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Effectiveness of tianeptine in patients with major depressive disorder and substance use disorder

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SUMMARY

Introduction. The depressive disorder coexists in a high prevalence with a substance-related disorder, which is associated with a worst prognosis. The therapeutic interventions for this co-morbidity lack of the appropriate scientific support. The existing evidence suggest that the currently available anti-depressive drugs are of minor efficacy in this group of patients. An alternative would be the use of different drugs with distinctive neurobiological mechanism of action. The aim of this study was to describe the clinical development of a series of patients affected by this comorbidity under treatment with tianeptine under usual clinical practices.

Methods. Study design corresponds to a post-authorization, observational, retrospective, multicentric, study under usual clinical practice study. The clinical history of the last consecutive 100 patients diagnosed of major depressive and substance-related disorders under treatment with tianeptine for at least 3 months was reviewed. The following scales were evaluated in 3 times (basal, intermediate, final): HDRS, ICG and SDS.

Results. Most patients were treated by a combination of anti-depressive drugs together with psychotherapy. At the end of follow-up, 70 % patients had a clinical remission in accordance with HDRS and 76 % of them had a mild or significant improvement in ICG. Regarding the use of substances, the most remarkable decreases were obtained in the consumption of alcohol, and cocaine.

Conclusion. Tianeptine could be a useful drug for the treatment of patients with dual diagnosis of depression and substance-related disorder, together with other therapeutic interventions.

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EFECTIVIDAD DE TIANEPTINA EN PACIENTES CON DEPRESIÓN MAYOR Y TRASTORNO POR USO DE SUSTANCIAS

RESUMEN

Introducción. La depresión coexiste frecuentemente con los trastornos por uso de sustancias (TUS), lo que conlleva un peor pronóstico. Existe una importante falta de evidencia sobre las intervenciones terapéuticas más efectivas para esta comorbilidad. Los estudios existentes sugieren que los antidepresivos disponibles actualmente son poco eficaces para estos pacientes. La disponibilidad terapéutica de antidepresivos con mecanismos neurobiológicos diferentes podría ser una alternativa. El objetivo es describir la evolución de un grupo de pacientes con esta comorbilidad que han realizado tratamiento con tianeptina en condiciones de práctica clínica habitual en consultas de deshabituación.

Metodología. Se diseñó un estudio postautorización, multicéntrico, retrospectivo y observacional de práctica clínica habitual. Se revisaron las historias clínicas de los 100 últimos pacientes diagnosticados de depresión mayor y TUS, tratados con tianeptina durante al menos 3 meses. Se evaluaron en tres ocasiones (inicial, intermedia y final a los 3 meses) las siguientes escalas: Escala de Evaluación para la Depresión de Hamilton (HDRS), Escala de Impresión Clínica Global (ICG) y Escala de Gravedad de la Adicción (SDS).

Resultados. La mayoría de los pacientes fueron tratados con una combinación de psicofármacos y psicoterapia. Al final del seguimiento 70 pacientes (70 %) obtuvieron una

remisión clínica según la escala HDRS y 76 pacientes (76 %) se clasificaron con mucha o moderada mejoría según ICG. Respecto al consumo, los descensos más destacados se produjeron en los trastornos por uso de alcohol y cocaína.

Conclusión. Tianeptina, en monoterapia o en combinación, puede ser un tratamiento de utilidad para pacientes con depresión dual de forma conjunta con otras medidas terapéuticas que traten de forma integrada estos pacientes complejos.

Palabras clave. Tianeptina, trastorno depresivo mayor, trastorno por uso de sustancias, depresión dual, estudio observacional.

INTRODUCTION

Major depressive disorder is one of the most prevalent and severe psychiatric disorders, due to its impact on the individuals affected and their families and the considerable strain that it places on health and social care services[1]. Depression very often co-occurs with substance use disorders (SUDs), as well as with behavioral addictions such as compulsive gambling, which entails a greater negative impact than the presence of one disorder alone[2]. Not only is dual depression highly prevalent, but greater clinical severity is also observed in patients suffering from it. This disorder has a more torpid course and there is less treatment adherence and compliance as well as a higher number of suicide attempts among these patients. They are also more resistant to usual treatments[2,3].

