist Service at the Hospital Psiqui trico of Madrid.

All the drugs will be packaged by the Chemist Service at the Hospital Psiqui trico of Madrid.

D. DETAILS REGARDING THE SPONSOR

Departamento de Psicolog a Biol gica y de la Salud
Facultad de Psicolog a, Universidad Aut noma de Madrid
28049 Cantoblanco. Madrid, Espa a.
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E. TECHNICAL DIRECTOR RESPONSIBLE FOR THE SUPPLY/CONTROL OF THE SAMPLES

E.1. MDMA and placebo
Mar a Jes s Vico Barranco. Clinical Pharmacist, H.P.M.

F. IDENTIFICATION OF THE MONITOR

Dr. Gregorio G mez-Jarabo
Departamento de Psicolog a Biol gica y de la Salud
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G. DETAILS REGARDING RESEARCHERS FOR THE STUDY

Main Researchers

Pedro Sopelana Rodr guez. Psychiatrist, H.P.M.
Jos Carlos Bouso Saiz. Psic logo, Psychology Department, U.A.M.

Clinical contributors:

Valent n Corc s Pando, M.D. in Psychiatry, H.P.M.
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M» Jes s Vico Barranco. Clinical Pharmacologist, H.P.M.
Beatriz de la Luz Navarro, Nursing Diploma, university student, H.P.M.
Ludgerio Espinosa Gil. Associate Professor of Methodology, Psychology Department, U.A.M.
C.I.S. Head of data processing.

H. CENTERS WHERE THE STUDY WILL TAKE PLACE

It is a one-center study taking place at:
Hospital Psiqui trico de Madrid
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I. EXPECTED DURATION OF THE TRIAL

The dose-finding pilot study consists of a single one-day session. In each session (experimental day) one of the possible treatments will be administered in the form of 1 capsule to be taken orally. The study is expected to take place within a one and a half year period.

4. JUSTIFICATION AND OBJECTIVES.

4.1. TOPIC BACKGROUND

1. Introduction

The use of psychoactive drugs with a therapeutic purpose is probably inherent to mankind. Its search was coupled with the need for nourishment since both, nutrition and cure of sickness, were fundamental for survival. Archaeological remains indicate that as early as Paleolithic man, psychoactive plants were used for healing, spiritual and hunting purposes (Furst, 1992). Certain hypothesis suggest that cave paintings such as those to be found at Altamira in northern Spain or those at Les Trois Fr res in the French Pyrenees, are in fact depictions of the tribe members ecstatic visions of hunting, religion and art, rather than prey depictions. Therefore it was not so much a portrayal of external reality but of the artist's visionary reality possibly induced by psychoactive substances (Lommel, 1963). Mckenna (1992) actually formulates a hypothesis presenting the highly hallucinogenic *Psilocybin* mushroom, as the precursor for the origin of the erect position of the first hominids in the African savannas.

Putting aside conjecture and moving to what is known, for many diverse cultures psychoactive drugs have been and continue to be mystical vehicles for communal integration and healing due to their strong capacity to induce altered states of consciousness (ASC). In the

remains of these still surviving primitive cultures, anthropologists describe numerous shamanic rites in which plants with psychoactive properties are used as a means to both diagnose and cure many of the endemic illnesses from which they suffer. Indeed Fericgla (1989) quotes a study by Erika Bourguignon in which more than 80% out of a sample of 488 cultures under study, used psychoactive substances for various purposes. Those cultures like the Inuit (Eskimos) whose environment does not allow for the presence of vegetation, resort to other vehicles such as meditation, fasting or sensorial isolation in order to achieve altered states of consciousness. The shaman makes use of these altered states of consciousness to enter the mythological world of his/her culture in order to diagnose illness or search for other information. In this way, the mental structures of his/her patient, who is normally also in an altered state, is reorganized so as to achieve the cure, which is but a better adaptation on the part of the subject to the cosmology of his culture (Fericgla, 1994).

Although the symptomatic treatment of physical illness was also practiced in antiquity, the medical model for symptomatic treatment of the cure of psychological disease or illness, was in fact incorporated by modern psychopharmacology. The discovery of anti-psychotic drugs was crucial for this change in the paradigm. However during the 50s and 60s, psychedelic substances were of great interest to psychiatry, due mainly to the discovery of LSD-25 (lysergic acid diethylamide) by the Swiss chemist Albert Hofmann. LSD-25 was used for clinical diagnosis as well as for the treatment of a series of mental and physical disorders, the published work runs into the thousands of articles (Hofmann, 1991). Aside from LSD, the substances most widely used were psilocybin (i.e. Leary *et al.*, 1965) and mescaline (i.e. Unger, 1963), giving way at a later date to substances with inferior hallucinogenic properties but greater potential for allowing communication like MDA- (i.e. Yensen *et al.*, 1976) and above all MDMA, as we will discuss later. The use of this kind of substances for the treatment of mental disorders supersedes the mere symptomatic treatment. In this case, the drug has no curative properties in its own right but produces a catalysis of emotional experiences when consumed by the patient during the psychotherapy session within a controlled framework, thus accelerating the psychotherapeutic process. Therefore it is a co-helper element for psychotherapy rather than a curative (symptomatic) element in itself.

2. MDMA or Ecstasy

2.1. History of MDMA

MDMA was first synthesized in 1912 by Merck laboratories and rediscovered by Alexander Shulgin in the 70s. The substance was originally synthesized by the German pharmaceutical company as a mediating agent in search for active therapeutic compounds. Although MDMA as such was never patented, the whole synthesis chain of which it was a part was patented (Shulgin, 1990). During the 50s the American military tested its toxicity on laboratory animals (Hardman *et al.*, 1978). The American chemist Alexander Shulgin was the first to discover the psychoactive properties of MDMA through a bioassay (Shulgin y Nichols, 1978). Having noted the special qualities of the drug, he offered it to the American psychiatrist Leo Zeff. After experimenting with the drug, Zeff dedicated the final years of his professional life to the training of a great number of American psychiatrists in its use, estimated to have been around 400 therapists (Saunders, 1993). Its use in a therapeutic context was rather large within the circle of Californian therapists, however, its use started to gradually shift toward a recreational context. This caused its prohibition by the FDA (Food and Drug Administration) in 1985, despite no fatal cases and only 8 emergency cases caused by its recreational use having being reported (Eisner, 1995).

In 1986 the DEA (Drug Enforcement Administration), disregarding judge Francis Young s advice suggesting that MDMA be included in Schedule III of controlled substances (Young, 1986), decided to include it in Schedule I instead. From then to now, only three methodologically controlled studies on human subjects measuring psychobiological variables (one in the USA, one in Barcelona and a third one in Switzerland) and one more measuring hormonal variables (Henry *et al.*, 1998) have been carried out. The final results for these three studies are yet to be published, unlike the preliminary data which will be discussed later. A study hoping to evaluate the safety and therapeutic effectiveness of MDMA on a group of women suffering from breast cancer, is currently in the process of seeking approval in the USA.

2.2. Toxicity of MDMA

If the number of complications resulting from its use is compared with the number of users, we can co nclude that the toxicity is quite low. The main studies on MDMA toxicity have focused on exploring its possible neurotoxic effects. Sufficient data is available from animal testing to categorically state that serotoninergic neurotoxicity has been noted in animals submitted to doses of between 10 to 100 times the average human dose for prolonged periods of time. Nevertheless, there are no controlled studies which prove neurotoxicity for humans.

Ricaurte *et al.* (1988) reported evidence of MDMA depleting the serotoninergic systems of the brain in primates with a single dose of between 2 and 3 times a human dose (5 mg/kg). However, a study by the same author also with primates, with doses of between 2,5-5 mg/kg, that is, slightly higher than that of humans, produced no neurotoxicity whatsoever anywhere in the brain (Ricaurte, 1993). This suggests that neurotoxicity in primates is dose-dependent and that it starts at 5 mg/kg, a higher dose than the average for humans.

As for humans, the only studies regarding neurotoxicity have been done retrospectively. Peroutka (1987) examined the cerebrospinal fluid in subjects with a history of MDMA use, with no variation found between the control group and the MDMA-using group. Ricaurte *et al.* (1990), in a similar study, found significant differences between the control group and the experimental group. The latter study however, has been criticized due to the fact that the control group, apart from having a history of consumption of other abused drugs, suffered from chronic back pain which seems to increase the spinal levels of 5-HT y 5-HIAA (Grob y Polland, 1997), serotonin and its main metabolism, respectively, which are often used to establish neurotoxicity markers for serotonin depletion.

A recent study by McCann *et al.* (1998) using neuroimaging techniques (Positron Emission Tomography) in order to measure MDMA-induced neurotoxicity among a group of users, compared to a group of non-users, found a 5-HT decrease in the consumers brains. Subjects who participated in this study had taken MDMA from 70 to 400 times, (228 times on average) in doses ranging from 150 to 1250 mg, the average dose being 386 mg. Moreover the majority of the subjects were polyconsumers of hallucinogens, amphetamines and phenylethylamines (amongst

them MDA, the neurotoxic properties of which seem clearer). Lastly, it is not clear if the two groups were rigorously defined in this study. In any case, not one subject from the MDMA group displayed neuropsychiatric disorders. This data is not suitable for extrapolation to subjects who take or may take low doses of MDMA on rare occasions with therapeutic aims. In fact, in order to state neurotoxicity, damage to neurons (structures) and not a decrease of neurotransmitters (functions), must be demonstrated. Furthermore, it is still to be proven that MDMA produces either structural damage or functional disorders when taken under the conditions set forth above. Strassman and Qualls (1995) administered DMT (a potent ultra-short effect hallucinogenic drug of the tryptamine family, structurally linked to serotonin and an active antiserotoninergic function) to two different groups of MDMA consumers, one consisted of heavy MDMA users, the other of occasional users. Significant differences were found between the two groups only in increase of pupil dilatation —of all the measured physiological parameters — being a smaller increase for the heavy consumers group. According to the author, these results contradict the expected outcome if MDMA had produced serotoninergic neurotoxicity in the latter group.

Usual doses administered in a psychotherapeutic context, are between 75 to 175 mg (1-2,5 mg/kg). For rats, the minimum dose capable of producing neurotoxicity on a long term bases, is for 10 mg/kg to be administered twice daily for four days (80 mg/kg in total). As for non-human primates, total doses of 20-80 mg/kg in a four day period can produce long term neurotoxicity. These doses, when extrapolated to humans, would be equal to 1,4-5,6 g in a four day period, which would mean between 15-56 medium doses in four days, a figure far from the MDMA administering regime used for humans in psychotherapeutic contexts (Hegadoren, *et al.*, 1999)

In conclusion, MDMA neurotoxicity in humans has not been demonstrated to date. As a matter of fact, neither functional nor behavioral deterioration associated with its consumption has been found in the subjects of the previously mentioned studies. On the other hand, phenfluramine, a related amphetamine with three times the neurotoxicity of MDMA, has been used for the treatment of obesity, among other disorders, with an estimated fifty million consumers in the past twenty five years. Functional or structural complications have not been reported from its use, which proves that a serotoninergic depletion (an aspect shared by both

substances) does not necessarily lead to neurological pathologies. Besides this, fluxotenine and other serotonin-receptor inhibitors tested on lab animals have been demonstrated to arrest MDMA neurotoxicity, which could perhaps be applicable to humans (McCann and Ricaurte, 1993). Whatever the case may be, more controlled and prospective studies are needed in order to accurately establish all the above mechanisms of the drug's activity.

Other pathologies have been described in the literature, such as hyperthermia (11 cases), stroke (8 cases), hyponatremia (9 cases), hepatotoxicity (29 cases), anxiety disorders (6 cases), depression disorders (7 cases), psychosis (13 cases), as well as thirty-seven deaths associated with MDMA consumption (Gamella and lvarez, 1997). Nevertheless, in the majority of these cases, no direct relation has been found between MDMA consumption and the pathology in question. In some cases the tests show a mixture with other substances, in others, previous physical pathologies seem to have been present, overdose, absence of significant levels of the drug in the plasma, etc. In very few cases, the cause-effect relation was clear, which leads to the presumption that the substance produces the alleged damage in an idiosyncratic manner. As well as this, the low proportion of problems reported among users and the complications registered in the literature, do not justify any clear declaration of MDMA toxicity, at least when taken within a safe environment, at a reasonable and known dosage, not in combination with other drugs and in a pathology-free state of health. In fact "the evidence shows that, in low doses, taken in a controlled situation without additional drugs or alcohol, by individuals free of a history of psychiatric disorders, the risks appear to be considerably low". (Grob y Poland, 1997).

