Clinical Psychopharmacology and Neuroscience - Manuscript Submission

- **Manuscript ID**: CPN-21-867
- **Title**: Inhaled loxapine as a rapid treatment for agitation in patients with personality disorder: a prospective study on the effects of time
- **Running Title**: Inhaled loxapine as treatment for agitation in personality disorder
- **Article Type**: Original Article
- **KeyWords**: psychomotor agitation, personality disorders, loxapine, antipsychotic agents

서식 있음: 왼쪽: 3 cm, 오른쪽: 3 cm, 위: 2.5 cm, 아래: 2.5 cm, 머리글의 가장자리와의 간격: 0 cm

ABSTRACT

Objective Agitation in patients diagnosed with Personality Disorders (PD) is one of the most frequent crises in emergency departments (ED). Although ~~M~~many medications have been tested, ~~but~~ their effectiveness ~~was~~ has been small or non-significant ~~or even small~~, and no specific drugs are supported by the available evidence. This study aimed to evaluate the efficacy of Inhaled loxapine (IL) as a therapeutic option for agitated patients with PD. **Methods** A naturalistic, unicentric, prospective study was carried out. Thirty subjects diagnosed with PD and attending the ED with episodes of agitation were recruited~~.~~ ~~M~~most of ~~them~~whom were women diagnosed with Borderline Personality Disorder. ~~They~~Subjects were treated with a single dose of IL (9.1mg)~~, and~~. ~~e~~Efficacy was assessed with the Clinical Global Impression (CGI) scale, the Excited Component of the Positive and Negative Syndrome Scale (PANSS-EC) and the Agitation-Calmness Evaluation Scale (ACES). Patients were followed 60 minutes after administration to measure IL effect and its duration. **Results** IL exhibited an overall efficacy in managing ~~from~~ mild to severe agitation, with a quick onset of effect and persistence. ~~The~~ 'eEffect of time', where IL efficacy is maintained over time, is more marked in higher-severity agitation. No additional treatments were needed to improve agitation during the follow-up time. **Conclusions** Results suggest that IL could be a safe and effective option to manage agitation in PD~~, although studies, including RCTs comparing IL efficacy with other drugs are needed, as well as samples including PD other than BPD~~.

Key words (6): psychomotor agitation, personality disorders, loxapine, antipsychotic agents

1 Introduction

Agitation is an excessive motor activity associated with a feeling of inner tension[1]~~,~~ which can progress to aggressive and violent behaviours[2]. ~~According to evidence, i~~Its prevalence ranges from 4.6%[3] to 10% [4] of all ~~the~~ episodes consulting ~~in~~ a Psychiatric Emergency Department (ED), ~~whereas~~while 20–50% of visits to psychiatric emergency services ~~present with~~show risk of agitation[5]. An inadequate treatment, especially a delayed intervention, has been linked to a greater risk of violent behaviour, coercive interventions (i.e., physical restraints) and longer admissions[6].

Agitation is common among patients diagnosed with personality disorders (PD), especially those exhibiting pathological impulsivity-related personality traits associated with low tolerance or poor skills to manage negative emotions. ~~This~~Such clinical profile is commonly identifiable both in Borderline Personality Disorder (BPD) and Antisocial Personality Disorder (APD)[7]. ~~Subjects diagnosed with PD frequently visit the Psychiatry Emergency Department (ED) due to states of crisis that might trigger agitation episodes. In~~As a matter of a fact, 9–27% of agitated patients consulting in the ED are diagnosed with BPD[8], ~~and it is~~this being the third most prevalent diagnosis that causes agitation after schizophrenia and bipolar disorder[3].

Since ~~T~~there is not enough evidence for specific treatment in agitated patients diagnosed with PD, ~~therefore~~ general recommendations, ranging from verbal interventions focused on behaviour control (i.e., de-escalation) to physical restraint, are applied[9,10]~~., ranging from verbal interventions focused on behaviour control (i.e., de-escalation) to physical restraint~~. Administering medication might be a useful way to calm the patient~~,~~ and ensure cooperativeness, ~~and hence~~ allowing for a proper assessment of the underpinning cause of agitation. ~~With this purpose~~In this sense, pharmacological treatment should aim at calming without sedating, ~~thus~~ allowing patients to~~can~~ participate in their own therapy[11].