There is a considerable lack of evidence on what the most effective therapeutic interventions for this comorbidity are, due to the fact that the presence of an SUD is usually an exclusion criterion in clinical trials for antidepressants. As a result, the most appropriate treatments for a very large population group are yet to be identified[3].

Along with this lack of evidence, existing studies suggest that the antidepressants currently available, principally selective serotonin reuptake inhibitors (SSRIs), are not very effective for treating the depression symptoms suffered by dual diagnosis patients[3,4]. Furthermore, antidepressants are not effective for treating the SUDs associated with depression, which would indicate that these patients should be treated with different drugs for the depression and the SUD, as well as with integrated psychotherapeutic interventions for both disorders[5].

Epidemiological studies highlight that dual depression is highly prevalent. In the Madrid Study on Dual Pathology on patients receiving treatment in the mental health or addiction networks, a prevalence rate of 30.9% was found for major depressive disorder among dual diagnosis patients[6]. In a meta-analysis of studies carried out on the general population between 1990 and 2014, the authors confirmed the strong association between depression and SUDs, obtaining an odds ratio of 3.8 for the association between illicit drug use disorders and major depressive disorder and an odds ratio of 2.4 between alcohol use disorder and major depressive disorder[7]. It has also been found that this dual pathology affects women more than men[5]. In this study, the course for women seemed to be worse according to their outcomes in the predictive model for remission based on the Hamilton scale (and also others), but those outcomes were not statistically significant (p=0.06). As they did not reach significance level, it was not possible to confirm this poorer response, although it is worth bearing in mind for future studies.

Therapeutic availability of antidepressants with different neurobiological mechanisms for amine modulation (noradrenaline, serotonin, dopamine), could be another consideration with regard to these patients. Although the monoamine hypothesis of depression is still prominent, other theories explaining this disorder are becoming increasingly important. So, where there are changes in neuroplasticity in structures such as the hippocampus, the amygdala or the prefrontal cortex[8], adverse effects due to chronic stress on certain neurotrophins such as BDNF or on the hypothalamic-pituitary-adrenal axis, and neuroinflammatory states[9,10], glutamatergic neurotransmission becomes significant. Along with experimental data, this implication is supported by the use of drugs such as ketamine for depressive disorders, which act on the NMDA receptor[11].

Tianeptine is an antidepressant that has recently come onto the market in Spain, which has a mechanism of action involving glutamatergic modulation,[10,12] differentiating it from the other groups of antidepressants currently available. Its effectiveness in treating depressive disorder has been demonstrated in placebo-controlled clinical trials and it has been found to be just as effective as tricyclic antidepressants and SSRIs[8]. Furthermore, in comparison to other antidepressants, a faster onset of action has been observed and it may be more effective on certain symptoms associated with depressive disorders, such as cognitive and somatic symptoms, pain and associated anxiety, as one study has demonstrated[12]. Tianeptine does not act on monoamines as is the case with other antidepressants and it has recently been determined that its action focuses on regulating glutamatergic transmission[9] and neuroplasticity in the amygdala and hippocampus[10].

Initial pre-clinical studies showed that tianeptine enhanced the signaling cascades associated with synaptic plasticity[10]. In electrophysiological experiments using hippocampus samples from mice, tianeptine increased the isolated frequency amplitude of the AMPA receptors[13]. Therefore,

tianeptine could protect against the consequences resulting from glutamatergic hyperactivity due to chronic stress and improve neuroplasticity in regions involved in depression by: acting at the glycine site of NMDA receptors, enhancing the effectiveness of the AMPA receptors through the phosphorylation of the GluA1 subunit, increasing the synthesis and traffic of those receptors and regulating the glutamate receptors in glial cells. In addition, various experimental studies have shown that tianeptine increases the secretion of neurotrophins such as BDNF and NGF in the hippocampus and the amygdala, which decrease as a result of stress. Furthermore, it enhances hippocampal neurogenesis, lessens hyperactivity of the hypothalamic-pituitary-adrenal axis and decreases pro-inflammatory cytokines in the hippocampus and the prefrontal cortex. In this way, tianeptine could prevent hippocampal atrophy and the increase in dendritic arborization in the basolateral nucleus of the amygdala, induced by chronic stress[9,10].

