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Pharmacological treatment of acute stress disorder with propranolol and hypnotics

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Introduction. Pharmacological treatment of trauma-related mobidity has neither the efficacy nor specificity desired. Thus, several attempts have been made to add new drugs to the usual treatments, in this case with propranolol and hypnotic drugs.

Method. We offered this treatment to the victims of the March 11, 2004 terrorism attack who were attended within the first week of this attack for psychiatric reasons (n = 21) and who also fulfilled criteria for acute stress disorder (ASD) (n = 15) and had no contraindications for the treatment (n = 3). Trauma intensity was measured with Horowitz impact of events scale (IES). Significant clinical data were collected.

Results. Propranolol treatment was associated with clinical remission of target symptoms in 63.6 % of the cases, partial response in 27.3 % and no response in 9.1 %. Hypnotic treatment was also associated with clinical remission in 61.5 % and partial response in 38.5 %. Statistically significant correlations were found at the beginning for IES with disability, and after the first month with the propranolol and hypnotic responses.

Conclusions. Propranolol and hypnotic treatments are useful in the decrease of ASD symptoms. IES is very useful to predict disability as well as poor response to propranolol or hypnotic drugs. More studies are needed to confirm the data obtained in our sample.

Key words:
Acute stress disorder. Propranolol. Hypnotics. Temporary disability. Horowitz impact of events scale.

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Tratamiento farmacológico del trastorno de estrés agudo con propanolol e hipnóticos

Introducción. El tratamiento farmacológico de la patología asociada a los traumas no presenta ni la eficacia ni la especifidad deseada, por lo que se realizan intentos constantes de añadir nuevos fármacos al arsenal terapéutico, en este caso con propanolol e hipnóticos.

Método. Se ofreció dicho tratamiento a las víctimas del 11 de marzo de 2004 recibidas la siguiente semana por causa psiquiátrica (n = 21) que cumplieran criterios de trastorno de estrés agudo (TEA) (n = 15) y que no presentaran contraindicaciones para ello (n = 3). Asimismo se evaluó la intensidad del trauma a través de la escala de intensidad de Horowitz (EIH) y se recogieron los datos clínicos principales de los pacientes.

Resultados. Los pacientes tratados con propanolol presentaron remisión de los síntomas diana en el 63,6 % de los casos, respuesta parcial en el 27,3 % y falta de respuesta en el 9,1 %. Por su parte, el tratamiento con hipnóticos presenta una remisión de los síntomas en el 61,5 % de los casos y una respuesta parcial en el 38,5 %. Se encuentran correlaciones significativas estadísticamente para la EIH al inicio con el tiempo de incapacidad y al mes con la respuesta al propranolol y a los hipnóticos en las distintas subescalas.

Conclusiones. El tratamiento con propanolol y con hipnóticos resulta útil en la disminución de la sintomatología del trastorno de estrés agudo. La EIH resulta de gran interés como predictor de incapacidad, así como la mala respuesta a propanolol y a hipnóticos. Son necesarios más estudios al respecto que confirmen los hallazgos de esta muestra.

Palabras clave:
Trastorno de estrés agudo. Propanolol. Hipnóticos. Incapacidad laboral. Escala de Intensidad del Trauma de Horowitz.

INTRODUCTION

Traumatic events may generate psychiatric pathology based on different personality mechanisms and traits that act as factors of vulnerability and resilience[1-3]. Subjects exposed to a trauma frequently develop adjustment reactions that may cause acute stress disorder (ASD), usual precursor to posttraumatic stress disorder (PTSD). Since they have been considered to be independent nosological entities[4], there

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has been an increase in the recognition of their capacity to become chronic and the disability that may develop as well as in their study, this radically modifying the subject's style of life and patterns of life coping.

Stimulus avoidance[5], reconsolidation of previous stimuli[6], and capacity to extinguish classic conditioners[7] stand out among the vulnerability and resilience factors because of their possible psychopharmacological influence. Norepinephrine (NE) is a common neurochemical nexus among these three factors, it being of great importance in the anxiety experience associated to the memory of the event[8-9]. This anxious experience is manifested through sympathetic nervous system mediated vegetative symptoms. Activation of its beta receptors causes the known tachycardias, hyperventilation, tremor, etc[10-11]. Furthermore, on the central level, NE is involved in the activation of the *locus ceruleus*, activating the recall of anxiety, as occurs in the anxiety disorder[12] and in PTSD[13]. That is why it is extremely interesting to use a single substance to act on the anxiety experience on the peripheral and central levels. Among the beta blockers, the substance with the most data available regarding its utility in patients with acute trauma[14-16] and that has the greatest functional availability for our setting[17] is propranolol since it acts on the peripheral and central levels, the beta blocker being that which best crosses the hematoencephalic barrier.