2.3. Psychopharmacological properties of MDMA

The chemical name for MDMA is 3,4-methylendioxy-metamphetamine. It is therefore, an amphetamine-derived methoxylate with a chemical structure similar to that of mescaline. Its chemical molecule consists of a benzene ring whose dorsal root is a ethylamine chain.

MDMA has two isomers, or racemic forms: dextro and levo. Only the *dextro* form, as opposed to the rest of the psychedelic amphetamines, has psychoactive potential due to the N-metilation, which the molecule undergoes, and which causes it to lose its psychedelic qualities.

Therefore, it is problematic to classify the substance as a psychedelic (Nichols, 1986). Furthermore, the functional properties of MDMA offer scant evidence of inhibition of dopamine reuptake, although it seems to promote dopamine secretion. Because of its functional properties, there seems little reason to believe that there would be inhibitory activity in the reuptake of dopamine, although secretion is promoted (Cam , 1995), especially when we keep in mind the dopamine liberating properties of amphetamines, which is a stronger stimulant of the CNS. MDMA also differs from the other psychedelic amphetamines which act by binding with the serotonin receptors and limiting their action. MDMA liberates and inhibits the reuptake of 5-HT, presenting scarce agonistic activity in the serotonergic receptors. In fact, it seems that the neuronal damage seen in laboratory animals given massive doses is concentrated at the level of the axon and receptor, leaving the cellular structures intact (O'Hearn*et al.*, 1988). However, despite these findings, repeated use or high doses may provoke some type of hallucinogenic effect and, more clearly, stimulant effects.

MDMA may be psychoactive in doses as low as 50 mg. The average dose is between 75 and 125 mg. Effects begin between 30 and 60 minutes after ingestion, peaking at 2-3 hours, and disappearing after 6 hours. The psychological effects, as stated above, do not include visual or auditory hallucination or the stimulation characteristic of amphetamines. Such stimulant effects only appear in very high doses, in which the experience is often quite unpleasant. While MDMA does not produce perceptual alterations, it tends to provoke a strong emotional experience accompanied by euphoria, in which feelings of affection and empathy are unusually strong. Meanwhile, with no loss in lucidity neurotic fear is lessened, allowing increased sincerity and profound interpersonal communication (Grinspoon y Bakalar, 1986).

The secondary effects of the MDMA experience include tightening of the jaw, loss of appetite, stimulation and fatigue. In cases of high and repeated doses, secondary effects may include tachycardia, dryness of mouth, sweating, insomnia and muscular pain. An overdose can result in convulsions, arrhythmia, and circulatory problems which may appear in doses greater than 250 mg (Eisner, 1995).

Use of MDMA is contraindicated for subjects with cardiac problems, glaucoma, hypertension, circulatory problems, hepatic disorders, diabetes or hypoglycemia. There is no physical dependence associated with MDMA, although some data suggests the possibility of psychological dependence. Continued doses rapidly produce tolerance, but if the user increases the amount taken, the pleasant effects disappear, leading to a disagreeable experience.

In summary, we can say that although MDMA is structurally similar to amphetamines, its characteristic effects are rather dissimilar. Similarly, despite its structural affinity with mescaline, there are no hallucinogenic qualities in the experience. In truth, both amphetamines and mescaline belong to the phenethylamines, the synthetic derivatives of which number into the hundreds (Shulgin y Shulgin, 1992). MDMA is a pure molecule which, while lacking both amphetamine-like and hallucinatory properties, exhibits novel psychological properties. Rather than the amphetamine-like stimulation of the CNS or the perceptual alterations of mescaline, we see psychological changes that fundamentally affect the emotional sphere, allowing the subject to experience an unusual capacity for open, sincere communication with another as much as introspection in her/himself. (Escohotado, 1995). This is why this substance has been classified as an empathogen/entactogen.

2.4. Principal applications of MDMA in psychotherapy

When compared to other psychopharmacological agents, the elevated safety and low toxicity of psychedelic substances seem clear. In fact, the psychedelics are distinguished by their low toxicity (Hollister, 1978). According to Hollister *et al.* (1991), 70% of the deaths caused by drug toxicity are attributable to drugs legally prescribed —at a rate of over 300 million doses annually. Furthermore, the risks of psychological complications associated with psychedelics has been exaggerated. In reality, it seems that the risks of psychedelic-enhanced psychotherapy are the same as those for any other deep and emotional psychotherapy (Grinspoon y Bakalar, 1981).

Concentrating on the specific case of MDMA, this drug has been described as being relatively benign when compared to classic psychedelics such as LSD or mescaline — with effects that are shorter in duration, easier to control, and relatively peaceful —which amplifies

communicative capacity in therapy and allows the creation of an emotional context in which intimate communication can take place. Within this context, depressive problems and anxiety can be seen at a remove, without the ego-interference or changes in body-image associated with most psychedelics, thereby permitting us to create an ideal framework for establishing the therapeutic alliance (Grinspoon y Bakalar, 1986).

As explained above, substances classified as phenethylamines have been given two new names: empathogens and entactogens. One could say that MDMA is a prototype of both appellations. The term *entactogen* was coined by David Nichols, meaning, generating contact with the interior (Nichols, 1986); the term *empathogen* was first used by Ralph Metzner in reference to the state of empathy the substance tends to generate (Adamson and Metzner, 1988).

In the years before its use was made illegal, MDMA was used in the treatment of depression, of psychological aspects of serious medical illness (such as those of terminal cancer), of various types of neurosis and psychosis, and as a enhancement to spiritual growth. Its clearest benefits were seen, however, in the treatment of PTSD and in couples therapy, due to the drug s capacity to lower the emotional barriers that may exist between the psychotherapist and the client, thereby tightening the therapeutic alliance and allowing more significant work to take place with the patient s problems (Stafford, 1992; Eisner, 1995). It is well-known that empathy is an essential element in this all-important therapeutic alliance, and that the healing process is also a function of the patient s capacity for introspection. In that both these processes are dramatically assisted by MDMA, it is an ideal medication to assist in psychotherapy (Stafford, 1995).

2.5. Human studies with MDMA

To date, there are no controlled studies that demonstrate the effectiveness of MDMA in psychotherapy. From the mid-70s to the mid-80s it was used by private psychotherapists, which is why no controlled studies were conducted on its therapeutic function. A few studies have been published on the psychological effects of the substance on physically healthy subjects,

which we will discuss below, but they are all flawed by faulty methodologies. Before these studies were published, a symposium was organized at the Esalen Institute (California) to update and present all the data that had been garnered up to that point concerning the use of MDMA in psychotherapy. Additionally, MDMA was administered to 13 volunteer subjects. None of them experienced complications, and all found the experience to be emotionally intense. They all characterized the experience as having been very positive, and all agreed that the substance increased *insight.* Aside from this anecdotal experience, the most important information to emerge from the conference was that: 1) The only complication arising from the use of MDMA is occasional anxiety and a few autonomic physical symptoms; 2) MDMA is unique in its ability to ease communication, especially in couples therapy. Furthermore, in its ability to reduce psychological defenses and emotional fear, MDMA facilitates a more direct expression of feelings and opinions, making it extremely useful in the treatment of psychological traumas (Greer, 1985).

Greer and Tolbert (1986) gave MDMA to 29 subjects in the first study with human subjects within a clinical context. Phenomenological impressions were noted before, during and after the sessions. No psychological tests were given, nor were any laboratory studies undertaken to measure metabolic and other organic functions. The study was not double-blind, and there was no control group. Between 75 and 150 mg of MDMA were administered, and in some cases, an additional dose of between 50 and 75 after two hours, to prolong the experience and ease the descent. All the subjects took the MDMA with therapeutic objectives, which included a range of psychological disorders but no severe mental disorders. Many variables were analyzed: benefits during the session, undesirable effects, the sense of having achieved the objectives for the session, change in the disorder, changes in interpersonal relations, etc., with the results being significantly positive in each area studied. According to the authors, the most important conclusions were the following: 1) MDMA was physically safe for all subjects, exhibiting no serious physical side-effects (only one subject suffered secondary effects lasting more than one week), although the authors warned of potential risk to people suffering from cardiovascular problems; 2) The most important effect of MDMA consists in its ability to ease direct communication between people who are in an emotional relationship, increasing communication both during and after the session; 3) MDMA increases self-understanding and insight, hence its great usefulness in psychotherapy.

Downing (1986) gave MDMA to 21 healthy subjects with a previous history of drug use and measured cardiovascular response and alterations in biochemical parameters. In addition, all subjects underwent a neurological evaluation before, during and after the administration of a dose from 1.7-4.19 mg/kg (average dose was 2.5 mg/kg). Moderate biochemical changes were registered, and there was an increase in both heart rate and blood pressure in all subjects from 1-2 hours after administration, though all subjects remained within normal ranges in both readings. Sixty percent of the subjects had returned to their baseline levels after 6 hours, and the rest had returned to baseline levels 24 hours after taking the substance. No observable psychological damage occurred during the 24 hours of the experiment. Nor were any negative psychological effects observed in the three-month follow-up period. All the subject suffered from mydriasis, 38% from nystagmus and jaw-clenching was common. Jaw reflex as well as moderate problems with motor coordination and balance were also noted. The author concluded that this data supported the general impressions of the professionals that MDMA is reasonably safe and that it produces positive changes in mood, has remarkably consistent and psychologicallypredictable effects, which are transitory and free from any apparent serious clinical toxicity. Finally, the subjects felt that the substance was safe and helpful within a controlled experimental setting.

Despite the prohibition against the use of MDMA for clinical and experimentalobjectives, the Swiss government agreed to allow several psychotherapists to use psychedelic substances for strictly clinical use from 1988 to 1995. (This permission has been granted again recently). Gasser (1995; 1996) questioned all the subjects of these clinical sessions from these years (171 subjects in total), asking them to rate their satisfaction and improvement during and after their treatment. The results were the following:

	During	**After**
Significant improvement	46.3%	65%

	During	After
Small improvement	38.8%	25.6%
No change	5.8%	4.1%
Small worsening	4.2%	2.5%
Fluctuations	5%	2.5%

As far as the influence on subjective experience: 64.5% of the subjects reported their sessions to have been very important on an emotional level; 56.2% said they were very important on an interpersonal level; 48.8% showed significant changes in biographical insight; 36.4% considered the treatment to have been important as a help in decision-making. The author concluded that psycholytic psychotherapy (the administration of small doses of psychedelics to promote intense experience) is a safe treatment. (An extensive interview with the psychotherapists who used MDMA in Switzerland between 1988 and 1995, as well as an explanation of the techniques they used can be seen in Saunders (1993)).

Recently, three other studies have been conducted using MDMA in human subjects, and in which psychological and physiological measures have been taken. In the first study, by Grob (1996), a double-blind design was used and a dose from 0.75-1.0 mg/kg was administered to six physically healthy volunteers with a history of previous use. All the subjects tolerated the dosage well with no observable physical or psychological problems. The drug produced a slight increase in heart rate and blood pressure. In endocrine response, ACTH and prolactin levels were measured, both of which passed the usual levels with a dose of 0.75 mg/kg, and were clearly stimulated by the 1.0 mg/kg dosage. The results of the final phase of the study, which consisted of 18 subjects given a dose of from 1.0-1.75 mg/kg and 1.5-2.5 mg/kg have not yet been published. In this phase of the study, in addition to the measures mentioned above, the following were also noted: cortisol levels, arousal, hedonic response, and neuropsychological tests were given to measure possible deterioration in cognitive or behavioral functioning. The FDA is currently reviewing these data in order to determine whether or not to authorize a second phase of this research in which MDMA would be administered to a group of breast-cancer patients. The

objective would be to evaluate potential beneficial effects of MDMA in a psychotherapeutic context for attenuating the physical pain and psychological problems that result from their condition.

The second study in which MDMA has been administered to humans was conducted a the Institut Municipal d'Investigaci M dica (IMIM) in Barcelona, and is also awaiting publication. Both physiological and psychological variables were measured in search for the effects of MDMA. A pilot study was first undertaken in which doses of 50, 100 and 150 mg were administered. Later, the definitive study was undertaken in which 8 healthy volunteers with previous history of MDMA use were chosen. Vital signs, psychomotor skills and subjective effects were measured. The study was double-blind, with randomized group assignment, crossed and controlled.