Recent studies show that tianeptine acts as a weak μ-opioid receptor (MOR) agonist and also suggest that the regulation of the glutamate pathway appears to take place indirectly, through opioid receptors, rather than through the AMPA and NMDA channels. It was also found to be a full delta opioid receptor (DOR) agonist but with lower potency and showed no effect at the kappa-opioid receptors (KOR)[14]. In that study, the authors emphasized the similarity between the activation of those circuits through the opioid effect of tianeptine and the effects exerted on circuits by the direct NMDA receptor antagonists, which also showed rapid onset of antidepressant action[14]. This is due to the fact that the activation of MORs and DORs in inhibitory interneurons in the hippocampus decreases their activity, disinhibiting CA1 glutamatergic neurons,[12] which is in line with prior evidence that tianeptine has an enhancing effect on excitability and synaptic plasticity in CA1[15]. Therefore, the authors hypothesized that the dual activation of opioid receptors (MOR y DOR) could be responsible for most of the antidepressant effects[14]. Nonetheless, the MOR receptor agonism does not lead to tolerance or withdrawal symptoms as in the case of morphine, which suggests that different transduction mechanisms come into play. This information on tianeptine's possible mechanism of action calls into question some reports of it being misused as a stimulant, although this concern about potential misuse of antidepressants has been mentioned in scientific literature for many years in relation to a wide range of antidepressants currently in clinical use[16]. In a clinical trial comparing tianeptine with a placebo and methylphenidate, psychostimulant effects were not found[17].

Table 1 Sociodemographic characteristics and use

	Absolute frequency (relative)
Marital status	
Single/never married	27 (27 %)
Married or steady partner	31 (31 %)
Separated/divorced	39 (39 %)
Widowed	3 (3 %)
Education	**Absolute frequency (relative)**
Primary	18 (45 %)
Secondary	18 (45 %)
University	4 (10 %)
Employment	**Absolute frequency (relative)**
Employed	41 (41 %)
Volunteer	1 (1 %)
Student	6 (6 %)
Homemaker	14 (14 %)
Retired	13 (13 %)
Unfit for work	18 (18 %)
Unemployed	5 (5 %)
Other	2 (2 %)
Somatic pathology	**Absolute frequency (relative)**
AHT*	12 (12 %)
Diabetes mellitus	12 (12 %)
Obesity	7 (7 %)
Hepatitis (HCV/HBV)**	12 (12 %)
Tuberculosis	0 (0 %)
HIV***	7 (7%)
Others****	20 (20 %)
Age of onset of use	**Mean (range)**
Alcohol	20.3 (12-51)
Cannabis	17.5 (13-26)
Cocaine	21.6 (15-35)
Heroine	22.3 (17-28)
Methadone	29.7 (24-39)
Other opiates	33.7 (26-40)
Sedatives	32.8 (16-49)
Compulsive gambling	38.4 (24-59)
Caffeine	17.2 (16-19)
Tobacco	15.7 (12-33)

* arterial hypertension. ** HCV: hepatitis C virus. HBV: hepatitis B virus. ***HIV: human immunodeficiency virus. ****Others: iron-deficiency anemia, hypothyroidism, liver disease, fibromyalgia, COPD, ulcerative colitis.

Lastly, it is worth assessing tianeptine as a treatment for patients with dual depression because its mechanism of action engages brain circuits and systems (glutamate, the opioide system) involved in dual pathology. Also, various studies have shown that it is well tolerated[18] and no significant sedation, weight gain[19,20] or sexual side effects[21], have been observed. It has been found to have positive cognitive effects[22] and anticonvulsant effects[23], is fast acting and pro-

motes swift improvement in suicidal ideation[24]. In addition, tianeptine offers the possibility of enhancing the outcomes of other antidepressants such as SSRIs when they are combined with it[25], meaning that it is of particular interest regarding this population.

As stated, individuals with a dual diagnosis tend to be excluded from clinical trials, which is why a study based on routine clinical practice, conducted on patients with dual depression who are being treated with tianeptine is useful. The aim of this study therefore, was to outline the clinical course of a group of patients diagnosed with major depressive disorder and a substance use disorder, who had been treated with tianeptine under routine clinical practice conditions.