There are significant difficulties, such as absence of etiological treatments, in the studies on the response to drug treatments after a trauma. This is due to the fact that there is only partial knowledge on its pathophysiology and individual variants of response to the drug[15]. In addition, there are differences in the pathogenic capacity of the different types of trauma[18-20]. A trauma caused by the amputation of a finger while one is doing his/her usual work is not the same as that caused by amputation of the same finger because of a letter bomb. Furthermore, harm suffered by a violent situation may vary based on whether it is an isolated event within a peaceful living experience or one more act within the situation of generalized violence. Violent and unexpected acts, such as terrorist attacks, have a very high pathogenic potential. The March 11, 2004 terrorist attacks in Madrid meant that those affected by it in person were exposed to a trauma of enormous proportions because they were subjected to visualization of tremendously bloody images after the explosions and physical sequels experienced individually. The simultaneous existence of this group of consecutive traumas has made it necessary for these patients to make a great effort in order to adapt to and integrate the experiences.

Incorporation of propranolol into the available therapeutic armamentarium seeks to favor adaptation and recovery of the functionality of the patients subjected to acute trauma, making it possible to recall what has occurred with the minimum anxious symptoms and decrease avoidance of everything that reminds them of the trauma.

MATERIAL AND METHOD

The patients seem in Ibermutuamur for psychiatric reasons as a consequence of the March 11 terrorist attack during the first week were enrolled in the study (n = 21). Treatment with propranolol was administered to the patients who fulfilled ASD criteria (n = 15), except for those with contraindications for the treatment or those who refused it. Three of the patients with ASD were excluded from the treatment, two cases due to basal high blood pressure and another case because of previously excessive blood pressure responses to propranolol. The remaining six cases did not fulfill ASD criteria, one because of personality disorder who tried to feign posttraumatic sequels, another due to usual cannabis consumption and another because of cocaine use relapse. The remaining patients did not fulfill criteria for other psychiatric diagnoses. Finally, one of those who had no pathology suffered depression and PTSD at 45 days.

Propranolol was administered orally, mainly in anticipation of situations that could cause important autonomic arousal, such as the exposure to feared situations or presence of intense flashbacks. Dosage was individualized based on response and tolerance to side effects, with a minimum of 5 mg and maximum of 20 mg in each dose. In this way, the mean daily dose was 19.55 mg (SD = 6.88).

Given the seriousness of the clinical pictures presented and possibility of permanent sequels, it was decided to offer all the necessary and available psychological and drug treatments from the very beginning[21,22]. All the patients received psychotherapy with training in anxiety management techniques, exposition therapy, cognitive techniques for intrusions and depressive symptoms and psychoeducation regarding the nature of their symptoms and condition[23]. Since this psychotherapy was performed in all the cases, we could not estimate the grade of efficacy in these patients compared to those with no psychotherapy. Hypnotic drugs were used symptomatically (n = 13), lormetazepam as first choice (n = 9) and zolpidem in case of resistance (n = 3) or previous positive experiences that made it the drug of choice (n = 1). Patients who had evolved to PTSD (33 %) had not initiated any treatment with selective serotonin reuptake inhibitors (SSRI) up to the time of diagnosis nor at one month after of the event.

DSM-IV[24] criteria were used for the clinical diagnoses, the SCID being applied[25]. It was considered that the use of Horowitz impact of events scale (IES)[26] was of interest in the first week and at one month of the event, using both a direct score and the variation. Clinical intensity was estimated at the beginning with the cinical global impression (CGI) scale and global activity evaluating scale (GAES)[24] At one month of treatment, response to drugs was evaluated according to the grades foreseen on the therapeutic response scale of the Expert Consensus Guideline Series[27] Furthermore, the period during which the patients had temporary disability for their usual work and the ASD dur-

ation were estimated. Statistical processing of the data was performed with the computer program SPSS 10.0, using the usual parameters for descriptive statistics. The χ^2 in comparison of categorical data, Mann-Whitney's U test for comparison between groups of ordinal variables, Student's *t* test for comparison between quantitative and qualitative variables of two groups, Pearson test for correlations between qualitative variables and Spearman's correlations between quantitative variables and ordinals were used for the inferential statistics. In all the tests, a p value less than or equal to 0.05 was considered significant, especially indicating those whose p was less than or equal to 0.01.