~~Considering~~Regarding pharmacological interventions, oral and intramuscular administration of benzodiazepines and antipsychotics are the most widely used choices~~., through oral and intramuscular administration~~. However, benzodiazepines can cause excessive sedation and hypotension~~,~~ and ~~they~~ might also lead to paradoxical reactions [12,13]~~. On the other hand~~, while antipsychotics might cause extrapyramidal symptoms and

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cardiac conduction abnormalities.~~,~~ This is also the case of ~~although~~ atypical antipsychotics, although these might show a better tolerability.~~Typical antipsychotics, on the other hand, might cause extrapyramidal symptoms and cardiac conduction abnormalities. Growing evidence suggests that atypical antipsychotics that provide better tolerability, might be as effective~~[14]. ~~Beyond agitation, a~~Antipsychotics have also shown a moderate effect on some relevant symptomatic dimensions of PD, especially ~~on~~ anger and (to a lesser extent)~~on~~ cognitive-perceptual symptoms ~~to a lesser extent~~[15]

Although loxapine is classified as a typical antipsychotic, its pharmacodynamics~~, which are characterized by high affinity antagonism both to dopamine D2 and serotonin 5HT2a receptors, are~~is closer to ~~the category~~ that of atypical antipsychotics[16]. Loxapine is widely used in some countries such as France~~,~~ as an intramuscular formulation~~,~~ for acute agitation[17]. ~~However, t~~The possibility of having an inhaled formulation that reaches the maximum blood concentration (Cmax) 2 minutes after intake~~,~~ makes loxapine especially interesting to treat agitation, as it guarantees a rapid onset of the effect[18]. Furthermore, it allows for a lower dose~~,~~ and hence fewer side effects. In comparison with the 9.1mg of inhaled formulation~~,~~ the amount of loxapine to treat agitation when administered intramuscularly might range from 200 up to ~~even~~ 600mg[19]. On the other hand, patient cooperation is needed for the administration of inhaled loxapine (IL), hindering its use for severe and disorganized agitation episodes[20]. Altogether, IL appears to be a suitable treatment for agitation episodes of PD~~,~~ where patient cooperation is more feasible and the severity is lower than in schizophrenia and bipolar disorders. However, IL administration must be done exclusively in hospital settings and supervised by healthcare professionals[21]

~~The inhaled version of loxapine was approved in 2012 by the U.S. Food and Drug Administration (US FDA) to treat agitation in patients diagnosed with schizophrenia and bipolar disorder[20,21]~~. Despite that indications for IL include only agitation in patients diagnosed with schizophrenia and bipolar disorder [22,23]~~ remain unchanged, there is an ~~,~~~~off-label use has been reported, especially for agitation~~s~~ in substance use disorders (SUD) and PD[24]. Evidence ~~F~~focusing on its use on PD~~, the evidence~~ is scarce and limited to a retrospective study[25] and a case series assessing the efficacy of IL for the agitation treatment of patients diagnosed with PD in different clinical settings[26].

This study aimed to analyse the safety and efficacy of IL in the treatment of agitated patients with PD as their main diagnosis consulting in the ED,~~ with PD as their main diagnosis.~~ focusing on its potentiality as a rapid acting and~~,~~ well-tolerated agent. ~~The~~Using a prospective design ~~would~~ allows to study the time effect of such drug across the study

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period.~~The prospective design would allow the study of the time effect on the clinical assessment that would be performed across the study period.~~

2 Methods

2.1 Study Design and informed consent statement

This is a naturalistic, unicentric and prospective study~~. This study~~ and was registered at the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) with EudraCT Number 2016-004884-38. Also, the study was approved by The Spanish Agency of Medicines and Medical Devices (AEMPs) and was registered at the Spanish Clinical Studies Registry (REec) with the registry number 17-0186. ~~It was also approved~~Approval was also recieved by the Vall d'Hebron Research Institute Ethical Committee (Approval code: FER-LOX-2016-01). All participants signed a written informed consent before participating in the study.