METHODOLOGY

DESIGN

A post-authorization, retrospective, descriptive, multicenter, observational study based on routine clinical practice was designed. It focused on patients with a DSM5 diagnosis of major depressive disorder along with a substance use disorder who were in maintenance therapy using background treatment to which tianeptine was added according to the authorized conditions of use. These patients were treated by their regular doctors, following authorized clinical protocols, therefore this was an observational study conducted under real-world conditions.

ETHICAL AND REGULATORY ISSUES

This study was carried out in compliance with the basic ethical principles and rules outlined in the current version of the World Medical Association Declaration of Helsinki and the Oviedo Convention, along with the current regulatory requirements set out by Spanish law (Law 29/2006 of July 26, on guarantees and rational use of medicines and health products and the specific guidelines set out in Order SAS 3470/2009).

Information was given verbally to the subjects taking part and their family members or legal representatives, explaining the different sections of the protocol. A copy of the Patient Information Sheet (PIS) and the informed consent were provided. Before commencing, the study was authorized by the Gregorio Marañón Hospital Clinical Research Ethics Committee (CREC).

The information collected for the study was handled in accordance with the provisions of Organic Law 15/1999, of December 13, on the protection of personal data (along with its subsequent regulations) and Law 41/2002, of November 14, regulating patient autonomy and rights and obligations with regard to clinical information and documentation. The patients in the study were identified using a code. Only the researchers had information on the source of the samples and data collected and therefore nobody else could link that to the patients.

PATIENTS

The patients were followed-up at the following centers that took part: Gregorio Marañón General University Hospital, Madrid, Vall d´Hebron University Hospital, Barcelona, Dr. Peset University Hospital, Valencia and the Institute for Addictions in Madrid. They were screened between March 2018 and February 2019 and all patients who fulfiled the eligibility criteria were included sequentially.

In order to be included in the study, they had to fulfil the following criteria: 1. to have given informed consent, 2. to be between 18 and 65 years old, 3. to fulfil the DSM5 criteria for major depressive disorder and to have been on maintenance treatment with tianeptine during the previous 3 months, 4. to have a disorder related to substance use and to have complied with routine clinical practice protocol for patients with major depression in the previous 3 months and 5. to have been treated with tianeptine under the authorized conditions of use. Patients were excluded if they fulfiled either of the following criteria: 1. patients who were pregnant or breastfeeding, 2. patients with concomitant disorders that could interfere with the assessment of the parameters being studied (for example: organic brain damage, a learning difficulty or dementia).

The following substances were assessed: Alcohol, Cannabis, Cocaine, Heroine, Methadone and other opiates and sedatives, along with compulsive gambling, caffeine and tobacco use. Age of onset of use can be seen in Table 2.

PROCEDURES

The medical records of the last 100 patients with a diagnosis of major depressive disorder and a comorbid SUD, who in addition to their background treatment had been on maintenance treatment with tianeptine for at least 3 months were reviewed, irrespective of the concomitant treatments they received. Demographic data and clinical characteristics were collected (including diagnostic scales) along with treatment details from the visit at 3 months (deemed to be the "final visit" although there were others subsequently), the baseline visit at the start of the treatment with tianeptine, and a visit that took place between those other two.

The routine clinical practice protocol for the treatment of dual affective disorders was followed, which consists of using a sociodemographic data collection questionnaire, as

Table 2 Baseline clinical characteristics of depression

	Patients (n=100)
Diagnosis of major depressive disorder	
Single episode: mild	7 (7 %)
Single episode: moderate	12 (12 %)
Single episode: severe	12 (12 %)
Recurrent episodes: mild	16 (16 %)
Recurrent episodes: moderate	39 (39 %)
Recurrent episodes: severe	8 (8 %)
Recurrent episodes: with psychotic features	6 (6 %)
Previous admissions	
Previous admissions	28 (28 %)
Number of previous admissions	4.1 (5.2) [1-25]
Number of admissions in the past year	0.6 (0.7) [0-3]
Severity	
Hamilton Scale	19.6 (8.9)
CGI Scale	
Normal	0
Borderline ill	0
Mildly ill	21 (21 %)
Moderately ill	36 (36 %)
Markedly ill	17 (17 %)
Severely ill	26 (26 %)