On different days, the subjects received either placebo, 75 or 125 mg of MDMA, or 40 mg of d-amphetamine. The results showed that all the pharmaceutical agents increased the blood pressure and heart rate (the amphetamine had these effects later), the MDMA increased pupil diameter. While the amphetamine caused a slight increase in psychomotor performance, the higher dose of MDMA produced a slight decrease. With the MDMA, higher readings were taken for euphoria, well-being and pleasant sensations. Furthermore, in the MDMA group a small change in visual and bodily perception was noted. No hallucinatory changes were noted. Most of the readings were dose-dependent. The authors concluded that MDMA presents an elevated risk of abuse and causes important changes in blood pressure and heart rate. Its use outside of the clinical context, with elevated temperatures and physical activity may potentiate its cardiovascular toxicity (Cam *et al.*, 1997; Mas *et al.*, 1999).

The last controlled double-blind study using placebo in human subjects was conducted in Switzerland, and is also yet to be published. In this study, a dose of 1.7 mg/kg of MDMA was administered to 16 subjects with no previous experience with the substance. Neuropsychological measures were taken using both PET scanning (Positron Emission Tomography) and EEG. After the neurological tests were completed, psychometric questionnaires were given. Preliminary analysis indicates that MDMA may cause changes in the cerebral blood flow, with the changes being centered primarily in the cerebellum and prefrontal cortex. The results of the questionnaire suggest that MDMA produces an increase in well-being and positive affect. No hallucinatory

effect was noted, although visual perception was affected; optical illusions and intensification of color perception were noted. A significant increase in blood pressure was found, as well as an insignificant increase in body temperature. In another study, the same authors administered 1.7 mg/kg of MDMA to 30 volunteers with no history of previous use and measured the inhibition of the reflex response to acoustical alarm and the Stroop test. The blood pressure and the body temperature were checked before and after the administration of the substance. The results of the alarm reflex response test were compared with the results of studies using laboratory animals. Interestingly, these results were diametrically opposed to those found in the animals, suggesting a different profile for the neurotransmitter liberation, the receptor mechanisms, or both. The authors suggest that these results demonstrate the difficulty of extrapolating from data obtained in laboratory experiments to human subjects, and that more research is needed to clarify these differences. As for the Stroop test, the process of selective attention remained intact, although many subjects found that under the effects of MDMA, their thoughts tended to stray from the test while a more automatic part of their minds seemed to remain in control of the situation and complete the test without difficulty (Gamma y Vollenweider, 1998; Vollenweider *et al.*, 1998).

In Nicaragua, a pilot study was carried out with people suffering from war-related trauma diagnosed as PTSD. Despite the questionable methodology of this study (unknown dosage levels, no control group, etc.), the results for this type of patients were promising. They used a sample of 20 patients. Two could not be evaluated, and in five subjects, the presenting symptoms worsened, necessitating medication.

The first evaluation was done after the substance was taken, with 50% of the subjects reporting positive reactions: less anxiety, better communication with others, relaxation, and better visual and auditory perception — without hallucinations or illusions. The other 50% experienced increase in symptoms and collateral effects in the autonomic nervous system. In the second evaluation of the subjects, from one to ten days afterwards, 72.2% responded positively, including those subjects who had positive responses in the first evaluation. The symptoms persisted in the others, aggravated in two cases. All the subjects in the study suffered some degree of secondary effects (moderate tachycardia, trembling, occasional nystagmus, etc.). These secondary effects were transitory and disappeared after a maximum of seven days. In the subjects who responded positively in both the first and second evaluation, increase in re-

socialization, sensory perception, sense of well-being and communication was observed. When considering the subjects who did not experience these positive effects, we need to keep in mind that they received the substance without having agreed to an informed consent —which seems to be standard practice in Nicaragua with any drug — (Saunders, 1993). This informed understanding of what one is experiencing is a critical element in ensuring a positive session with MDMA. The author concluded that MDMA has the capacity to reduce non-psychotic reactive manifestations and that a greater methodological control is needed to confirm the potential positive effects of the drug with this type of patients (Madriz, unpublished document).

Finally, there are three controlled, double-blind studies in which MDE -N-ethyl-3,4-methylenedioxyethylamphetamine- (a phenethylamine structurally related to MDMA and with similar effects, though weaker and with lower toxicity in laboratory animals) was given to healthy human volunteers. In the first of these studies, the investigators found significant increase in cortisol, PRL, blood pressure, heart rate and a slight decrease of the GH. The authors concluded that the neuroendocrine and cardiac effects of MDE are similar to those of the other phenethylamines, except in the secretion of GH (Gouzoulis *et al.*, 1993). In the second study, psychological variables were measured. These effects were characterized by a particularly stable state in which insight, empathy and peaceful feelings were all increased. All subjects experienced stimulation to the sympathetic nervous system with increases in psychomotor activity, verbalization and ease of communication. One subject had a dysphoric reaction and another suffered anxiety attacks for a few days after the experiment, probably due to the fact that insufficient attention was paid to the *setting* (the context in which the drug was administered). The authors concluded that MDMA and MDE represent a new class of psychoactive compounds distinct from the classic psychedelics (Hermle *et al.*, 1993). In the last study, sleep patterns were studied in healthy subjects who had been given MDE. The patterns were similar to those caused by amphetamines, confirming the stimulant effects of the substance (Gouzoulis, *et al.*, 1992).

2.6. Conclusions

Although we cannot scientifically state that MDMA has psychotherapeutic usefulness (Cam , 1989), its widespread use by a large number of psychotherapists during the 70s and 80s (Greer, 1985; Wolfson, 1986; Shulgin y Shulgin, 1992; Stafford, 1992; Mengel, 1992; Eisner, 1995; Capdevila, 1995; Greer y Tolbert, 1998),
and the lack of serious complications in the studies presented above suggest the need for more methodologically sound studies in which MDMA can be studied as a substance of possible importance in psychotherapy. Additionally, when the substance was included on list I of controlled substances, the OMS invited the scientific community to continue investigating this interesting substance under the protection of article 7 of the International Convention of Psychotropic Substances, according to which the signatory nations may allow scientists and researchers access to a drug included on this list for experimental purposes (Doblin, 1995). In fact, as we stated above, the FDA is in the process of reviewing a protocol submitted by Dr. Charles Grob, of UCLA, to use the substance for therapeutic purposes. If this protocol is approved, it will be the first controlled study using MDMA in psychotherapy since its prohibition in 1986.

Liester *et al.* (1992) published a study in which they interviewed 20 psychiatrists who had experienced MDMA for various reasons (self exploration, deepening of interpersonal relations, desire to have a pleasant experience, or mere curiosity). A semi-structured questionnaire was used, focussing on the effects produced by the drug, adverse effects, long and short-term lasting effects, neurotoxicity, and the psychiatrists opinions concerning the potential usefulness of the substance in psychotherapy. The results are as follows: 17 therapists (85%) supported research into using the drug in psychotherapy and of the other 3 subjects, two were ambivalent and the last was completely opposed to its use. These three subjects had at least one unpleasant experience each with MDMA. More than half of the therapists concluded that the MDMA experience has a high or very high potential to assist the therapeutic process, particularly in its ability to increase feelings of empathy. They also concluded that it has a high potential for abuse, especially if taken by unprepared people and with little care taken to ensure the necessary conditions.

Although we do not intend to deny the dangers associated with the abuse of MDMA — especially now that patterns of use have become so reckless with regard to the context (or

setting), and the purity of what is sold on the black market is questionable at best — we do believe that more research is warranted into the usefulness of MDMA in the psychotherapeutic context. In this context, the possible negative reactions can be anticipated and appropriately handled, and the patient would benefit greatly from the intense emotional liberation the substance allows. We do not see this focus as being in opposition to those who have studied the possible drawbacks and dangers related to abuse of the substance. We agree that the abuse of MDMA is quickly becoming a social and medical problem, but the studies presented in these pages demonstrate that, used for concrete problems and under experienced medical and psychotherapeutic supervision, MDMA can help to quickly and effectively alleviate such serious and widespread psychological problems as depression, relational difficulties and posttraumatic stress disorder.

3. Posttraumatic Stress Disorder

3.1. General Description

The DSM-IV defines Posttraumatic Stress Disorder (PTSD) as anxiety disorder generated when a person has experienced, witnessed or faced a stressor which involves death, the threat of death, serious bodily injury or risk to the physical integrity of the self or of another person and which causes reactions characterized by intense fear, feelings of helplessness or of terror (APA 1994). Although PTSD was not recognized as a diagnostic category until the publication of the DSM-III in 1980, the syndrome had been described since the Napoleonic Wars (Gonz lez de Rivera, 1994) and during the American civil war, the First World War (where Freud described the syndrome), after the Second World War (where the psychological symptoms began to be taken into account) and, most significantly, during and after the war in Vietnam (Alburquerque, 1992). In fact, PTSD is a syndrome classically associated with war. It had been called traumatic neurosis, war neurosis and stress response disorder (de Pa l, 1995), before arriving at its current denomination, Posttraumatic Stress Disorder. In the DSM-III-R, the diagnostic criteria for PTSD were elaborated, although its definition, which is still quite restrictive, was not modified until the publication of the DSM-IV.

The concept of PTSD is more accepted by the scientific community than the criteria for

classification. This is why, while the DSM-IV considers PTSD to be an anxiety-related disorder, the CIE-10 classifies it as a syndrome related more to stress (O.M.S., 1992). Similarly, it can be found among the dissociative disorders in that in some manifestations (in war veterans, for example), dissociation is the major symptom (Corral *et al.*, 1992). The controversy undoubtedly arises from the lack of knowledge concerning this disorder. An example of this can be found in the fact that the overly restrictive diagnostic criteria found in the DSM-III have become, with the DSM-IV, much more complete and reflect the advances still being realized in our understanding of this syndrome. PTSD is no longer considered to be a disorder limited to ex-combatants. It seems that there are many sectors of society in which PTSD can be found, such as victims of natural disasters, traffic accidents, terminal diseases, physical assault, of any type of violent crime and, especially, victims of sexual assault (Echebur a and Corral, 1997). In fact, between 1.3 and 9% of the general population is estimated to suffer from PTSD, which would make this disorder more widespread than schizophrenia. Furthermore, an estimated 13% of the psychiatric population suffers from PTSD, which would make it the most common disorder currently (van der Kolk *et al.*, 1995). The highest levels are found in ex-combatants and in female victims of sexual assault (Echebur a *et al.*, 1995), as we will discuss below. In addition, these two groups are the most extensively studied among those who suffer from PTSD.

3.2. Clinical Features

The DSM-IV lists the following diagnostic criteria for PTSD, characterized by three main types of symptoms:

1) Persistent re-experiencing of the traumatic experience through intrusive memories, recurrent dreams, flashbacks and intense psychological and physical distress when internal or external stimuli symbolize or in some way remind the patient of his/her trauma.

2) Persistent avoidance of stimuli associated with the trauma and a numbing of general responsiveness (which didn t exist before the trauma), which can be seen in attempts to avoid thoughts, activities, places, etc., which remind the patient of the trauma, or in incapacity to recall some of the important details of the trauma, sense of distance from others, limited affect and

foreshortened future.

3) Persistent symptoms of anxiety or increased arousal that were not present before the trauma. These symptoms may include difficulty falling or staying asleep that may be due to recurrent nightmares, during which the traumatic event is relived, hypervigilance, and exaggerated startle response.

In addition to these three types of symptoms, the disorder is accompanied by clinically significant distress or impairment in social, occupational, or other important areas of functioning. The full symptom picture must be present for more than one month.

The disorder is considered to be *acute* if symptoms have not persisted for more than three months, *chronic* when they have lasted for more than three months, and *with delayed onset*, if at least six months have passed between the traumatic event and the onset of symptoms (A.P.A., 1994).

This clinical picture includes a cognitive numbing (Gonz lez de Rivera, 1990) associated with an emotional numbing or loss of affect which is seen in the inability to express and experience affection or feelings of intimacy and tenderness (Corral *et al.*, 1992). As a result of this, patients lose interest in the activities they pursued before the traumatic event, leading to a restriction of occupational and social interaction. This is why the level of social support received after the aggression plays such an important role in recovery.