2.2 Participants

~~The sample consisted of 30~~Thirty adult patients ~~who had been~~ were consecutively recruited for the study from December 2017 to June 2019 when they attended the Psychiatry ED for agitation as the highest priority goal treatment.

~~The i~~Inclusion criteria for this study included being aged between 18 and 65 years, presenting moderate-severe agitation according to CGI-S scoring (GCI-S≥3 and ≤5), being diagnosed with PD according to the Diagnostic and Statistical Manual of Mental Disorder 5th edition (DSM-5), and understanding and signing the informed consent for the study. ~~The e~~Exclusion criteria were not being pregnant (a pregnancy test was performed if necessary~~,~~ to ensure this criterion), having no organic conditions that could cause psychiatric symptoms or compromise the understanding of the study information, not being diagnosed with any psychotic or bipolar disorder, and not showing signs of acute intoxication. All patients recruited met all the inclusion criteria and none of them met the exclusion criteria.

2.3 Measurements

CGI-S (Clinical Global Impression – Severity)[27] a 7-point scale that measures the clinical severity of the episode from the clinician's point of view. Severity ranges from 1 (normal)

to 7 (extremely ill).

CGI-I Scale (Clinical Global Impression - Improvement): a 7-point scale that assesses clinical improvement from the clinician's point of view[28]. It rates clinical improvement ranging from 1 (much improvement) to 7 (much worsening).

PANSS-EC (Excited Component of the Positive and Negative Syndrome Scale (PANSS-EC)[29]: A 5-item scale (low impulse control, tension, hostility, lack of cooperation and excitement), with a rating from 1 to 7 per item. Scores higher than 20 indicate severe agitation.

ACES (Agitation-Calmness Evaluation Scale)[30]: A single item that evaluates general agitation and sedation at the moment of the assessment. It ranges from 1 (severe agitation) to 9 (unarousable).

At the beginning of the study, a site initiation visit (SIV) was carried out, ~~and~~in which ~~-~~all the research staff ~~were~~was informed about the study, ~~and~~ trained to properly conduct the scales involved ~~properly; also,~~ and solve any further doubts ~~was solved~~. In addition, two additional meetings were scheduled during the study, ~~two meetings were scheduled, where~~ in which the research staff refreshed the instructions. ~~about how to complete the scales involved in it.~~

Spanish versions of all scales were used., ~~and d~~Data was also gathered by the treating clinician attending each patient in the ED.

2.4 Procedure

Once a patient with PD in a state of agitation was admitted to the Psychiatry ED, the most suitable treatment was assessed by the ~~responsible~~ clinician. ~~assessed the most suitable treatment~~. If patients did not respond to standard verbal interventions (de-escalation), were ~~candidates~~ suitable for treatment with IL 9.1 mg~~,~~ and agreed to participate, informed consent was gathered and and IL was administed by the clinician. ~~administered it after gathering informed consent~~ . ~~The S~~Consecutive subject inclusion ~~of subjects~~ for the study was ~~consecutive to achieve~~ performed until a final sample size of n = 30 was achieved. ~~7~~Seven patients declined to participate ~~D~~during the recruitment period~~, 7 patients declined to participate~~. ~~The r~~We ensured that the ~~R~~recruitment procedures did not imply any modification in the medical treatment that the participants could receive ~~if they did~~ in case they did not wish to participate.

~~B~~In all cases, baseline assessment (T0) was performed ~~always~~ within 30 minutes before the initial administration of the trial drug. ~~and included s~~Socio demographic information, as well as clinical data, was gathered. Agitation severity was ~~also~~ assessed with the Clinical Global Impression–Severity (CGI-S) scale, the PANSS-EC and the ACES.