The quantitive outcomes are shown as mean (standard deviation) [Range]. The qualitative outcomes are shown as absolute frequency (relative frequency)

well as a set of assessment instruments that were periodically administered. These were:

1) the Hamilton Depression Rating Scale (HDRS), which was designed to provide a measure of the intensity or severity of depression[26]. The shorter, 17-item, adapted and validated Spanish version was used[27]. In its original version it is a clinician-administered scale that is scored by the observer and should be completed by an experienced therapist at the end of a clinical interview. Each item was assessed using three (absent, mild, severe) or five ratings (absent, mild, moderate, severe, extreme), according to the intensity of the symptoms presented by the patient. The scale does not specify the scoring criteria for the items in detail, so the interviewer's clinical judgment must be used to designate the level of severity. The time frame for the assessment relates to the time when it took place and/or the days or the week prior to it.

2) The Clinical Global Impression Scale (CGI), which assesses the severity of symptoms. The CGI-S scale for Severity of Illness was applied using the following ratings based on clinical criteria:

1. Normal, not at all ill , 2. Borderline mentally ill, 3. Mildly ill, 4. Moderately ill, 5. Markedly ill, 6. Severely ill, 7. Among the most extremely ill patients.

The CGI-I scale for Global Improvement was also applied using the following ratings, again based on clinical criteria:

1. Very much improved, 2. Much improved; 3.Minimally improved; 4. No change 5. Minimally worse, 6. Much worse 7. Very much worse.

3) the Severity of Dependence Scale (SDS)[28,29]. It contains five items that measure the effect of substance use on patients' lives and each item has a Likert-type response, from zero to four. It assesses psychological aspects of substance use such as worrying about it and feeling that it is getting out of control. This scale has been used in relation to various substances[30, 31,32,33,34,35] and there is a Spanish version of it[36].

Safety was assessed by reviewing patients' medical records for any possible spontaneous adverse reactions.

STATISTICAL ANALYSIS

A general descriptive analysis was carried out both of the qualitative variables (by tabulating absolute and relative frequencies) and the quantitative variables (by calculating the arithmetic mean, standard deviation and 95% confidence interval for the mean). Chi-square tests (□2) were used for the discrete variables and the Student's t-test for paired samples in the case of continuous variables where they satisfied normality criteria.

The outcome measures used were: the change in the Hamilton scale score from the baseline visit to the final visit, the change in the CGI scores, the decrease in the SDS score and the change in the percentage of patients who met the criteria for the various SUDs. Furthermore, response variables were created (a 50% decrease from the baseline score) and remission variables (a final score of 7 or less) based on the change observed in the Hamilton scale. A two-category improvement variable was also generated based on the CGI scale (improvement included in the "very much improved" and "much improved" categories of the CGI-I, or "no change"). A measure for overall progress was devised that required remission according to the previously mentioned categories along with "very much improved" or "much improved" results based on the CGI-I scale. For these outcome variables, predictive logistic regression models were created by entering the clinically relevant variables (age, sex, type of depression, use of various drugs and concomitant use of different psychiatric drugs) and those that had a significance

Table 3 Baseline SUD characteristics

Substances	Lifetime	At the start of the study
Alcohol	60 (60 %)	44 (73.3 %)
Cannabis	24 (24 %)	22 (91.7 %)
Cocaine	34 (34 %)	22 (64.7 %)
Opiates (heroine)	15 (15 %)	5 (33.3 %)
Opiates (methadone)	4 (4 %)	4 (100 %)
Opiates (others)	3 (3 %)	2 (66.7 %)
Sedatives	18 (18 %)	15 (83.3 %)
Compulsive gambling	5 (5 %)	3 (60 %)
Caffeine	19 (19 %)	17 (89.5 %)
Tobacco	69 (69 %)	65 (94.2 %)

N= 100 patients.
The quantitive outcomes are shown as mean (standard deviation).