Diagnosis of PTSD is not simple, in that the patient often presents with a host of associated disorders, such as depression, substance abuse, obsessions, anxiety, personality disorders, rage, etc. This is why it is so important to perform an extensive psychological evaluation so as to not confuse PTSD with some of its associated symptoms. In fact, amnesia associated with the traumatic event can often interfere with the patients ability to understand and explain their experience, which is why many seek help for the secondary symptoms and not for PTSD as such (The Harvard Mental Health Letter, 1996). It is estimated that approximately 80% of PTSD sufferers also suffer from some of these associated disorders, with obsessive-compulsive disorder and emotional distress being the most common (Helzer *et al.*, 1987).

In terms of the etiology of the syndrome, the internal factors (the importance given to the traumatic event) are considered to be as important as the external aspects (the intensity and severity of the trauma as well as the level of exposure). Other factors may cause increased vulnerability to the appearance of the syndrome as well, such as substance abuse, a history of other psychological disorders, physical abuse and so on (Gonz lez de Rivera, 1990). The more severe the original event was, the less important these personal variables appear to be (de Pa l, 1995). Furthermore, it seems more likely that PTSD will develop if the traumatic incident was caused by human action (Echebur a *et al.*, 1995). In addition to the relation with the traumatic event, other hypothesis have been developed to explain the etiology of PTSD —behavioral, cognitive, biological and interpersonal. Most researchers use an integrative model, drawing from each of these hypotheses (de Pa l, 1995).

For evaluating and diagnosing PTSD, interviews, questionnaires, psychometric tests and physical tests like skin conductivity, cardiac latency EMG, and the clonidine test, among others, are used. The therapies utilized in the treatment of PTSD include behavioral approaches (systematic desensitization and exposure), cognitive-behavioral (stress inoculation), cognitive, abreaction-based, hypnosis, and family or group therapy.

With respect to psychopharmacological treatments, Frank *et al.* (1988) found that phenelzine (an MAO inhibitor) and imipramine (a tricyclic antidepressant) were significantly more effective than placebo in reducing the symptoms of re-experiencing (nightmares, traumatic memories, flashbacks), when administered for 8 weeks, with phenelzine being superior to imipramine. Shestatzky, *et al.* (1987), found no significant differences between phenelzine and a placebo however. Nor did Reist *et al.* (1988) find any difference between a tricyclic antidepressant (desipramine) and a placebo after four weeks of treatment. Davidson *et al.* (1990) found a small reduction in the major symptoms of PTSD comparing amitriptiline (another tricyclic) to a placebo. Finally, both propanolol (Famularo *et al.*, 1988) and carbamacepine (Wolf *et al.*, 1990) were found to be superior to placebo. Some serotonin re-uptake inhibitors (SRIs) have also had positive results (Marshall *et al.* 1998; Rothbaum, *et al.* 1996; McDougle *et al.*, 1990; Shay, 1992). Finally, the FDA in the United States is currently considering approving setraline (a SRI) for the treatment of PTSD (it would be the first medication specifically approved for this disorder).

3.3. PTSD in victims of sexual assault

Approximately 25% of the victims of any crime are at risk of developing PTSD (Corral *et al.*, 1992), 40-50% of the victims of domestic abuse (Echebur a *et al.*, 1996), and the proportion may be as high as 50-60% of the victims of sexual assault (Corral *et al.*, 1992). Sexual assault is the crime most frequently suffered by women, in fact between 15 and 25% of women have suffered some type of sexual aggression or abuse during their lifetime (Koss, 1983). The characteristics of the aggression are not influential at the time the PTSD develops, unless it was especially cruel (Echebur a *et al.*, 1995). This type of victim fit each of the diagnostic criteria for PTSD specified in the DSM-IV.

The female victim of sexual assault first passes through a period of generalized psychological distress, characterized by anxiety, fear, feelings of vulnerability, stress and behavioral confusion, which tends to last about three months. After this period, there begins a period characterized by anxiety, phobic behavior, changes in sexual functioning, which tend to become chronic (Kilpatrick, 1992b), with little difference noted in measurements taken from the first 3-6 months of the development of chronic problems and after four years (Kilpatrick, 1992a). In fact, the initial stress is a good predictor of future stress (Kilpatrick, 1992a). This is why it is important to distinguish, when designing the treatment, between recent victims and those not so recent (with recent being defined as up to three months after the traumatic incident), because after this period has passed, the symptoms tend to become chronic, as mentioned earlier.

The probability of developing PTSD in victims of sexual assault is especially elevated due to the fact that in the majority of these cases, the assault happened in a place the victim had considered to be safe. In these cases, one of the most common symptoms is a heightened state of arousal as well as a generalization of fear to include places that were previously considered to be safe, with nightmares being relatively secondary (Echebur a y Corral, 1995). Generally, the typical symptoms of PTSD often include depression, loss of self-esteem, feelings of guilt, avoidance behavior in interpersonal relations, expressive deficits and sexual problems (Echebur a *et al.*, 1995). Some 80% of these victims continue to manifest some type of symptom one year after the incident — symptoms which do not disappearwith the passage of time (Corral *et al.*,

1992).

3.4. Treatment of PTSD in victims of sexual assault

As stated earlier, the first thing one must do in designing an effective treatment strategy is to distinguish between recent and non-recent victims, which will be different in each case. However, the main goals of treatment will be the same in any approach, that is, to face the stress and help to improve self-esteem and the victim s sense of ego-strength (Echebur a *et al.*, 1990).

We have already mentioned the low rate at which victims of sexual assault seek psychological help. This is partially due to the fact that this type of victim normally don t see themselves as patients (Foa *et al.*, 1991). Furthermore, the classic symptom of avoidance, in addition to aggravating the symptoms by progressively limiting interpersonal relations, interferes with the victim s ability to seek help because of her fear of remembering and speaking about her experience. This fear of remembering the trauma also interferes with the establishment of a good therapeutic alliance. This is why one of the most common treatment methods is centered on provoking a re-experience of the assault in a safe atmosphere, where the patient can relive the assault with a relatively high degree of personal control, and in this manner acquire a greater degree of control over her memories of the assault. Those victims who are able to relive the trauma in a setting with these characteristics have better chances of long-term recovery (Meichenbaum, 1994). This is due to the fact that reliving the experience in this manner may deactivate the patient s fear structures as she finds herself in a safe setting, in the presence of emotional support (Echebur a y Corral, 1995). These types of global re-living experiences are easier to achieve in altered states of consciousness, like those produced by hypnosis or by some psychoactive drugs (Gonz lez de Rivera, 1994).

Generally speaking, no treatment design has proven to be very effective with recent victims, regardless of its theoretical orientation, although prompt treatment is crucially important in preventing later symptoms and avoiding a chronic condition (Sarasua *et al.*, 1993). The crisis intervention model (Slaikeu, 1988) and brief cognitive-behavioral approaches (Kilpatrick, 1992c; Corral *et al.*, 1995a) have proved to be the most useful approaches.

As for non-recent victims, there does not seem to be much difference between the effectiveness of the various approaches. In their complete review of the subject, Echebur a s group (1995) concluded that behavioral techniques showed better empirical results, especially those centered on stress inoculation, exposure therapy, assertiveness training, cognitive therapy and systematic desensitization, although none of these techniques was clearly superior to the rest. Foa *et al.* (1991) found stress inoculation to be more effective than exposure therapy in the short term, although the latter showed better long-term results. Patients were more likely to abandon this therapy however, due to its being more aggressive. Frank *et al.* (1988) found no significant differences between systematic desensitization and Beck s cognitive therapy. Finally, Corral *et al.* (1995b) had better results administering a treatment composed of exposure and cognitive re-evaluation than with a placebo combined with relaxation training. On the other hand, other types of therapy are being successfully employed, though without any experimental evidence. These include group therapy with or without medication (van der Kolk *et al.*, 1995), and holistic therapy (Ochberg, 1993). Brom *et al.* (1989) compared systematic densensitization, hypnosis, and brief psychodynamic therapy in a sample of 112 people suffering from PTSD due to various causes. These patients were compared to a control group taken from the waiting list, and these researchers found that the three modalities were all significantly better than nothing, but that there was no significant difference between them in terms of effectiveness.

In conclusion, research into PTSD in victims of sexual assault is still in its infancy. There are few studies with rigorous controls that demonstrate the effectiveness of one psychotherapeutic approach over another, not only in victims of sexual assault, but in PTSD sufferers in general. Therefore, more well-designed studies comparing the effectiveness of the psychotherapeutic techniques presently available are needed before we can decide which is best for this type of patient.

Given that until now all available psychotherapeutic techniques show similar effectiveness, it becomes more urgent to investigate which non-specific factors are those which contribute to better therapeutic success.

4. Conclusions

MDMA is a drug which, because of its psychopharmacological properties, produces a subjective sense of well-being in which psychological defenses disappear or are greatly reduced. This undefended state leads subjects to experience a great deal of empathy, as well as greatly facilitating the sharing of intimate information and increasing the capacity for introspection and the analysis of deeply-held feelings. Within a psychotherapeutic context, this quality of the substance can help to create a fearless environment where the subject can re-experience her trauma without the terror she has heretofore associated with it. This successful reliving of the traumatic event is thought to give the patient a greater sense of subjective control over the memory — thereby reducing the symptoms of the PTSD. This ease of accessing and expressing deep feelings breaks the affective hold of the disorder on the patient, permitting an acceleration of the process of establishing therapeutic alliance as well, which is the variable most predictive of therapeutic changes (Poch and vila, 1998). We can conclude therefore, that MDMA acts upon precisely those symptoms which are most incapacitating for victims of sexual assault suffering from PTSD: avoidance (with the associated increase in phobic behavior patterns) and uncontrolled re-experience of the trauma.

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6. Additional experimental documentation structured in pharmacokinetics, pharmacodynamics, toxicological data in animals, clinical toxicology, adverse effects and neurotoxicity.

1.1. Pharmacokinetics.

1.1.1. Absorption.- Verevey *et al.* (1988) administered 40 mg of MDMA orally to a 40 year old man and took blood and urine samples for 24 (blood) and 72 (urine) after administration. The highest concentration was observed at 2 hours postingestion, and was 105.6 ng/ml. Helmlin *et al.* (1996) gave 1.5 mg/kg of MDMA in the course of psychological treatment of a 40 year old woman and a 23 year old man. The maximum concentrations were observed at the 2 hour mark in both volunteers, being 330.3 and 331.3 ng/ml, respectively. The plasma concentrations of the principal metabolite of MDMA, MDA, was 10 ng/ml at 6 hours after ingestion and 15.3 ng/ml at 2 and a half hours after taking the substance. Henry *et al.* (1998) gave 40 mg of MDMA orally to 8 volunteers, and the maximum values observed were between 40 and 50 ng/ml 4 hours post-ingestion.

1.1.2. Distribution.- MDMA followed a monocompartmental distribution process in the studies cited above. Henry *et al.* (1998) did not provide relevant data.

1.1.3. Metabolism.- MDMA is eliminated by humans via the urine as MDA (Verebey *et al.*1988). In this study, the plasmatic concentrations of MDA reached their maximum levels 2 hours post-ingestion,with a value of 14.1 ng/ml. In the study by Helmlin *et al.* (1996), the MDA concentrations in the urine fluctuated between 0.11 and 2.30 μg/ml in the female subject in the 5 hours after administration, and between 0 y 1.58 μg/ml in the male subject at 21.5 hours. Concerning hydroxilate metabolites, Hemlin *et al.* (1996) FOUND 4-hydroxi-3-metoximetamphetamine (HMMA), 3,4-Dihydroximetamphetamine (HMA) and 3,4-Dihydroxiamphetamine(HHA) in the urine. Of these, the most significant was the HMMA, with maximum concentrations of 24.58 and 35.08 μg/ml for each volunteer, obtained at 5 and 16 hours after ingestion, respectively.

