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MDMA and serotonin: based on two cases

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3,4-methylenedioxyamphetamine (MDMA) or «ecstasy» damages serotonin neurons in all animal species and there is growing evidence that this finding also applies to humans.

This fact, together with the increasing extended use in the young population, has important repercussions in the appearance of specific psychopathologic and cognitive disturbances associated to its use.

The authors present two clinical cases, in which psychopathological and cognitive symptoms are detected in MDMA users that support this hypothesis. Problems in the diagnosis of psychiatric disorders associated to MDMA and its clinical and therapeutic implications are discussed.

Key words:
MDMA. Serotonin. Psychopatology. Cognitive disorder.

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MDMA y serotonina: a propósito de dos casos

La 3,4-metilenodioximetanfetamina (MDMA) o «éxtasis» produce lesiones en neuronas serotoninérgicas en todas las especies animales y cada vez existen más evidencias que estos hallazgos pueden ser extrapolados a humanos.

Este hecho, junto con su uso cada vez más extendido en la población joven, tiene importantes repercusiones en la aparición de determinados trastornos psicopatólogicos y alteraciones cognitivas asociados a su consumo.

Los autores presentan dos casos donde se detectan síntomas psicóticos y neurocognitivos en consumidores de MDMA que apoyan esta hipótesis, y discuten las dificultades diagnósticas relacionadas con los tratornos psiquiátricos asociados al consumo de drogas, así como sus implicaciones clínicas y terapéuticas.

Palabras clave:
MDMA. Serotonina. Psicopatología. Alteración cognitiva.

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INTRODUCTION

3,4-methylenodioxymetanphetamina (MDMA) or «ecstasy» is a synthetic analogue of phenyl-ethyl amphetamine, which was patented in 1914 by Merck and mainly acts by favoring serotonin release and inhibiting its reuptake and, to a lesser degree and in an unknown way, releasing dopamine.

Shulgin and Nichols (1978) described the psychoactive profile of MDMA for the first time and proposed its use ad coadjuvant in psychotherapy thanks to its enactogen properties[1]. At the beginning of the eighties, its use as a recreational and abuse drug rapidly extended and it was forbidden in Spain in 1985. During the 90's, its use became popular, it being associated to certain types of music and mass parties («raves»). Since then, there has been an exponential increase of police confiscation of MDMA pills[2].

The different studies performed on consumption patterns conclude that the use of MDMA is preferentially recreational. Above all, it is used by non-marginal young subjects, the onset age of consumption being about 28 years. It is especially used by males from urban areas, with self-limited consumption associated to other substances (in this order: alcohol, cannabis, amphetamine and cocaine)[3].

Although the prevalence of its use is difficult to estimate accurately, the Report of the National Plan on Drugs 2000 with a survey to the general 15-65 year old population finds that: 2.4 % had tried ecstasy; 0.8 % in the last year and 0.2% in the last month. Prevalence is 4.7 % from 25 to 29 years, 1.9 % in the last year and 0.6% in the last month. Use became stabilized between the years 97 and 99 after a previous increase[4]. In the survey on drug use in the year 2000 school population (students 14-18 years) in the last 12 months, prevalence was 4.1 % and 6.1% had consumed it at some time. Mean age for onset of use was 15.4 years. Age range with greatest consumption decreased in this last survey between 16 and 18 years. Continued consumption of ecstasy decreased after the first use[4]. However, prevalence of use during lifetime, previous year and previous month was 10.9 %, 7.8 % and 4.5 % respectively also in our setting,

but in the population who did their Military Service between the years 1995 and 1999[5]. MDMA consumption in this study was related with higher levels of seeking sensations and neuroticism and psychoticism measured with the Eynsenck Personality Scale-Adult (EPQ-A) scale.

The effects of its long term use are being investigated at present. MDMA causes lesions in serotoninergic neurons in every animal species[6,7] and also dopaminergic alterations at very high doses[8]. Extension of these findings to humans is controversial and suggests an important debate, although several studies with functional neuroimaging suggest this same possibility[9-16]. Its clarification is clearly important given the implication of these neurotransmitters in cognitive and emotional functioning of the human beings.

At present, we have sufficient data to be able to verify that the damage caused in the serotoninergic system supposes alterations of cognitive performance of MDMA users[17-19]. Clinical evidence suggests that these abnormalities are maintained in non-consumption periods (20-24) and are more noticeable in regular consumers than in sporadic ones[25,26].

In this sense, the most consistently documented alterations are those related with memory and verbal learning[20,27,28]. It has been observed that MDMA users have significantly lower performance than the controls on these tests, which are very sensitive to temporal region functioning damage or alteration.

The following have also been mentioned in regular consumers: increase in task performance reaction times to visual and auditory stimuli, difficulties in focalization of attention together with cognitive alteration pattern characteristic of a frontal dysfunction[28,29]; attention difficulties such as major distractibility, alteration in working memory, executive functioning and, greatly related with the last process, prospective memory alterations (understood as capacity oriented towards the future of remembering what one should do at a certain time).

We present two clinical cases that support the results of the studies reviewed.

CLINICAL CASE 1

A case is presented of an 18 year old male who began psychiatric treatment 4 months before coming to our medical office, when he was still a minor, due to a picture characterized by intense feelings of depersonalization (he did not recognize himself in the mirror, he sees himself as if he were outside of himself and feels as if his limbs separate from his body...), and sensorial-perceptive disorders in form of vision of the tail of the movements. All of this is accompanied by intense anxiety and other psychopathological phenomena: disorder of experience of time, dysmegalopsias, dialogue and imperative auditory hallucinations, experiences of control, self-reference delusions and obsessive ruminations of songs or words.