RESULTS

Mean age in the general group (n = 21) was 34.43 years (SD = 10.99), minimum of 21 and maximum of 55, while distribution by gender was 28.6 % for women and 71.4 % for men. ASD was experienced by 71.4 % of the patients (n = 15), with mean duration of 22.33 days (SD = 7.99). Mean age of these patients was 34.80 (SD = 10.99), 40 % being women and 60 % men. Patients with ASD considered the most important symptom to be re-experience (61.5 %), followed by dissociation (15.4 %), psychosocial deterioration (15.4 %) and avoidance (7.7 %), as shown in figure 1. Progression to PTSD occurred in 30 % of the patients seen (n = 6), with mean age of 36.5 (SD = 10.89) and distribution by gender of 33.3 % women and 66.7 % men. The primary symptom of PTSD was sociolaboral deterioration in 40 %, hyperarousal in 40 % more and re-experience in 20 % (fig. 2).

Treatment with propranolol was indicated in 57.14 % (n = 12), with a mean age of 37.08 (SD = 10.91), women accounting for 33.3 % and men 66.7 %. Good response or complete remission of the symptoms was obtained in 63.6 % of the cases, partial response in 27.3 %, and no response in 9.1 % (fig. 3). Mean age of the patients who were not treated with propranolol (n = 9) was 30.89 (SD = 8.98), women accounting for 22.2 % and men 77.8 %. Differences in age and gender regarding treatment with propranolol were not statistically significant.

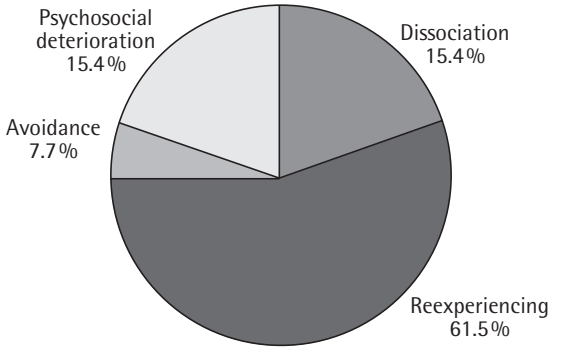

Figure 1 *Main symptoms among patients who have ASD (n = 15). Evaluation by the patients.*

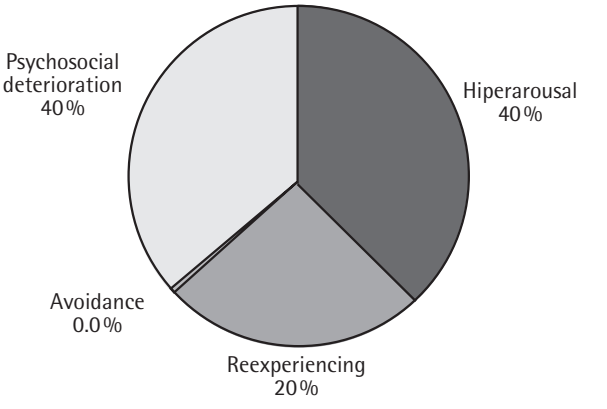

Figure 2 *Main symptoms among the patients who finally had PTSD (n = 6). Evaluation by the patients themselves.*

This difference in symptom intensity of patients with ASD between those who received treatment with propranolol and those who did not is seen in the IES, CGI ($p < 0.05$) and GAES (tables 1 and 2). There was more intense improvement in the patients with ASD who were treated with propranolol at one month of the event than those who did not, especially, there being statistical significance in the intrusion subscale on the Horowitz impact of events scale ($p < 0.05$).