1.1.4. Elimination.- In the study by Verebey *et al.* (1988), the elimination half-life of MDMA was found to be 7.2 hours, with the compound most present in the excretion being unaltered MDMA. The investigators recovered a total of 36 mg (72% of the administered dosage) at 72 hours after

administration. In the study by Hemlin *et al.* (1996), the concentrations of MDMA excreted in the urine were from 13.09 to 28.14 µg/ml in the female subject and from 0 to 18.12 µg/ml in the male. The maximum concentrations were obtained at 5 and at 21.5 hours after ingestion, respectively. After giving 1.5 mg/kg of MDMA to two patients, Lanz *et al.* (1997) found that the compound was excreted principally in an unaltered form, with a reading of 52.44 (37.98%) for each patient at 72 hours post-ingestion. Concerning the excreted proportion of steroisomers, the predominant was R-(-)-MDMA during the 72 hours of sample collection. Finally, Fallon *et al.* (1998) gave 20 mg of MDMA and performed an enantoiomeric analysis of blood plasma and urine. The elimination half-life of (R) and of the (S)-MDMA was 4.8 and 3.2 hours, respectively. The recovery of enantiomerics of the MDA was 0.60% for the (R)-MDA and 0.68% for the (S)-MDA, while in the plasma, the concentration of the (S)-MDA enantoisomer was greater then that of the (R).

The only controlled study published so far in which pharmacokinetic data was obtained is that of Mas *et al.* (1999). In this study, 8 healthy volunteers with previous experience with MDMA were given doses of 125 and 75 mg of MDMA, 40 mg of amphetamine or placebo, after which psychological and physiological parameters were recorded. The pharmacological data provided by this study is the most complete available to date. The results were as follows: maximum concentration for the doses of 125 and 75 mg of MDMA were 236.4 and 130.9 ng/ml, reaching their maximum levels at 2.4 and 1.8 hours after ingestion, respectively. The elimination half-life was 8.7 hours for the higher dosage and 7.9 hours for the lower. Between 8 and 9% of the MDMA appeared in the plasma in unaltered form. The plasma concentrations decreased according to a monoexponential model. The concentrations of the MDA metabolite reached its maximum concentration at 5 and 7 hours post-ingestion, with values of 13.7 and 7.8 ng/l, respectively, for the dosages of 125 and 75 mg. The elimination half-life of the MDA fluctuated between 16 and 28 hours.

In another recent, controlled, pharmacokinetic study awaiting publication, 0.5 and 1.5 mg/kg of MDMA were administered to 8 healthy volunteers. For the lower dosage, the maximum plasma concentration of S-(+)-MDMA was 95 ng/ml at 2.9 hours and 195 ng/ml at 3.8 hours for R-(-)-MDMA. For the higher dosage, of 1.5 mg/kg, the maximum concentrations observed were

of 635 ng/ml at 4 hours of S-(+)-MDMA and of 1450 ng/ml at 6.6 hours for the R-(-)-MDMA (Jones, 1999).

1.2. Pharmacodynamics.

There are no data about the pharmacological action mechanixms of MDMA in human subjects, so all of this type of data has been extrapolated from laboratory animals. MDMA acts upon the seretoninergic, dopaminergic and noadrenergic systems, with the dextro isomer being the strongest. Its principal action mechanism is the indirect stimulation of the liberation of 5-HT (serotonin) and the inhibition of its reuptake. Contrary to the rest of the hallucinogenic amphetamines, MDMA has little agonistic activity on the 5-HT receptors. MDMA is less potent than amphetamine and MDA in terms of inhibiting the reuptake of noradrenaline and dopamine, although it promotes the liberation of the latter (Cam , 1995). Although the major effect of MDMA on the pre and postsynaptic receptors seems to be concentrated on the serotonin reuptake sites, a lesser affinity has been observed for the 5-HT2 receptors as well, where MDMA acts as an agonist. MDMA seems to express an affinity for the 5-HT1 receptors as well, though less significant than those previously mentioned. MDMA also presents affinity for the α2-adrenergic receptors as well as that M1-muscarinicos of acetylcholine. MDMA s affinity for noradrenaline and dopamine reuptake sites is clearly less than that observed for the serotonin reuptake sites. The substance also inhibits onoaminoxidase (MAO) decreases tryptophan-hydroxylase activity (Mas, 1999).

This pattern of pharmacological action proceeds in a biphasic manner, producing the following neurochemical changes: the acute effects produce an increase in 5-HT concentrations in the synapses, followed a few hours later by a rapid decrease in serotonin and its primary metablolite (5-HIAA) as well as a decrease in the activity of the tryptophan hydroxylase enzyme, without any alteration to the 5-HT uptake sites in the presynaptic nerve terminals. All measures return to normal within 24 hours. In this acute phase, dopamine is also released. Long term effects include a slow but persistent decrease in levels of 5-HT and 5-HIAA. The activity of TPH is maintained and it seems to be a decrease in the density of the uptake sites for 5-HT in the

presynaptic terminals. The recovery of these neurochemical parameters is very slow (several months), if it happens at all. This action mechanism is more or less intense, depending upon the animal species being studied, the administration pattern, and the doses of MDMA given (Lorenzo, 1998).

1.3. Toxicological data in animal models

Several studies of the toxicology of MDMA in animals have been published. The first of these was by Hardman *et al.* (1973) which looked at the toxicity of the substance in several laboratory animals. They found an LD50 (mg/kg) of 97 (i.p.), 49 (i.p.), 98 (i.p.) 14 (i.v.) and 22 (i.v.) for the mouse, the rat, the guinea pig, the dog and the monkey, respectively. The LD50 (mmol/kg) was 0.42, 0.21, 0.43, 0.06 and 0.09, respectively. They also mentioned the tendency for MDMA to produce mydriasis, piloerection, salivation and hypothermia at toxic dosages. In a later study in which an oral dose of 100 mg/kg of MDMA was administered orally, no cerebral lesions were found, and none of the animals died (Frith *et al.*, 1987). Slikker *et al.* (1986) gave mice an oral dose of more than 80 mg/kg continually and, as in the study by O Hearn *et al.* (1986) in which 20 mg/kg were administered subcutaneously, no deaths occurred —nor were any pathologies observed in the sacrificed animals. Dosages of more than 15 mg/kg given to dogs showed signs of testicular atrophy and an exaggerated enlargement of the prostate with the highest dosages; a weight loss was observed in the animals but no signs of neuropathology were observed (Frith *et al.*, 1987).

Like amphetamines and fenfluramine, MDMA is clearly neurotoxic in animals when administered at high and/or continuous dosages. The neurotoxicity of MDMA is of a serotoninergic type. There are three hypotheses seeking to explain the possible neurotoxic mechanism of action of MDMA, although none of them has found confirming data so far: 1) possible formation of a toxic metabolite of MDMA; 2) possible formation of a toxic metabolite of 5-HT; and, 3) possible formation of a toxic metabolite of dopamine. We know that an warmer environment increases the generation of neurotoxicity. The toxic metabolite hypothesis is based upon the fact that when administered intraventricularly, MDMA did not produce neurotoxicity in any of the animals studied (Colado, 1998).

Mice are the least affected in terms of neurotoxicity after administration of massive doses of MDMA, which may be due to the relatively lower levels of serotoninergic neurons they possess. A decrease in serotonin was observed in cats which were given continuous dosages of between 0.25 and 5.0 mg/kg of MDMA (which was eliminated with pretreatment with p-cloroamphetamine) as with the guinea pigs (Shulgin, 1990).

The best studies of MDMA neurotoxicity have been conducted with rats. In these studies, various dose sizes, regimes and routes of administration have been used. All of them have concluded that there was a depletion of 5-HT and long-term damage to the axons (although the cellular bodies remained intact), with both types of deterioration being dose-dependent. In some of these studies, the minimum dosage that consistently produced long-term neurotoxic effects was 10 mg/kg administered twice a day for 4 days (total dosage of 80 mg/kg over 4 days). However, in the majority of the studies, a dosage of 20 mg/kg twice a day for 4 days (total dosage of 160 mg/kg in 4 days) was needed to provoke serotonergic neurotoxicity. These data, extrapolated to humans, indicate that a minimum dosage of 1.4 g per day for 4 days would be needed to generate neurotoxicity. Given that humans are more sensitive to the possible neurotoxic effects of MDMA than rats, the minimum toxic dosage is surely smaller than this figure (Hegadoren *et al.*, 1999).

Finally, studies done with non-human primates are the most reliable for extrapolating to humans, although within limits it is possible that humans are more sensitive to the neurotoxic effects of MDMA than other primates. In non-human primates, the minimum dosages of MDMA that have been shown to produce long-term neurotoxicity have been between 20 and 80 mg/kg over 4 days (Fischer *et al.*, 1995; Insel *et al.*, 1989; Ricaurte *et al.*, 1988a) (extrapolated to humans, these doses would be between 1.4 and 5.6 g). The primate study in which the doses most approximate those taken recreationally by humans is that by Ricaurte *et al.* (1988) in which MDMA was found to deplete the serotoninergic systems in the thalamus and hypothalamus in non-human primates with a single dose of 5 mg/kg. In another study by the same author, also with primates, between 2.5 mg/kg (once every two weeks over 4 months) and 5 mg/kg (single

dose) were administered. No serotonergic depletion or neuronal damage was observed in any region of the brain (Ricaurte, 1993).

1.4. Clinical Toxicology

MDMA intoxication can be accompanied by arterial hypertension, an increase in heart rate, arrythmia, panic attacks and acute hepatic insufficiency. Other pathologies have also been described, such as hyperthermia (11 cases), cerebro-vascular accidents (8 cases), hyponatremia (9 cases), hepatoxicity (29 cases), anxiety attacks (6 cases), depressive episodes (7 cases), psychosis (13 cases), as well as 37 deaths associated with the consumption of MDMA. However, it should be noted that in most of these cases no clear connection was found between the consumption of MDMA and the pathology described. In some cases the analysis showed the presence of other drugs in the system, and others were called into question by previous physical pathologies, overdose, lack of significant levels of MDMA in the plasma, etc. (Gamella y lvarez, 1997).

1.5. Adverse reactions

The most important acute secondary effects produced by MDMA are bruxism, loss of appetite, difficulty in concentration, changes in balance and trembling in the legs. Short term effects (24 hours) include loss of appetite and energy, thirst and fatigue (Vollenweider *et al.*, 1998).

1.6. *Neurotoxicity*

1.6.1. Retrospective studies.- Peroutka *et al.* (1987) examined the cerebrospinal fluid in subjects with a history of MDMA abuse as well as in a control group of MDMA-na ve subjects, finding no differences in the levels of 5-HIAA between the two groups. In a similar study, Ricaurte *et al.* (1990), found significant differences in the 5-HIAA levels of users of MDMA and controls, which would indicate some level of neurotoxicity in the experimental group. In this study, the control group was comprised of patients with chronic back pain. It is known that pain is among the serotonergic mechanisms and that the levels of 5-HIAA are elevated, which is why

this study should be interpreted with caution (Grob and Polland, 1997). McCann *et al.* (1994) found 15% less 5-HIAA in a group of users compared with a group of non-users in another study similar to those cited above. However, the control group before the experiment was different from the control used post-experiment. Therefore, these data can be attributed to the MDMA or to the mispairing of the groups. The subjects of the experimental group scored lower on tests of impulsivity and hostility and showed no behavioral or functional deterioration. This result seems contradictory, in that serotonin is implicated in the mechanisms of hostility and impulsivity. In a study in which EEG readings were taken of MDMA users and controls during sleep, a reduced quantity of total and type II sleep was observed in the experimental group. Although the study s authors interpreted this as indicative of neurotoxicity (Allen *et al.*, 1993), Grob and Polland (1997) saw these data as indicative of an improvement in sleep patterns, in that the members of the experimental group spent more time in REM sleep as well as in phases III and IV of non-REM, which are the most restorative phases. Another study failed to show any significant differences in prolactin levels between users and non-users, using the L-tryptophan test (Price *et al.*, 1989), although subclinical scores were observed in some subjects on some neuropsychological tests (Krystal *et al*, 1992). Grob and Polland (1997) also criticize the methodology used in this study.

In a recent study, McCann *et al.* (1998) used Positron Emission Tomography (PET) neuroimaging techniques to measure the neurotoxicity produced by MDMA in a group of consumers compared to a group of non-consumers. They found a decrease in the density of reuptake sites for serotonin in the brains of the users. The members of the experimental group did not exhibit any neuropsychiatric disorders. Subjects who had taken MDMA between 70 and 400 times participated in this study (the average was 228 times) in dosages of between 150 and 1250 mg (the average dose was 386 mg). Furthermore, most of the subjects used several drugs regularly, including psychedelics, amphetamines and phenethylamines similar to MDMA (among them, MDA, the neurotoxic properties of which seem to be quite clear). Finally, it is not clear that the MDMA group and the control group were rigorously paired.