Table 4 Treatment with tianeptine and other concomitant treatments

	Baseline visit (n=100)	Final visit (n=100)
Tianeptine		
Dosis 37,5 mg/8 h	98 (98 %)	98 (98 %)
Dosis 25 mg/8 h	1 (1 %)	1 (1 %)
Dosis 50 mg/8 h	1 (1 %)	1 (1 %)
Other antidepressants		
Dual	20 (20 %)	20 (20 %)
SSRI	17 (17 %)	17 (17 %)
Mirtazapine	7 (7 %)	7 (7 %)
Vortioxetine	7 (7 %)	7 (7 %)
Trazodone	6 (6 %)	6 (6 %)
Agomelatine	5 (5 %)	5 (5 %)
Bupropion	5 (5 %)	5 (5 %)
Lithium	1 (1 %)	1 (1 %)
Tricyclics	1 (1 %)	1 (1 %)
Other concomitant medication		
Benzodiazepines	36 (36 %)	29 (29 %)
Anticonvulsants	30 (30 %)	28 (28 %)
Oral antipsychotics	22 (22 %)	20 (20 %)
Opioid agonists	12 (12 %)	14 (14 %)
Opioid antagonists	5 (5 %)	7 (7 %)
Alcohol dependence	4 (4 %)	8 (8 %)
Sympathomimetics	1 (1 %)	1 (1 %)
Psychotherapy	73 (73 %)	73 (73 %)
Individual	70 (70 %)	70 (70 %)
Group	21 (21 %)	21 (21 %)

The outcomes are shown as absolute frequency (relative frequency).

level of p<0.1 in the bivariate analysis. In all the statistical tests carried out with the outcome variables a significance level of 0.05 was used. The data analysis was conducted using the SPSS v.20 statistical package.

RESULTS

100 patients were reviewed (51% of whom were male), with a mean age of 46.1 (SD=10.96) (ranging from 19 to 65). Table 1 sets out the most relevant sociodemographic characteristics of the sample and Table 2 shows the clinical characteristics for depression. Table 3 sets out current and lifetime prevalence of the different SUDs, along with age of onset of use. In addition to the patients mentioned above, there was one patient with an amphetamine use disorder and another who misused diuretics. The different doses of tianeptine that were administered as well as the concomitant use of other antidepressant treatments in 68 of the patients is shown in Table 4.

COURSE OF AFFECTIVE SYMPTOMATOLOGY

At the end of follow-up a significant overall improvement was observed in the HDRS (mean±SD: 19.6±8.9 compared with 6.1±4.6; p<0.001). When the items were assessed individually, a significant decrease was found in all of them, except late insomnia, general somatic symptoms and loss of insight (Figure 1). A response was observed (a 50% decrease from the initial score) in 69% of the patients and remission (final score <7) in 70% of them. Women seemed to show worse outcomes since the difference found in them was not significant. None of the models including sociodemographic characteristics, initial severity or the presence of different types of substance use as independent variables were significant.

Regarding the CGI scale, at the end of follow-up a clear improvement was found (Figure 2), with a statistically significant decrease in severity (mean±SD: 2.0±1.7; p<0.001). There was also a notable global improvement, since most of the patients were rated as very much improved (53%) or much improved (23%). No changes were found in 11 of the patients (11%) and 4 worsened (4%).

Taking both scales together, it was concluded that treatment with tianeptine was effective in 60% of the patients (in that they showed remission on the HDRS and improvement on the CGI scale).

When the 14 patients receiving monotherapy with tianeptine were assessed, the outcomes were similar to those found in the patients receiving other concomitant antidepressant treatments.

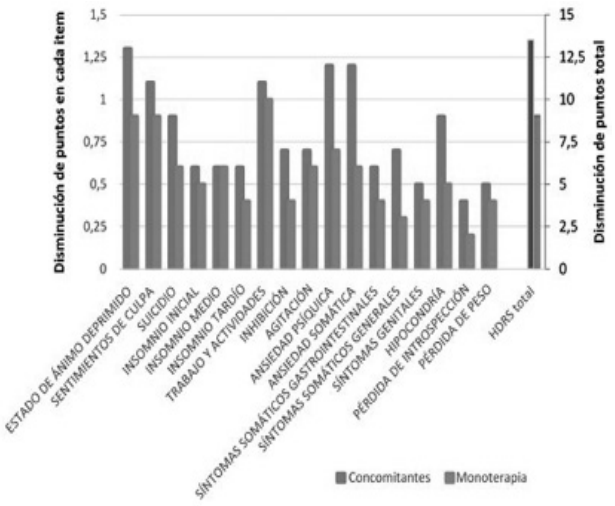

Figure 1 Decrease in scores for individual and global items on the Hamilton Scale (HDRS) after follow-up compared to baseline values both for patients who received tianeptine as monotherapy and those who received other concomitant treatments