~~Subsequently, c~~Clinical efficacy in agitated PD patients was assessed through changes in the scores of PANSS-EC (main indicator), ACES and CGI-I at two time points: 10 (T1) and 60 (T3) minutes after the administration. Safety assessments were performed, including blood pressure, heart rate and oxygen saturation at 10 (T1), 20 (T2) and 60 (T3) minutes after drug administration.

~~Once a patient with PD in a state of agitation was admitted to the Psychiatry ED, the responsible clinician assessed the most suitable treatment. If patients did not respond to standard verbal interventions (de-escalation) and were candidates for treatment with IL 9.1 mg, the physician informed the patient about the study. If the patient agreed to participate, the clinician requested the patient's consent and checked that the candidate met all the inclusion criteria and did not meet any exclusion criterion. The inclusion of subjects for the study was consecutive to achieve a final sample size of n = 30. During the recruitment period, 7 patients declined to participate. The recruitment procedures did not imply any modification in the medical treatment that the participants could receive if they did not participate.~~

~~In addition, baseline assessment (T0) was performed as close as possible to the initial administration of the trial drug and always within 30 minutes before it. Baseline assessment included socio demographic information, as well as clinical data such as psychiatric and non-psychiatric comorbidities, type of PD, and previous pharmacological treatment. At T0, agitation severity was also assessed with the Clinical Global Impression–Severity (CGI-S) scale (Busner and Targum, 2007), the PANSS-EC [27] and the ACES [28]. After baseline assessment, patients were treated with a single dose of 9.1mg of IL.~~

~~Subsequently, clinical efficacy in agitated PD patients was assessed through changes in the scores of PANSS-EC (main indicator), ACES and CGI-I at two time points: 10 (T1) and 60 (T3) minutes after the administration. Safety assessments were performed which included blood pressure, heart rate and oxygen saturation at 10 (T1), 20 (T2) and 60 (T3) minutes after drug administration. Patients were also warned about the presence of adverse events that had been associated with IL and about the onset of other signs and symptoms~~

~~throughout the study period. Finally, we also documented how the episode ended (i.e., discharge vs. inpatient), as an additional measure of efficacy.~~

2.5 Statistical analysis

A Wilcoxon signed-rank test was performed to assess differences in improvement (CGI-S Scale) 10 and 60 minutes after administration, as well as differences in the PANSS and ACES scales. ~~Bonferroni correction was performed to avoid Type I error.~~ A total of 22 Wilcoxon tests were made, and a *p*-value of 0.002 (0.05/22) was considered significant after Bonferroni correction. To assess safety, a Friedman rank test was performed on repeated measures of oxygen saturation, cardiac frequency, and systolic and diastolic arterial tension.

서식 지정함: 영어(미국)

To evaluate the effect of time on the different scales and how this effect may vary on the scale, we performed a series of mixed-effects logistic regression models~~, using the R package 'ordinal'~~. For each value ~~of a scale~~, the scale was dichotomised ~~into two groups, one of individuals with a score lower than or equal to that value and other of individuals with score higher than that value~~. We used a binary variable of whether individuals belonged to one group or another as the dependent variable, and the variable time, measured in minutes, as the independent variable, including a random intercept to account for the correlation of scores within patients. Scale values at the extremes of a scale with less than 3 patients were combined with the value next to it in the scale. We also performed a sensitivity analysis, including age and sex as covariates in the model.

All statistical analyses were conducted using the SPSS 19.0 version for Windows (Version 19.0, SPSS Inc., Chicago, IL, USA) and R v3.6.3.

3 Results

Patients were aged between 19 and 57 (mean = 39, SD = 9.73) and were mostly women (N=20, 66.7%). Table 1 shows the main demographic characteristics, comorbidities and baseline treatment. Substance use disorders (SUD) (N=14, 46.6%) and affective disorders (N=10, 33.3%)~~T~~ where the most prevalent comorbid disorders~~. were substance use disorders (SUD) (N=14, 46.6%) and affective disorders (N=10, 33.3%)~~. As for the baseline treatment, 90% of patients were taking an antidepressant, whereas 66.6% were taking antipsychotics, 56.6% benzodiazepines and 46.6% mood stabilizers.