Recent studies have found significant differences between MDMA users and non-users

in short term memory loss (Bolla *et al.*, 1998) and in higher impulsivity scores (Morgan, 1998). These data must be taken with a grain of salt in that the groups were not rigorously paired, the MDMA users also used other drugs, the doses are unknown, and the purity of the ecstasy purchased on the black market is highly suspect.

1.6.2. Prospective studies.- Greer and Tolbert (1986) gave doses of between 75 and 150 mg of MDMA to 29 subjects in a psychotherapeutic context. In addition to the psychological benefits described, the substance caused no physical problems for any of the subjects. Downing (1986) gave MDMA to 21 healthy subjects and measured their cardiovascular response as well as biochemical changes. The subjects also underwent neurological testing before, during and after their experience with the substance (doses between 1.7 and 4.19 mg/kg — average dose 2.5 mg/kg). Moderate biochemical changes were noted, as well as slight increases in heart rate and blood pressure — though both remained within normal ranges. These increases were observed between 1 and 2 hours post-ingestion; returning to normal in 60% of the cases within 6 hours and within 24 hours for the rest of the subjects. No observable psychological distress was noted or reported during the 24 hours the experiment lasted, nor during the three month follow-up period. All subjects suffered from mydriasis, 38% from nystagmus and jaw tension, jaw reflex and minor effects on motor coordination and balance were frequently noted.

Grob *et al.* (1996) conducted the first controlled study of MDMA using human subjects, in which doses of between 0.75 and 1.0 mg/kg were given to 6 healthy volunteers with history of previous consumption. All subjects tolerated the dosage without any physical or psychological disturbances. The medication produced a slight (not significant) increase in blood pressure and heart rate readings. Endocrine response was measured (ACTH and prolactin), both of which passed their secretion threshold with the 0.75 mg/kg dose and were clearly stimulated by the 1.0 mg/kg dose. The complete phase, which consisted of 18 subjects who were administered dosages of between 1.0-1.75 mg/kg and 1.5-2.5 mg/kg, showed that the medium and high dosages produced slight increases in temperature as well as dose-dependent increases in blood pressure, with a gradual decline afterwards. No significant neuropsychiatric differences were found between the experimental group and control group, nor in the experimental group pre and post-treatment

(Grob, 1998).

Another controlled study of MDMA in humans sought to measure the physical as well as psychological effects. A pilot study was first conducted in which doses of 50, 100 and 150 mg of the substance were administered. Afterwards, a definitive study was conduced in which 8 healthy volunteers with previous use were selected. Vital signs were measured, as well as psychomotor functioning and subjective effects. The study was double-blind design with random group assignment, crossed and controlled. On different days, the subjects received either placebo, 75 or 125 mg of MDMA or 40 mg of *d*-amphetamine. The results showed that the active drugs increased the blood pressure and heart rate significantly (with a later effect for the amphetamine); MDMA increased pupil diameter. There were no significant changes in temperature in any of the treatment conditions. While the amphetamine caused a small increase in psychomotor performance, the higher dosage of MDMA produced a slight decrease. Subjective impressions of euphoria, well-being and pleasant sensations were noted with the MDMA. Furthermore, there were slight changes in visual and bodily perception with the MDMA, with no hallucinatory changes noted. In most of the parameters measured, the response was dose-dependent (Cam *et al.*, 1997; Mas *et al.*, 1999).

In the last double-blind, placebo controlled study published to date, 1.7 mg/kg of MDMA were administered to 16 subjects with no history of previous use. EEG and PET (Positron Emission Tomography) readings were taken simultaneously. After the neurological tests psychometric questionnaires were given to the subjects. Preliminary analysis indicates that MDMA produced changes in the cerebral blood flow when compared to the placebo. The most notable effect was in the prefrontal cortex. No significant differences were noted in any of the neurological parameters studied when pre and post-experiment readings were compared. Results on psychometric scales indicate that MDMA produces an increase in feelings of well-being and positive affect. No hallucinatory effects were noted although visual perception was altered (optical illusions and intensification of color perception). A significant increase in blood pressure and a non-significant increase in temperature were also noted.

In another study, the same authors administered 1.7 mg/kg of MDMA to 13 volunteers

without history of previous consumption and measured inhibition of startle response to acoustic alarm and to the Stroop test. The blood pressure and temperature were also monitored before and after the drug was given. The results of the startle response test, when compared to those observed in animals, indicates that the human response is diametrically opposite to that of laboratory rats, indicating a different neurological profile for the drug in these two models. The authors state that these data demonstrate the difficulty of extrapolating data found in animal studies to humans, and suggest the need for further study to clarify these differences. On the Stroop test, the processing of selective attention remained intact (Gamma y Vollenweider, 1998; Vollenweider *et al.*, 1998).

These last investigations have great relevance, in that they are the only prospective studies of neurotoxicity using subjects with no previous use of MDMA. The fact that no significant changes in serotonergic functioning were observed in this type of subject when pre and post administration results were compared, suggests that at therapeutic dose levels such as those proposed in this protocol, there is little risk of inducing any long term neuropsychological damage to the experimental subjects.

In a controlled study awaiting publication, doses between 1.1 and 2.1 mg/kg (total dosages between 60 and 198 mg) of MDMA were administered to a group of subjects with history of previous use, and psychological and physiological parameters were measured. Significant increases in blood pressure and heart rate were observed, reaching maximum levels 1 to 2 hours after ingestion and returning to baseline levels after 6 hours. The MDMA was physically safe for all subjects studied (Tancer, 1999).

Strassman and Qualls (1995) administered DMT (a strong hallucinogenic drug of the tryptamine family with extremely short action structurally similar to serotonin, and which acts as a serotonin antagonist) to two groups of MDMA users. One of these groups was composed of subjects who had used MDMA many times, and the other of occasional users. The only significant differences noted between the two groups was in pupil dilation (among all the physiological parameters measured), which was less dramatic in the chronic user group. These

data, according to the author, run counter to the expectation that MDMA would have caused serotonergic neurotoxicity in this group of subjects.

Finally, three studies have been published in which 3,4-Methylenedioxyethylamphetamine (MDE) (a substance structurally related to MDMA) was administered to healthy subjects. In the first of these studies significant increases were noted in cortisol, PRL, blood pressure and heart rate were noted, as well as a slight decrease in GH. The authors conclude that the neuroendocrine and cardiovascular effects of MDE are similar to other phenethylamines, except in the secretion of GH (Gouzoulis *et al.*, 1993). In the second study, psychological variables were measured (Hermle *et al.*, 1993) and in the last, sleep patterns under the effects of MDE were noted to be similar to those produced by amphetamines (Gouzoulis *et al.*, 1992).

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4.2. OBJECTIVES

As mentioned earllier, there are no controlled studies of the therapeutic effects of MDMA in humans. With these antecedents, the objectives of the proposed investigation will be:

1. To determine the most effective therapeutic dose of MDMA as an adjunct to psychotherapy with women suffering from PTSD as a result of having suffered sexual assault.
2. To evaluate the therapeutic effictiveness of MDMA as an adjunct to psychotherapy with women suffering from PTSD as a result of having suffered sexual assault.

5. TYPE OF CLINICAL STUDY AND ITS DESIGN

The goal of this study is to determine the most effective therapeutic dosage of MDMA, in combination with psychotherapy, for the treatment of chronic PTSD. To achieve this, five groups of physically healthy women diagnosed with PTSD as a consequence of some type of sexual assault will be selected. Groups 1 and 5 will each have 4 subjects. Three subjects from each of these groups will participate in an experimental session in which she will receive a dose of MDMA, and one subject from each group will receive a placebo. Groups 2, 3 and 4 will each have 7 subjects. Of these 7 subjects in each group, 5 will receive one dose of MDMA and 2 will receive a placebo. The dosage levels will be increased in each group in such a way that the first group will receive 50 mg, the second will receive 75 mg, members of the third group will receive a dose of 100 mg, the fourth group will receive a dose of 125 mg, and the fifth will receive a last dosage of 150 mg. As has been mentioned above in the literature review, these five dosage levels are within the safe range for experimental subjects. The dosages will be studied as they are given, and larger dosages will not be administered if the previous dosage levels were not well tolerated. The experimental design for each group will be double-blind, randomized and placebo-controlled.

With this design, we hope to observe, on one hand, what dosage level of MDMA, in combination with psychotherapy, is most efficient in the treatment of chronic PTSD, and on the other hand, what effective dosage level is safest.

6. SUBJECT SELECTION

The experimental subjects of the study will be women who are physically healthy and diagnosed with post-traumatic stress syndrome resulting from having suffered sexual abuse. Twenty-nine subjects will be chosen (5 for groups 1 and 5, and 7 each for groups 2, 3 and 4).

The subjects will be informed about the characteristics of the study and they will receive an information sheet. If they decide to participate, they will sign a consent form. We will perform a clinical history (anamnesis and physical examinations), a structured interview using the DSM-IV, an intake analysis (biochemical, hemotological, coagulation, urine and hepatitis screening), as well as an ECG.

Sample size

In that this is to be a pilot study, and the first study of this type, it is impossible to accurately predict the exact size of the subject group. However, we anticipate that 29 subjects will be sufficient for establishing significant differences among the dosage levels proposed.

Inclusion criteria

1. Women between 18 and 60 years of age with a diagnosis of chronic PTSD according to the guidelines established in the DSM-IV as a result of sexual abuse of any type.
2. Have a score greater than 15 on the global scale and over 5, 6 and 4 on the subscales of re-experience, avoidance, and arousal increase, respectively, on the PTSD Severity of Symptoms Scale (Echebur a *et al.*, 1997).
3. At least three months have passed since the sexual abuse took place.
4. Clinical history and physical examination do not indicate presence of organic illness. The subjects cannot take any drug or medication during the period of the study.
5. The ECG and the general analysis of blood and urine performed on intake must be

normal. Minor variation from standard scores are acceptable (+/- 10%).

6. The body-weight of each subject must be within 15% of the established norms relative to her height, and will fall between 50 and 80 kg.
7. Accept the procedures of the study and sign the informed consent form.
8. Have failed at least one previous treatment for resolving the PTSD.

Exclusion criteria

1. Subjects with a history of schizophrenic or related disorders (F.2), mood disorders (F.3) or personality disorders (F.6) before suffering the sexual abuse.
2. Subjects with a history of drug abuse or abuse of medications according to the criteria specified in the DSM-IV before suffering the sexual abuse.
3. Subjects who have suffered from any serious organic illness or major surgery in the three months prior to the study.
4. Subjects with psychiatric disorders (as detailed in #1) in primary family members.
5. Daily consumption of alcohol greater than 50 g.
6. Smokers of more than 20 cigarettes per day.
7. Taking medication regularly in the month previous to the study.
8. History of allergy or adverse reaction to medication.
9. History of cardio-vascular, gastro-intestinal, hepatic, or renal pathology or of any other type that suggests an alteration in the absorption, distribution, metabolism or excretion of the medication, or which suggests heightened gastro-intestinal sensitivity to medication.
10. Subjects unable to understand the nature and consequences of the study or the procedures they are asked to follow.
11. Subjects who test positive for Hepatitis B, and/or C.
12. Subjects in fertile years who do not use a reliable birth-control method (oral contraceptives, IUD, tubal ligation).

Diagnostic criteria for the pathologies in the study

Subjects will be physically healthy. The PTSD will be diagnosed using the Severity of Symptoms Scale for PTSD (Echebur a *et al.*, 1997). For a subject to be included in the study, she must have a score greater than 15 on the global scale and greater than 5, 6, and 4 on the reexperience, avoidance and increased arousal subscales, respectively.

Criteria for removal and anticipated analysis of subjects removed from the study or those who choose to abandon the study

The subjects can withdraw from the study at any time they wish; those who drop out will be replaced with new cases so that the number of subjects in each treatment group will be as outlined. Only results from patients who have concluded the study will be considered.

Any subject who has adverse reaction that, in the judgement of the lead researcher, places her health in jeopardy, as well as those subjects who fail to comply with the rules of the study will be withdrawn.

Treatment of subjects excluded previous to randomization and treatment

Not applicable.

Approximate time frame for recruitment of subjects and screening of available patients

In the two weeks before the experimental sessions begin (administration of the medication being studied) the selection of patients will proceed, using clinical history, physical examination, ECG and general analysis of blood and urine samples.