Treatment with hypnotics was carried out by 61.9 % of the patients (n = 13), with a mean of 38.08 years (SD = 9.93), women accounting for 30.8 % and men 69.2 %. Those who did not follow treatment with hypnotics had an age of 30.5 years, with 33.3 % women and 66.7 % men. However, although there were differences in the severity of the symptoms of the patients treated with and without hypnotics (CGI, GAES and

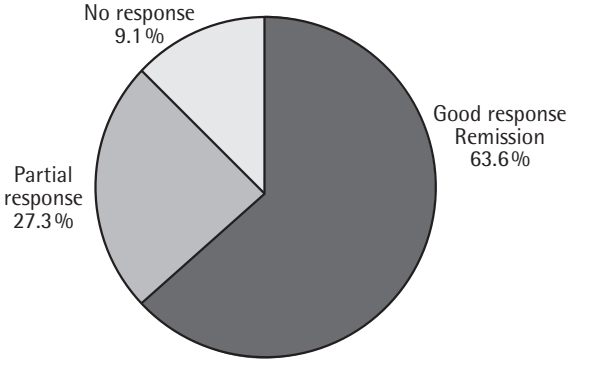

Figure 3 *Degree of response to treatment with propanolol in patients who had ASD (n = 15) after the March 11th terrorist attacks.*

Table 1 Symptom intensity in patients with ASD not treated with propranolol (n=3)

	Minimun	Maximun	Mean	SD
Clinical global impression	2.00	5.00	3.2222	0.8333
Global activity evaluating scale	60.00	95.00	90.000	11.456
Horowitz impact of events scale basal	28.00	52.00	43.750	10.904
Horowitz Impact of events scale. Intrusions basal	20.00	29.00	26.750	4.500
Horowitz impact of events scale. Avoidance basal	8.00	23.00	17.00	8.683
Horowitz impact of events scale 1 month	14.00	47.00	53.500	15.926
Horowitz impact of events scale. Intrusions 1 month	12.00	27.00	20.250	6.994
Horowitz impact of events scale. Avoidance 1 month	2.00	21.00	13.250	8.995
Differential IES-1	4.00	18.00	10.250	6.849
Differential IES-I1	2.00	12.00	6.500	4.434
Differential IES-A1	0.00	6.00	3.750	2.872

Table 2 Symptom intensity in patients with ASD treated with propranolol (n=12)

	Minimun	Maximun	Mean	SD
Clinical global impression	3.00	6.00	4.6000	0.8433
Global activity evaluating scale	40.00	95.00	79.500	16.906
Horowitz impact of events scale basal	37.00	73.00	56.666	10.603
Horowitz impact of events scale. Intrusions basal	22.00	35.00	30.666	5.331
Horowitz impact of events scale. Avoidance basal	15.00	38.00	26.000	8.301
Horowitz impact of events scale 1 month	2.00	57.00	31.727	19.565
Horowitz impact of events scale. Intrusions 1 month	0.00	29.00	14.818	8.483
Horowitz impact of events scale. Avoidance 1 month	1.00	32.00	16.909	12.053
Differential IES-1	–2.00	65.00	23.818	19.140
Differential IES-I1	0.00	35.00	15.454	9.893
Differential IES-A1	–9.00	35.00	8.363	12.468

IES), no significant difference was observed in the variation of the trauma intensity by administration of the drug. In spite of everything, it should be stated that there was complete remission or good response in 61.5%, and partial improvement in 38.5% of the cases (fig. 4).

The Horowitz trauma impact scale (tables 1 and 2) makes it possible to indicate the cases with greater functional alteration from the beginning, since there is an intense correlation between the intrusions subscale at the onset with time on temporary disability (TD) ($r=0.878$; $p<0.05$) (fig. 5). Mean time of TD of the patients was 10.0 weeks (SD = 10.68). This scale, which was repeated at one month of the trauma, helped us to indicate the evolution, since there is a correlation (table 3) between the positive response to propranolol in the global IES-A-1m score ($r=-0.691$; $p<0.05$) and in the intrusion subscale ($r=-0.678$; $p<0.05$) as well as with the response to hypnotics in the global scale ($r=-0.751$; $p<0.05$) and the intrusion subscale ($r=-0.748$; $p<0.05$). This scale also shows correlations with ASD duration for IES-1m ($r=0.636$; $p<0.05$), IES-I-1m ($r=0.608$; $p<0.05$) and for IES-A-1m ($r=0.579$; $p<$ v0.05). Personal depressive background also has an association with IES-1m ($p<0.01$), IES-I-1m ($p<0.01$), EIH-A-1m ($p<0.05$), age ($p<0.05$), and disability period ($p<0.01$). Precisely, the period of temporary disability (TD), in addition to with IES-I basal, correlates, as is to be expected, with the duration of ASD ($r=0.649$; $p<0.05$) (fig. 6) and with the response to propranolol in patients with ASD criteria ($r=-0.704$; $p<0.05$) (fig. 7).