서식 지정함: 강조

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~~The i~~Included patients showed a baseline mean CGI-S score of 4.63 (SD = 0.718), implying a consideration of 'moderately to markedly ill'. The median score of CGI-I was 2 ('markedly improved') at T1 and 1 ('very much improved') at T3. These results did not remain significant after Bonferroni correction (z = -2.985, p = 0.003). ~~The~~ ACES scale results showed a significant increase from a median of 2 ('moderate agitation') at baseline to 4 ('normal state') at T1 (z = -4.713, $p = 2x10^{-6}$), maintaining this state of 'normality' at T3 (z = -4.866, p = 0,000001). ~~The~~ PANSS-EC scores had a median of 21.50 at baseline, decreasing to a median of 8 at T1 (z = -4.788, $p = 2x10^{-6}$), and to a median of 5 (z = -4.787, $p = 2x10^{-6}$) at T3. All subscales showed a similar tendency towards a significant score decrease across time at the two assessment points after IL administration. Complete results are detailed in Table 2. All the included subjects were discharged from the Psychiatric ED~~,~~ and no additional medication was needed over the study period.

INSERT TABLE 2 AROUND HERE

No significant adverse effects were registered. A significant decrease of the basal arterial tension and cardiac frequency was observed at T1, T2 and T3 assessment points ($p < 0.001$). Oxygen saturation (O2Sat) remained stable over the study period. The scores of systolic arterial tension~~s~~ (SAT), diastolic arterial tension (DAT) and cardiac frequency remained at physiological levels (See Table 3).

INSERT TABLE 3 AROUND HERE

~~For~~In all scales except for the ACES, time was significantly associated ($p < 0.05$) with a reduction ~~of~~in the score. For the ACES~~s~~, on the other hand, ~~the trend was in the opposite direction, with time~~ increas~~ed~~ing ~~over time~~the score. In addition, we observed that the odds of moving through the different values of the scale as time passed were not constant. ~~The r~~Results suggest~~,~~ (for all scales except for the ACES)~~,~~ greater effects of time for higher values of the scales, implying ~~, therefore,~~ a faster change between higher values than between lower values (See Figure and, for more details, see Supplementary Table 1). We also performed a sensitivity analysis to assess the effect of age and sex on the results. Overall, adjusting the model for age and sex did not seem to alter the results.

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4 Discussion

Results of our study show that a single dose of inhaled loxapine (IL) can be a safe and effective treatment for agitation of patients with PD attending a psychiatric ED. IL had a rapid-onset and a, lasting effect on improving agitation in patients with PD, while maintaining a good safety profile, and no incidence of interactions or adverse reactions. AsSince agitated PD patients represent roughly 9–27% of agitated emergency episodes[31] and no specific treatment is approved specifically for this particular group, IL may be an option for this treatment gap.

Significant changes in ACES and PANSS-EC scores were observed early on at the 10 min assessment point. This is a very interesting fact becauseconsidering a fast decrease of symptoms is the main goal of agitation of the pharmacological treatment of agitation when non-pharmacological strategies do not work [6]. In this regard, the IL administration mechanism , (through inhalation directly delivered to the alveoli), allows IV-like pharmacokinetics, producing a rapid onset of the effect while requiring a low total dose [18]. This interpretation is reinforced by the fact that there were no significant differences in CGI points between T1 (10 minutes after administration) and T2 (60 minutes).

This is also suggested by the study of the effect of time: changes in the assessment scores are observed over time, indicating that clinical improvement is maintained. Furthermore, this time effect is more marked in those agitation episodes with higher severity, which could be due to a possible 'ceiling effect' in patients presenting less severe agitations. Therefore, it appears that IL therapeutic efficacy is persistent. Note that no additional doses or other medications were required, no physical restraint was necessary, and most of the patients were discharged without needing to be admitted, altogether suggesting a potential benefit in the mid-term management of the crisis.