7. DESCRIPTION OF TREATMENT

Dosage selection

The chosen dosages are within the range of those previously used in psychotherapy and those presently being used in other controlled studies of MDMA in human subjects. In that this is a pilot study aimed at determining the most effective dosages, we intend to administer MDMA within a dosage range that allows evaluation of its possible effectiveness and which provides data concerning its safety in human patients. The dosages proposed for this study are of 50, 75, 100, 125 and 150 mg. We expect to find the most therapeutically effective dosage that is well-tolerated between 75 and 125 mg. We do not expect the 50 mg dosage to produce discernible effects, and that 150 mg, while therapeutic, may produce minor side-effects (sweating, nervousness). Below, we discuss the justification for the chosen dosages. As mentioned above, this study would allow us to determine the most effective dosage levels and to test the evaluation methods as well as the psychotherapeutic strategies appropriate to MDMA-assisted treatment.

Treatment scheme

We propose a pilot study which includes 29 subjects distributed over five dosage levels. Each dosage level will include patients treated with MDMA and patients given a placebo. In order to limit the maximum number of patients, we propose that the groups receiving 50 and 150 mg be the smallest, and that the others include more patients. According to this scheme, groups 1 and 5 will each have 4 subjects, while groups 2, 3, and 4 will each have 7 subjects. The study will begin with the lowest dosage level (group 1) and continue to the following level if acceptable tolerance is confirmed. Hence, the dosage will be increased only when the previous dosage has been shown to be well-tolerated.

The following is the proposed structure of the dosage-ranging study:

- Group 1 (4 subjects): 50 mg of MDMA (3 subjects)
  placebo (1 subject)
- Group 2 (7 subjects): 75 mg of MDMA (5 subjetcs)
  placebo (2 subjects)
- Group 3 (7 subjects): 100 mg of MDMA (5 subjects)
  placebo (2 subjects)
- Group 4 (7 subjects): 125 mg of MDMA (5 subjects)
  placebo (2 subjects)
- Group 5 (4 subjects): 150 mg of MDMA (3 subjects)
  placebo (1 subject)

According to this structure, the subjects will receive one dose of MDMA and one dose of placebo, randomly chosen. Five subjects from groups 2, 3, and 4 will each receive the active drug while two subjects will receive the placebo. Three subjects from groups 1 and 5 will each receive MDMA and one subject from each group will get the placebo. In this way, we can compare five different levels with only one dose administered to each subject.

Justification for the proposed dosages

In pharmacological studies of MDMA in humans, it has been difficult to distinguish differences in a limited number of subjects using dosages that differ by 25 mg. Therefore, it is possible that the dosage structure we propose will not allow us to establish significant differences between dosages that differ by only 25 mg. However, we do expect to establish significant differences between dosages that differ by more than 25 mg (for example, between 75 and 125 mg).

As mentioned above, the pharmacological studies published to date have demonstrated that 50 mg is the minimum dosage which produces subjective effects clearly distinguishable from placebo. The therapeutic effects of MDMA derive more from the subjective effects than from

the pharmacological effects the substance produces. Therefore, a dosage of 50 mg could well be too little to have therapeutic effect. This is why only 4 subjects have been included in group 1. On the other hand, the 150 mg dosage could produce secondary effects which may interfere with the positive therapeutic effects and therefore reduce the therapeutic usefulness. This is why only 4 subjects have been included in group 5. In other words, the motivation for including fewer subjects in groups 1 and 5 is that the effect-safety ratio may be imbalanced in these two groups.

The dosages that we expect to have a positive effect-safety ratio are those of 75, 100, and 125 mg. Although the proposed structure of the study will not, a priori, permit us to distinguish between the effects produced by 75 or 100 mg, nor between those produced by 100 or 125 mg, we do expect to see differences between those effects produced by 75 and 125 mg, which were the dosage levels most commonly used in psychotherapeutic practice before 1986, and which are those considered most effective in this setting. Additionally, the 100 mg dosage will allow us to establish differences between an amount with a good effect-safety ratio (100 mg) and with amounts where this ratio is not so well-established (50 and 150 mg).

During the experimental phases (administration of the substance) of this pilot study, the subjects blood pressure and heart rate will be measured every 30 minutes in order to better control the physiological effects of the substance and to avoid any possible risks to the health of the patients.

As has already been explained, the dosages will only be increased if the previous dosage has been well-tolerated. We understand tolerance to mean:

- **Cardiovascular effects:** increases in blood pressure to levels not greater than 120 mm Hg in the diastolic and no greater than 180 mm Hg in the systolic reading, and heart rate no greater than 120 beats per minute. Changes below these limits will be considered significant if they are accompanied by other indications of cardiovascular toxicity. If any of these limits is passed by more than two subjects per group treated with MDMA in at least three measurements, the study will be halted and greater dosages will not be

studied. Previous studies done by Farmacología Clínica with MDMA have shown increases in blood pressure and heart rate much smaller than those described. The increases have been self-limiting and all measures have spontaneously returned to normal levels in less than an hour.

- **Psychiatric effects:** If more than two subjects in groups treated with MDMA experience any type of psychological or psychiatric disorder observable by the researchers and which requires treatment, the study will be stopped and no greater dosages will be administered.

If there is an increase in blood pressure greater than that set forth above, we will attempt to calm the patient, she will be led to a bed in a quiet place and if appropriate, a sublingual or oral benzodiazepine derivative will be administered. If appropriate, a betablocker will be administered intravenously. If heart rate rises above 120 beats per minute, the same procedure as that outlined above will be followed, and a benzodiazepine derivative will be administered sub-lingually or orally. If any of these symptoms is accompanied by other symptoms with organic effects, the study will immediately be suspended.

The psychological disorders that have been described in the relevant literature and which may develop are primarily panic attack and anxiety crisis. If the non-pharmacological attempts to calm the patient have been ineffective (speaking with her, letting her relax in a quiet place), a benzodiazepine derivative will be administered sub-lingually or orally. As described earlier, if any two subjects in a group treated with MDMA suffer any of these disorders, or any other that has not been anticipated, the study will be stopped.

The subjects are not permitted to take any other drugs or medications during the experimental phase of the study, nor are they permitted to receive psychotherapy outside of the study until the treatment has been completed. Any exception to these conditions will trigger immediate exclusion from the study. The subjects can quit the study at any point they deem appropriate.

All the substances used in both studies will be provided by the Pharmacy Service of the Psychiatric Hospital of Madrid (Servicio de Farmacia del Hospital Psiqui trico de Madrid) in identical capsules to assure the double-blind nature of the study. Once prepared, the medication, will be held at the same facility (Servicio de Farmacia del Hospital Psiqui trico de Madrid), in a location appropriate for samples to be used in clinical research.

The administration of the substances will be done by one of the researchers, who will note the hour in the appropriate CRD. A registration sheet will be maintained to note the arrival and departure of the substances.

Concomitant Treatments

At least 30 days must have passed between the suspension of any treatment and the inclusion of the subject in this study.

No additional medications are permitted during the study. Any other medication must be taken only by prescription from one of the physicians on the research team (dosage, time and cause will be registered on the corresponding individual information sheet).

8. PROGRESS OF THE STUDY AND EVALUATION OF THE RESPONSE

The total treatment of this dose-ranging pilot study is composed of six sessions, one of them an experimental session using MDMA or a placebo — depending upon the group in question. The other five sessions involve diagnosis, evaluation and psychotherapy. All subjects will be treated by the same psychotherapists (a man and a woman) and will be evaluated by a member of the team other than the psychotherapists (the evaluator will be blind to the treatment), in order to avoid any influence from the therapists upon the evaluation measurements. The interval between sessions is explained below.

Progress of the study

1. Patient selection

The selection process will commence upon final approval of the protocol and run up to 2 weeks prior to the beginning of the study. The subjects will receive information about the study verbally and will also receive an information sheet. They must also sign the informed consent form for participation in the study. Those who agree to participate will be scheduled for a medical examination, which will include clinical history and general analysis of blood and urine. The general analysis will consist of a biochemical profile (glucose, creatine, hepatic enzymes, and bilirubin, CPK, LDH, uric acid, urea, cholesterol, triglycerides, total proteins and albumin, K, Na), hemogram (hemoglobin, hematies and its levels, leukocytes and formula), coagulation (platelets, PTT and TP), VSG, elemental analysis of urine (glucose, proteins, hematies, leukocytes, cetonic bodies), and serology (HB and HC) and screening for drug abuse in the urine as well.

2. Progress of the sessions

The content of each of the sessions will be the following:

- Day 1: Explanation of the study and informed consent. Psychiatric interview, Severity of Symptoms Scale for PTSD, electrocardiogram (ECG), blood pressure, temperature and body weight, analysis of blood and urine in order to confirm that the vital sign and metabolic functioning of the patient are within normal ranges. This session corresponds to the description offered earlier in this document. Psychological testing will also be done: semistructured interview about sexual assault, the STAI (State Trait Anxiety Inventory); BDI; HRS; MFS III; maladjustment scale; AE/R. Once the diagnostic tests have been done, the psychotherapists will discuss the relevant aspects of the study with the subject, and begin psychotherapy. At the end of the session, the HAq will be administered. The HAq will also be given at the end of each of the proposed sessions. The answers to the questionnaires will remain unknown to the psychotherapists until the treatment has been completed.

- Day 2: The therapist will spend an hour with the subjects within a psychotherapeutic context, with the intention to reinforce the therapeutic alliance and to better prepare the subject for the experimental session. At the end of this session the HAq will be administered. This session will take place one week after Day 1 described above.

- Day 3: The therapist will spend an hour with the subjects within a psychotherapeutic context, with the intention to reinforce the therapeutic alliance and to better prepare the subject for the experimental session. At the end of this session the HAq will be administered. This session will take place one week after Day 2 described above.

- Day 4: Experimental session with MDMA or placebo. The subject will at all times be accompanied by a psychotherapist to help with the emerging experiences. The HAq will be given once the session has concluded. The session will be considered complete when the experimenter feels it is appropriate. The subject cannot leave the area where the study is being conducted until the physician has determined that the physical effects of the medication have completely disappeared. The subject will return to her home either accompanied by a family member or in a taxi, in order to avoid driving a car. This session will take place seven days after Day 3, described above.

- Day 5: This session will take place one day after the previous session, and will consist in the subject and therapist spending an hour together, within the psychotherapeutic context, in order to integrate the experiences that came up during Day 4. At the end of the session, the UKU, HRS-S and HAq will be administered.

- Day 6: In this session the subjects will finish the process of integrating the experiences that emerged during the entire therapeutic process and the treatment will be concluded. Additionally, the same questionnaires and evaluation scales as those given on Day 1 will be administered, except for the semi-structured interview about sexual abuse and the HRS-S (Scale for the evaluation of subjective effects of hallucinogens). This session will take place seven days

after Day 5.

Day 6 will represent the end of the study. All sessions will be recorded (audio) in order to analyze and evaluate the possible differences in the techniques employed by the psychotherapists as well as other factors that may be relevant. We intend to ensure that the style and techniques utilized by the psychotherapists be as uniform as possible with all the subjects in all the sessions and experimental conditions so that it will be possible to attribute the potential differences found in all the patients in each group to the medication.

Throughout the entire time the study is under way, a psychotherapist from the team will be available 24 hours per day should any complications arise in any of the subjects.

Follow-up sessions will be conducted one, three, six, nine and twelve months after the conclusion of the study in order to evaluate the stability of the treatment results.

The psychotherapeutic model that will be used falls within the bounds of brief systems therapy. The techniques and effectiveness of this model are well-known and accepted within the sciences of psychology and psychotherapy. The psychotherapeutic psychiatrists who will perform the psychotherapy in this study have been educated and trained in this psychotherapeutic method and they use it regularly in their professional work at the public service of the mental health department (Servicios p blicos de Salud Mental). The psychotherapeutic techniques to be employed are appropriate to the standard treatments used in this psychotherapeutic model.