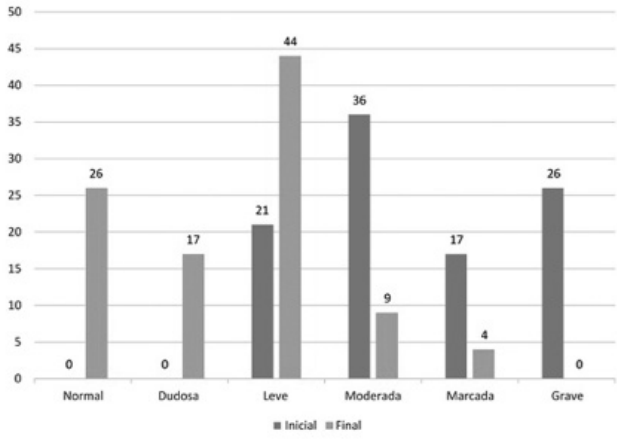

Figure 2 Change in the number of patients in each CGI scale severity of illness category between baseline and end of follow-up

COURSE OF SUBSTANCE USE

Regarding substance use, Figure 3 shows the percentage of patients who met the criteria for the various SUDs before and after treatment. A decrease was found in all types of use, except caffeine, which remained unchanged (17%). The most notable decreases were in alcohol use disorders (from 44% to 27%) and cocaine use (from 22% to 8%).

Figure 4 shows the changes in the scores on the SDS for each substance. All the types of SUD improved with the treatment, although this improvement as regards tobacco, cannabis and gambling was not significant (in the latter this was due to the small number of subjects). The most notable improvements were found in relation to cocaine and sedative use. A binomial variable was therefore devised (a favorable score of 4 or less, or unfavorable) for the creation of a predictive logistic regression model of this course in which no significant variables were found.

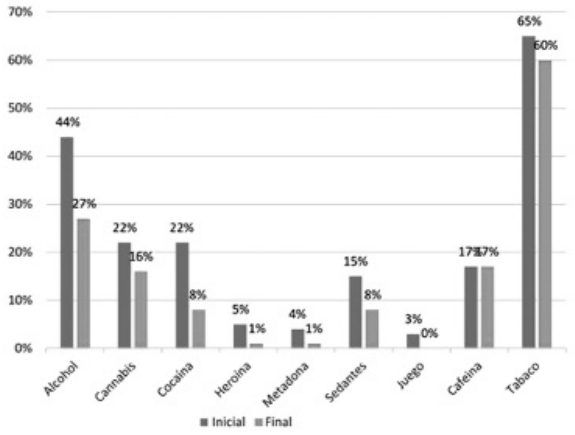

Figure 3 Change in percentage of users according to substance between baseline and end of treatment

No changes were made to the tianeptine doses

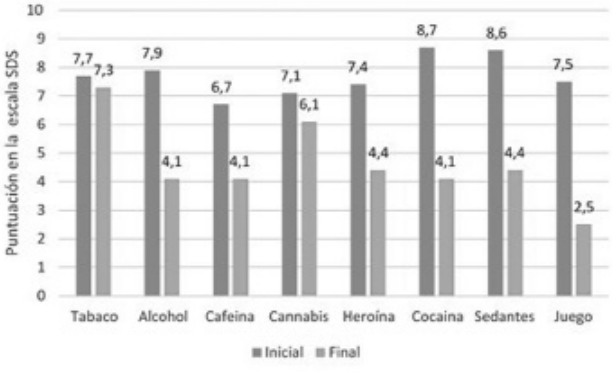

Figure 4 Changes in the SDS according to substance before and after treatment

during the follow-up period, so there were 98 patients on 37.5 mg per day, one on 50 mg and another on 25 mg. Likewise, no significant changes were made to the other concomitant treatments.