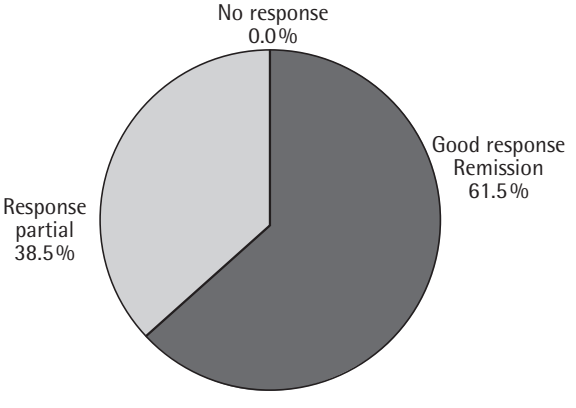

Figure 4 *Degree of response to treatment with hypnotics in patients who had ASD TEA (n = 15) after the March 11th terrorist attacks.*

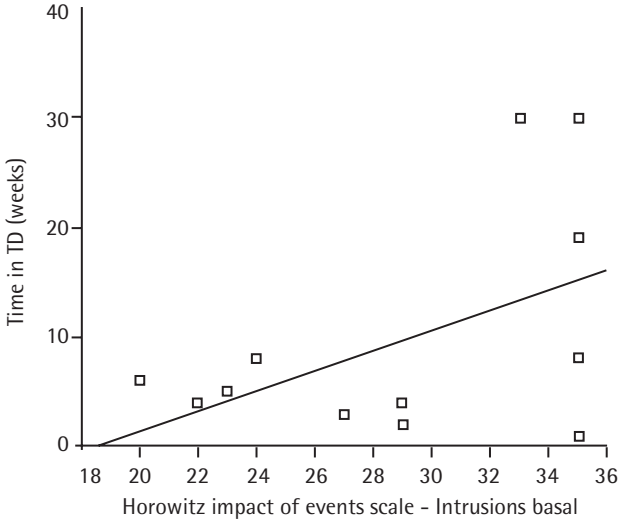

Figure 5 *Correlation (r = 0.878; p <0.05) between score in intrusions of the Horowitz Impact of Events Scale after the trauma (IES-I basal) and weeks of temporary disability (TD) in our sample.*

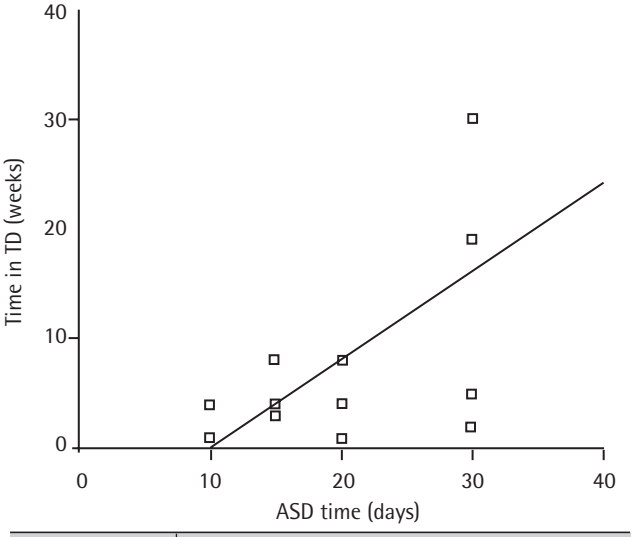

Figure 6 *Correlation between weeks of temporary disability (TD) and duration of the ASD episode (r = 0,649; p <0,05).*