He has no somatic background of interest. His father is diagnosed of schizophrenia. Regular consumer of cannabis in the last year, consecutively during the last three-four weekends. Prior to the onset of the symptoms causing the visit, he consumed $1^1/_2$ ecstasies per weekend. Since then, and up to the time he came to the medical visit for the first time, he has had very sporadic and short «flash-back» phenomena.

The complementary examinations showed the following results: complete blood count, biochemistry, urine analyses, MRI and EEG as well as neurological examination within normal limit. SPECT after a dose of 99mTC ECD (he was receiving at that time only treatment with lorazepam at a 2.5 mg/8 h dose): bilateral superior mesial frontal hypoperfusion, with signs of cortical thinning, that is extended to parietal regions, above all in right hemisphere; and involvement of bilateral temporal lobe, more significantly, the left one.

During more than one year of follow-up, there has been no change in the symptoms that remain chronic: psychedelic phenomena, depersonalization-derealization, hallucinations, referential delusion and obsessive symptoms. Even more, the patient feels increasingly more hopeless due to the lack of response to treatment received and has an intense sensation of being handicapped as a result of these symptoms. He progressively stops going out and discontinues any activity until he recovers.

Furthermore, he has great sensitivity to extrapyramidal effects with appearance of torsion dystonias with haloperidol and pimocide.

Treatments received are summarized with two alternatives: the use of antipsychotics (haloperidol, risperidone, pimozide, olanzapine and fluphenazine decanoate at therapeutic doses and times) with poor results and selective serotonin reuptake inhibitors (SSRI) (sertraline and fluoxetine) that caused an exacerbation of the derealization symptoms. During the entire time, he has received benzodiazepines, there also being periods in which he only has taken these drugs without there being any improvement.

CLINICAL CASE 2

A case is presented of a 29 year old male under treatment since 17 years of age with several therapies and approaches. Every weekend, he has consumed 1-2 ecstasy and cannabis pills since he was 16 years old. He consulted for the first time at 17 for a depersonalization-derealization picture. Since then, he has had these symptoms at some times in «flash-back» form and since age 22, chronically. At

some time, he has bean dependent on benzodiazepines and possible delusion due to deprivation. Beginning at 19 years of age, he added cocaine use during weekends. He has been abstinent from all abuse drugs for the last two years. He has never taken opiates or LSD.

Besides the depersonalization-derealization phenomena, he has complained of intense anxiety, worsening of cognitive functions and abulia. He generally spends hours at home, in bed, or going back and forth without any specific activity and failing within a few days at all attempts made to work. He attributes this to always being «distracted and disoriented.» He reports continuous complaints about his condition and himself, physical complaints and alexithymia. He also describes «forgetfulness» in form of lack of memory, difficulty to drive and time disorientation.

He has no somatic or family background of interest.

The complementary examinations performed (complete blood test, biochemistry, EEG, CT scan, MRI) are normal. Personality studies manifest an impulsive and immature personality, without detecting any serious involvement except in attention disorders in the neuropsychology tests.

During these years, he has come to several therapies, coming to a drug dependence care center for at least for one year where he was discharged due to his consumption pattern during weekends and presence of psychiatric disease. He has received many treatments with different SSRIs, tricyclic antidepressants, carbamazepine and classic new generation antipsychotics, with no results. The patient states he feels better with only the effects of psychostimulants.

DISCUSSION

Attribution of psychiatric pictures to drug consumption is always suggestive although a series of aspects should be considered. On the one hand, it is difficult to determine, especially in chronic courses, if the drug is the final cause or simply acts as a process catalyzer in a vulnerable person, for whom we also lack knowledge on his/her previous functioning. On the other hand, there is no guarantee on the composition of the drug consumed and, in most of the cases, the patients consume multiple drugs, so that attribution to one or another becomes a very speculative process.

However, neurotoxicity of ecstasy in animals is also known, at least on the serotoninergic neuron level and at doses equivalent to those used in humans recreationally[7]. Equally, we know the implication of failures in serotoninergic system functioning in different mental disorders[30] and there are descriptions of psychiatric and cognitive disorders associated to MDMA use in the literature[31-33].

In the first case, we have a young patient with a chronic psychotic disorder whose father has been diagnosed of schizophrenia. Although we could consider this as the diagnosis of choice, several factors make us consider the toxic origin of the picture. In the first place, its debut after repeated use of ecstasy and in the second place, a predominance of the «psychedelic» symptoms and anxiety above any other symptom together with the important brain involvement in the functional study, and finally, his poor response to antipsychotic treatment, awareness of the disease and egodystonic experience of the symptoms. There are numerous cases of psychosis reported after MDMA use[34-37], some of them with chronic course[38-39].

The second case poses more diagnostic difficulties. Here we have a patient with years of treatment and multiple drug consumption. Although we do not doubt the possible existence of a dual diagnosis, together with a personality disorder, it is likely that the cognitive difficulties of the patient, his degree of anxiety and depersonalization-derealization symptoms could be explained by the lesions associated to ecstasy consumption. Alterations in cognitive performance have been observed in up to 52 % of the consumers[40]. This second case shows difficulties posed to the consumer whose daily functioning is affected as a possible consequence of these deficits, still present two years after discontinuation of consumption. This fact corroborates that the cognitive alterations do not even reverse in prolonged abstinence periods, which suggests the presence of a neurotoxic lesion[41].

Every day, we know more about the brain functioning and on toxicity of certain substances. This can also help use in the knowledge of the physiopathology of mental diseases, but we should also consider our daily practice and be capable of incorporating new diseases for which the conventional solutions have poor response. That is why the primary, secondary and tertiary prevention program planning, which is becoming the day to day process of our care as multiple diagnoses, begins to be a requirement.

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