SAFETY

During the review no severe or unexpected adverse reactions were found. None of the patients included stopped taking the medication due to safety or tolerability. There were no reports of possible adverse affects relating to the drug or complaints about tolerability.

DISCUSSION

This study presents the outcomes of treatment with tianeptine (and other treatments) under routine clinical conditions of a broad sample of patients with dual depression who were followed up over at least three months.

From a scientific evidence point of view, it could be argued that randomized, controlled clinical trials with a sufficient number of patients have greater internal validity and are less subject to bias, therefore the outcomes obtained are of higher scientific quality. However, in research involving complex disorders such as dual depression, patients are usually under-represented in the clinical trials carried out while a drug is being developed. The position can be even more complicated in cases such as the one at hand, where a single treatment may not be sufficient, since certain drugs are required for the addictive disorder and others for the mood disorder. In these situations, observational studies with a real-world design, such as the one used here and with a sufficient number of patients, have greater external validity and provide information that is relevant from a clinical point of view. They should therefore be used to complement usual clinical trials.

Another limitation of this study was its three-month duration, which may seem too short to allow data to be gathered on patients who subsequently dropped out as a result of the treatment being ineffective or poor tolerance. Nonetheless, this is a typical follow-up period in studies on these types of patients.

Lastly, as is generally the case with these types of studies, there was considerable clinical heterogeneity among the patients who in addition were receiving various types of treatment, with concomitant use of numerous psychiatric drugs and psychotherapeutic techniques. Because of that and the small number of patients in the monotherapy group treated with tianeptine, it has not been possible to clearly determine the contribution made by each treatment to improvement in mood and substance use. For the majority of the patients (68%), tianeptine was used along with another antidepressant, therefore the role of tianeptine on its own in the outcomes is more difficult to assess. Although significant changes were found in depression symptoms in the tianeptine monotherapy subgroup, the fact that there were so few patients means that the outcomes cannot be extrapolated, and the decrease in substance use cannot be ruled out as the reason for improvement in mood. Nonetheless, it does seem that effectiveness is greater when other treatments are added, which is to be expected.

This study assessed the effectiveness of tianeptine (as monotherapy and in combination with other antidepressants) both on the course of depression and of substance dependence in dual diagnosis patients. The outcomes showed considerable improvement in affective symptoms. It is generally thought that treatment of dual depression is complicated and not very effective and that the usual antidepressant treatments are poorly tolerated and not particularly useful[3]. This suggests that integrated forms of treatment, in which psychiatric drugs are used concomitantly to treat the affective symptoms and the addiction, together with psychotherapeutic interventions for both disorders, provide good outcomes, although there is no data on possible losses to follow-up. These integrated treatments are more effective than parallel or sequential treatments[37].

Likewise, there was a notable improvement both in the percentage of patients who overcame an addiction and in severity of addiction. The improvement was less marked with tobacco and cannabis use, which might indicate that either the treatment is less effective for these substances or that they are more difficult to give up[38]. It could also be due to the fact that they are considered "lesser" drugs and are often used along with others, so the clinicians treating these patients were biased and did not make as much effort to reduce their use.

One of the types of use that decreased the most in the patients in this study was alcohol use. Treatment with tianeptine had previously demonstrated its effectiveness in decreasing alcohol use in experiments on animals[39,40] and promoting improvement in patients with depression and alcohol dependence in some clinical trials[20,41], but it had not been studied with other substances. The ability of tianeptine to act as a mu opioid agonist and to increase striatal dopamine[9] makes it a worthwhile candidate for study in relation to opioid and other substance addictions.

The fact that no adverse reactions are described in the patients' medical records is a favorable indication of the safety and good tolerability of the drug reviewed.

Therefore it can be concluded that the use of tianeptine

in routine clinical practice with dual depression patients, both as monotherapy and in combination with other antidepressants, could be beneficial in conjunction with further psychiatric drugs and psychotherapeutic interventions that provide integrated treatment for these complex patients.

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CONFLICT OF INTERESTS

J.Algorta is an employee of Exeltis Healthcare and has contributed as an author to the analysis of the outcomes and to the drafting and review of the text, but he was not involved in the financing. The rest of the authors confirm that they have no conflicts of interest.

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