DISCUSSION

It is very likely that the absence of statistical significance of the differences found in the different groups (ASD, Trauma, PTSD) regarding age and gender distribution is due to the size of the study subgroups, which are too small to be able to show these differences statistically. Thus, the older age of the group that developed PTSD versus the general group[28] and a larger proportion of women among the groups with pathology, both ASD and PTSD, coincide with the previously existing bibliography in regards to vulnerability to the increased trauma in the women[1,29]. This is probably related to the constant variability of the hormone levels. Experts in the distribution and epidemiology of post-traumatic pathology[18,30-31] coincide in stating the importance of the presence of personal backgrounds and previous traumas. Both situations generally become more frequent as age increases, so that it could be expected that patients who had PTSD would be older than those you did not. Precisely, in our sample, presence of personal depressive backgrounds showed an association with older age, longer duration of ASD and with TD time, indicating a greater degree of disability as the traumas accumulate and the adjustment mechanisms decrease on a probable sensitivity for harm of the noradrenergic and serotoninergic systems, usually involved in depression.

The descriptive data available regarding the principal symptoms in the different stress disorders also provide interesting reflections. At first, the main symptom for the patients is re-experiencing. However, as time goes by and the PTSD becomes established, the patients give more importance to hyperarousal and sociolaboral deterioration. In this regards, the different actions made on the patients must be taken into account. In the first place, the psychoeducative approach made on the pathology that is occurring and the

Table 3 **Significant correlations found in our sample for the Horowitz impact of events scale both in its general component (IES-1m) and in the intrusions subscales (IES-I-1m) and avoidance one (IES-A-1m) for the degree of response to propranolol, degree of response to the hypnotics, duration of the ASD and personal backgrounds of depression**

	EIH-1m	EIH-I-1m	EIH-E-1m
Degree of response to propranolol	r = –0.691; p < 0.05	r = –0.678; p < 0.05	
Degree of response to hypnotics	r = –0.751; p < 0.05	r = –0.748; p < 0.05	
Duration of ASD	r = 0.636; p < 0.05	r = 0.608; p < 0.05	r = 0.579; p < 0.05
Depressive PB	p < 0.01	p < 0.01	p < 0.05

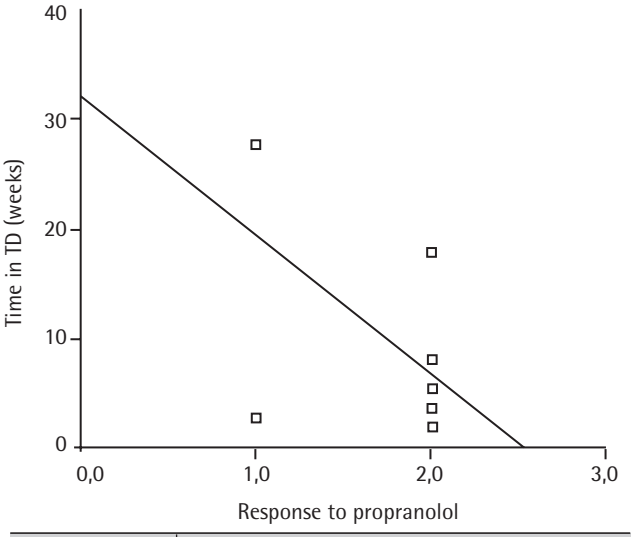

Figure 7 *Correlation between weeks of temporary disability (TD) and degree of response to propranolol (r = –0,704; p < 0,05) in patients diagnosed of ASD.*

type of response given to an abnormal situation[23] may have decreased the importance given to some very uncomfortable symptoms that are allowed to exist without dealing with them in order to decrease the recourses used in the re-experiencing. In addition, it must be considered if the purpose of the treatment with propranolol has been fulfilled from the psychopharmacological approach. The purpose of noradrenergic blockage of the *locus ceruleus*[13] is to allow recall of what occurred without an intense associated experience of anxiety. In this way, the patients who received treatment with propranolol were able to normalize their relationship with their memories and fears, decreasing the malaise caused by the consequent recall of what occurred.

Continuing with the characteristics of the patients who received drug treatment, it is important to stress that CGI was more serious in the propranolol treated patients ($p < 0.05$). This greater seriousness may be consistent with the symptoms established in the target (experience of anxiety associated to recall, and behavioral avoidance due to vegetative symptoms) in the onset of the follow-up. This is because this symptomatology is precisely the most specific one of the potentially serious disorders such as ASD,[32] on the contrary to insomnia (target of the hypnotics), which is less specific and more ubiquitous in the psychiatric nosology.