TREATMENT SCHEME

	Semi-structured interview DSM- IV, ECG and analyses	Psychometric scales	Experimental session: MDMA or placebo	Psychotherapy session
Day 1	X	X (Except UKU and HRS-S)		X
Day 2		X (Except UKU)		X

Day 3		X (HAq)		X
Day 4		X (HAq)	X	X
Day 5		X (UKU, HRS-S, HAq)		X
Day 6		X (Except semi-str. Interview and HRS-S)		X

3. Criteria for clinical assessment and evaluation

The psychological evaluation and the validation of results will proceed according to a repeated measurement, multigroup experimental design: in pretreatment (Day 1), in post-treatment (Day 6), and in the follow-up sessions at 1, 3, 6, 9 and 12 months afterwards. As stated above, the evaluations will be carried out by a member of the team other than the psychotherapist (blind evaluator), who will also perform the follow-up evaluations.

The psychological tests and scales that will be used are the following:

3.1. Severity of symptoms scale for posttraumatic stress disorder (Echebur a *et al.*, 1997).

This is a semi-structured interview useful for evaluating the principal symptoms (re-experiencing, avoidance, increased arousal, and psychophysiological symptoms) and the of the PTSD according to the criteria set forth in the DSM-IV. The scale is sensitive to therapeutic changes and has been demonstrated to be useful in planning treatment and in research involving populations like that of the present study.

3.2. Semi-structured interview about sexual abuse (Echebur a *et al.*, 1995).

Collects sociodemographic data about the victims, about the situational and descriptive characteristics of the aggression(s) and aggressor(s), about the personal characteristics of the victim before the aggression, and about the personal consequences resulting from the aggression.

3.3. The state-trait anxiety inventory (STAI) (Spielberger, Gorsuch y Lushene, 1970).

Comprised of two separate self-reporting scales which measure two independent concepts of anxiety, as state (S) and as trait (T). The anxiety state, which is the one which will be used in this study, is defined as a transitory emotional state or condition of the human organism, characterized by subjective feelings of tension and apprehension and by autonomic hyperactivity. It is variable in duration and intensity. The anxiety trait refers to a stable propensity toward anxiety which is seen in individuals differing tendencies to interpret situations as being threatening and as a consequence, tends to elevate their anxiety state. Each scale has 20 items on a Likert scale from 0 to 3. It has an alpha coefficient of 0.89 and a test-retest reliability, with an interval of 104 days, of 0.77. The Spanish version was adapted by Seisdedos (1982). The STAI has been shown to be useful in distinguishing between victims and non-victims for at least one year after the assault (Kilpatrick y Veronen, 1984).

3.4. Beck depression inventory (BDI) (Beck *et al.,* 1961).

This is composed of 21 items, each of which evaluates a symptom of depression. Each item has four possible responses, from 0 to 3 according to the intensity of the symptom. It evaluates depression, giving greatest importance to cognitive symptoms. Its internal consistency is 0.86 and its validity from 0.73-0.74. The Spanish version was done by Conde y Franch (1984).

3.5. Hamilton Rating Scale: HRS (Hamilton, 1960).

As opposed to the BDI, this scale is focused more on the behavioral and physiological symptoms of depression, which makes it a good complement to the previous scale. It is composed of 21 items plus one final item to specify other symptoms, which are measured on a scale of either 3 or 5 points, depending on the item. The interjudging reliability is 0.90 and the scale has been shown to be valid for distinguishing depressed patients from those suffering from other disorders. The Spanish version of this scale was also adapted by Conde y Franch (1984).

3.6. MFS III Modified fear scale, from Veronen y Kilpatrick (1980). (Spanish version by Echebur a *et al.*, 1995).

This is the only instrument available until now for measuring specific fear reactions in relation to rape. It s a self-reporting instrument based upon the Fear Questionnaire by Wolpe and Lange, to which 42 items related to aspects specific to sexual assault have been added. These 42 items form the Subscale of fears related to sexual assault, which is what we will be using in this study. It is structured on a Likert scale (from 1 to 5), the test-retest reliability is between 0.60 and 0.70 with an interval of 2.5 months. The internal consistency fluctuates between 0.81 and 0.94. The scale has been shown to be able to discriminate between victims and non-victims for at least three years after the assault.

3.7. Maladjustment scale (Echebur a y Corral, 1998).

Composed of six items, each of which refers to one of the following factors related to social and work-related adjustment: work and/or studies, social life, free time, intimate relationships, family life, and overall life. Each item is graded on a Likert scale from 1 to 6.

3.8. The Rosenberg self-esteem scale (AE/R) (Rosenberg, 1965).

This is a cognitive-type measure consisting of 10 items on a Likert scale from 1 to 4 which evaluates elements from self-acceptance to self-esteem expressed in a general sense. Although this instrument was originally designed for university students, its acceptable indexes of reliability and validity make it a useful and easily-used tool for studying clinical populations (Maldonado, 1988).

3.9. Hallucinogen Rating Scale (HRS-S) (Strassman *et al.*, 1994).

The Spanish version is called the Escala de Evaluaci n de los Efectos Subjetivos de los Alucin genos (modified for MDMA) (Evaluation scale of subjective effects of hallucinogens).

Spanish version 1.2. was done by Riba *et al.* (1999) and is a translation of the Hallucinogen Rating Scale (version 3.06P) developed by Strassman *et al.* (1994). It consists of 100 items distributed in 6 clinical factors: *Somathesia* (measures internal somatic effects, profound and tactile); *Affect* (measures emotional and affective responses); *Volition* (measures the subject s capacity for interacting with herself and with her surroundings); *Cognition* (evaluates alterations in thought patterns and content); and *Perception* (measures visual, auditory, taste and smell experiences). The reliability of the scales (translated version) was evaluated in two separate studies using the Cronbach alpha coefficient, resulting in very similar values in both studies. The questionnaire shows good reliability and validity, which indicate its appropriateness for studying subjective effects of hallucinogens.

3.10. UKU scale of secondary effects (Lingjaerde *et al.*, 1987).

This is a scale that evaluates the clinical secondary effects of the use of psychoactive medications at therapeutic dosages, whether in daily use or in clinical studies. It consists of 43 items in four groups: psychological, neurological, anatomical and others. Each symptom is evaluated as being absent (0), mild (1), moderate (2), or severe (3).

3.11. The Penn helping alliance questionnaire (HAq) (Alexander y Luborsky, 1984).

This is a scale for measuring the patient s experience of the helping alliance, which must be completed by the patient at the end of each session. It consists of 11 items which the patient completes using a scale running from +3 to —3 according to the degree of agreement she feels with each statement, 2 open questions about ways in which her condition has improved or worsened after treatment, and one question about overall improvement on the Likert scale running from 1 to 5. The Spanish version of this questionnaire was done by vila (1991).

9. ADVERSE REACTIONS.

The following definitions will be used (RD 561/1993, 16-04-93):

Adverse reaction

Any undesirable experience that a subject has during a clinical study, considered to be related to the products under investigation.

Serious: That which produces death, threat to life, permanent disability, or leads to hospitalization or prolongs hospitalization. Furthermore, congenital anomalies and malignant processes are always considered serious.

Unexpected: This is an experience not described (in nature, seriousness or frequency) in the researcher s notebook.

Life-threatening: Those which, without the appropriate therapeutic intervention, could have led to the death of the subject.

The researcher is required to immediately notify the sponsor of the study of any unexpected or serious adverse effects. The sponsor will notify the AEM and the Ethical Committees of Clinical Investigation involved with the project of the unexpected and serious reactions that may be related to the treatments under investigation and that have occurred in Spain or in other countries, according to the guidelines specified in the following steps (without prejudice to the regulations of the Autonomous Communities):

The adverse reactions leading to death or which are determined to be life-threatening will be reported within 72 hours, at most; if all the information is not available at that time, this can be completed within 15 days. Other adverse reactions that are serious or unexpected will be reported within 15 days. The above will be reported by filling in a specific form (see appendix VI).

Information about anticipated serious reactions, not serious reactions, and those not considered to be related to the treatment under study will be tabulated and included on the annual report or at the end of the clinical study.

In the case of this study, unexpected adverse reactions will be defined as those which are different from the known adverse reactions to these substances.

The potential adverse effects (undesirable effects) and pharmacological effects will be registered every 30 minutes as well as when the manifest spontaneously in the subject or become evident to the researcher. The information that is thus obtained will be noted in the official register of the investigation in the observations section. These notations will include the type of effect, its severity, duration, time of occurrence, final result and type of corrective actions taken in response. If required, the specific forms mentioned above will be completed as well.

If undesirable effects are noted (clinical or analytical), the subjects will remain under medical observation until the effects have passed.

If the observed undesirable effects are clinically significant, the affected patient will be removed from the study and the possible suspension of the project will be considered.

10. ETHICAL CONSIDERATIONS

The Helsinki, Tokio, Venice (1992) and South Africa (1996) declarations on international ethics, the recommendations of the OMS, and the legal codes based upon Spanish law as it applies to clinical studies (Ley del Medicamento 25/1990, Real Decreto 561/1993).

The patients will sign an informed consent before the study begins. This will include information about the goals, progression and limits of the study covering the principal researchers and their collaborators. Additionally, the patients will also receive a paper describing the characteristics of the study. A copy of the informed consent as well as of the information sheet

are included with this document (see appendix V).

The clinical researchers agree to professional discretion concerning the progress of the study; the protocol and the appended documentation as well as the data collection sheets and all the information generated during the study will be considered confidential. This data can only be used by the researchers for specific purposes related to this protocol. The medication will be kept under lock and key.

The sponsor of the study is covered by an insurance policy that covers incidents that could result from the medications being studied (see appendix VI).

11. PRACTICAL CONSIDERATIONS

11.1 Responsibilities of the study participants

The sponsor, monitor and researcher will abide by the regulations described in sections 14, 15 and 16 of RD 561/1993 of 16 April, 1993.

Patients must accept the procedures that the protocol requires them to follow.

- They must agree to avoid any self-given medication during the study.
- They agree not to eat on selection and study days.
- No consumption of coffee or alcohol, colas, chocolate or cacao will be permitted in the 24 hours before each clinical day (days 1 and 2) or until 24 hours after the beginning of each clinical day of the study.
- Consumption of tobacco will not be permitted until two hours after the administration of the

medication.

- Patients will be informed of their right to leave the study at any time they may wish.

11.2. Corrections

The corrections, writing in the margins, and deletions that appear in the Data Collection Notebook must be legible and always be accompanied by the corresponding clarifying signature (or with initials) of the appropriate investigator and the date on which the corrections were made.

11.3. Management of the samples

The samples of the medication will be delivered to the principal researchers in the weeks before the study begins. They will be kept in a locked closet. The closet will have a register for recording the delivery and removal of the samples. Once the study is finished, the empty containers and any left over medication will be conserved.

11.4. Filing of the documentation pertaining to the study.

The sponsor is responsible for the filing of the documentation of the study. The time guidelines set forth in the Royal Decree about Clinical Studies will be followed.

The researcher will be responsible for keeping the identification codes of the subjects for at least fifteen years after the conclusion or interruption of the study.

The clinical histories of the subjects and all other original data will be kept for the maximum amount of time allowed by the hospital, the institution or the private office where the study is carried out.

11.5. Publication conditions.

All the individual and collective data, as well as the results derived from them, will be confidential, and can not be distributed, commented upon or publicized without the knowledge and authorization of the sponsor of the study.

12. STATISTICAL ANALYSIS

The results of the study will be presented in a precise format, including tables and numerical graphs with corresponding illustrations.

The results obtained in the psychopathological scales will be compared using a ANOVA/ANCOVA of repeated measures. If the ANOVA model yields results which are statistically significant, different groups will be compared using the multiple comparison test (Tukey Test) with a level of significance not more than $p \leq 0.05$. The statistical program SPSS will be used to analyze the results.

13. BIBLIOGRAPHY

See part 4 of this protocol.

Agreement and signature of the principal investigators:

Signed by: Pedro Antonio Sopelana Rodr guez Jose Carlos Bouso Saiz

APPENDIX I: DATA COLLECTION BOOK (DCB)

The same as described above.

APPENDIX II: MANUAL OF THE INVESTIGATOR AND BASIC BIBLIOGRAPHY

The same as described above.

APPENDIX III: SHEET FOR NOTIFICATION OF ADVERSE EFFECTS

The same as described above.

APPENDIX IV: ANALYTICAL SUMMARIES OF THE SAMPLES TO BE USED

Will be sent as soon as the samples have been obtained and analyzed.

APPENDIX V: INFORMATION SHEET FOR THE PARTICIPATING SUBJECTS AND INFORMED CONSENT

APPENDIX VI: INSURANCE POLICY PROPOSAL

The same as described above.

APPENDIXES II, III, IV, V and VI.