The correlation presented between decreased intensity of the symptoms measured especially through the IES with the degree of response to propranolol and to hypnotics is in line with previous works regarding the efficacy of these substances for post-traumatic symptoms[33-35]. A very important role in the improvement of the quality of rest and especially in the quality of life is given to the drug treatments, both with propranolol and hypnotics, as a greater decrease is obtained in the intensity of the trauma. However, the responses to propranolol and to the hypnotics in our group differ in their correlations in regards to the influence in the disability period. The correlation existing between the duration of the TD period and response to propranolol seems to indicate the efficacy of the beta blocker to permit coping of the situations of daily life related with trauma, both physically through exposition and mentally through recall and use of memories. This clinically confirms the great involvement of norepinephrine in the physical and psychic experience of anxiety[13].

The study of the results of the IES, especially of its correlations and associations, makes it possible for us to identify markers that may act as predictors of the evolution. Thus, as we have seen previously, response to propranolol and to hypnotics have a correlation with IES-1m and with IES-I-1m, indicating that the improvement in anxious symptoms and night time rest makes it possible to decrease the intensity of the trauma at one month, mainly helped by the decrease of intrusive symptoms (IES-I-1m).

Similarly, IES-1m, and its two subscales (IES-I-1m and IES-A-1m) have a correlation with the duration of ASD and their high scores are associated to the presence of personal depressive backgrounds. Correlation of the EIH-1m scores and its subscales with duration of ASD is consistent with the internal structure of the scale and the symptoms characteristic of the pathology studied[26]. Intrusions and avoidance, along with the associated sociolaboral deterioration, are maintained at high levels of intensity while they fulfill criteria for ASD[32]. This elevated symptom intensity may be facilitated through the previously damaged neurochemical structures, as in the case of norepinephrine and serotonin[13]. Thus, the association presented between the personal depressive backgrounds and symptom intensity of the IES at one month of the event can be justified.

In addition, the IES at onset seems to act as a predictor of the duration of the disability period, as is indicated by the correlation found between the IES and the TD time. Capacity to indicate the symptom that causes greater sociolaboral dysfunction, estimated from the TD time, seems to be a characteristic of the original scale. Although the last version of this scale[26] includes a third subscale regarding hyperarousal, the version used is that which provides the greatest experience in research regarding trauma[37] and makes it possible to indicate both pathogenic capacities of the different traumas as well as therapeutic ones of the different actions. Thus, based on the data of our sample, we can consider the general score of IES at the first week as a predictor of disability.

Speaking about the limitations of the study, very special consideration should be given to the sample size and the need to apply sufficient effective treatments from our setting. Basically for ethics reasons, we cannot leave any patient without treatment. The presence of this number of patients prevents us from dividing the sample and randomly applying each one of the different drug and psychotherapy

treatments individually. However, protocolization and normalization of the psychiatric treatments, as is recommended in situations of disaster and catastrophe[38,39], make it possible for us to conduct a study in which the psychotherapeutic treatment has been homogenized and its effect in the patients who take one psychodrug treatment or another is similar. In this way, the differential elements of the study group on ASD are the drug treatments that have been administered. In spite of the limitation of the sample size, it is important to state that there are no previous pharmacological studies of these characteristics in our setting, since the simultaneity of so many patients in a single trauma of the size of March 11th is uncommon.

CONCLUSIONS

Pharmacological treatments with propranolol and hypnotics are associated in our sample with decrease of the trauma-related symptoms, measured with the IES. They have greater improvement of the most cognitive symptoms, as intrusions. Thus, these treatments have helped our patients to normalize social and professional activity.

The score of the IES at onset, after the trauma, personal depressive backgrounds and bad response to propranolol have been indicated as predictors of disability in our population as all of them correlate with TD time, a sign of the difficult to carry out the normal life.

Although the conclusions presented are coherent with previous research in this regards, more studies with larger samples that permit the development of the study towards the pathological and therapeutic subgroups and that can confirm the data presented herein seem to be needed. Inclusion of control groups, or the study of the patients who have remained on the waiting list, may help us to know more in regards to the role of the hypnotics in the reestablishment of the sleep repairing function and the role of propranolol as extinguisher of anxious hyperactivation after exposure to trauma or its recall, on both the central and peripheral levels.

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