Based on the results showing a median value of 4 at the ACES assessment (meaning 'normal') at the 60 minute time points, meaning 'normal', together with an optimal calming effect according to the observed improvements in the CGI and PANSS-EC, it could be argued that IL achieves the therapeutic goal with a mild sedative effect. Therefore, IL would follow be in line with the recommendations of treating agitation without sedating, whichtand would allow a higher implication of patients in their therapy [11]. Regarding safety issues, oxygen saturation maintained high levels across the study time, with no episodes of bronchoconstriction, and heart rate and blood pressure remained withinat a normal range. In addition to the absence of significant side effects, an indirect sign of the

therapeutic effect can be interpreted in the significant progressive reduction of heart rate and blood pressure levels at the different assessment points[32,33]. ~~As mentioned before,~~ These aspects are relevant since other pharmacological treatments, sometimes from the same family of antipsychotics, have exhibited a higher risk of serious side effects and should be avoided if possible [12–14]. ~~To sum up,~~In summary, IL could be a safer, more tolerable and less invasive medication for agitation in PD patients than anxiolytics and antipsychotics, avoiding significant sedation~~,~~ and allowing also for a higher participation of the patient in his/her own treatment.

Despite IL has only been approved for agitation treatment of patients diagnosed with schizophrenia or bipolar disorder, other studies have evaluated its efficacy and security in off-label uses~~, like~~such as substance intoxications and dual disorders [20–22], which have showed~~ing~~ similarly good results in tolerability and safety. It is important to note~~worthy~~ that the results of our study are in line with the recent publication of Patrizi et al.[23] in agitated PD patients.

To our knowledge, this is the first prospective study that aims to test IL efficacy and safety to treat agitation of patients diagnosed with PD in an ED setting. A prospective design has been chosen ~~is preferable,~~ as it increases the reliability of the association between the treatment and the observed effect, it allows controlling variables such as time effect, and avoids recall bias. Furthermore, ~~the naturalistic focus of the study,~~ treating acute agitated patients in the ED~~,~~ adds the advantage that the data ,was~~were~~ gathered in a similar setting to the day-to-day environment that clinicians face when dealing with agitation, allowing for a better external validity of these results.

서식 지정함: 강조 없음

S~~However, several~~ome study limitations ~~can be observed in the study~~must be highlighted. First, as patients with PD were consecutively included in the study due to the indication of treating agitation, and all patients were treated with IL, ~~so~~ its efficacy could not be directly compared with other treatments. ~~,~~Nevertheless, since as to date~~,~~ no specific recommendations for the treatment of agitation in PD patients have been proposed ~~with the current evidence~~, ~~so~~ there is not a gold-standard drug to perform a direct comparison [8]. Second, results of the mixed effect logistic regression models must be interpreted with caution, ~~given that, in some instances,~~as there are not enough data to obtain robust estimates~~,~~ or even to estimate confidence intervals~~.~~, even though ~~However,~~ our data appear to support ~~we could detect some~~ a maintained efficacy trend~~s~~ over time, especially in highest severity agitations~~all~~. Third, a small sample size may make it difficult to determine if a particular outcome is a true finding, and in some cases a type II error may occur.

Finally, the majority of the subjects included in the sample were diagnosed with BPD, ~~which limits~~limiting the ~~extrapolation~~ generalization of the study results to other PD ~~that could also benefit from this treatment~~. However, our findings can be clinically relevant considering that BPD, together with APD, are the PDs with ~~Still, it is worth noting that BPD and APD, which were the most represented disorders in our sample, are the PD with~~ the highest association with agitation [6].

5 Conclusions

According to the results of our prospective, naturalistic study, IL could be a safe and ~~useful~~ effective ~~and safe~~ option to treat ~~for managing~~ agitation ~~in~~ of PD in hospital EDs ~~patients~~, especially for those patients diagnosed with BPD ~~and in an ED~~. The therapeutic target could be achieved quickly, with patients' participating in their own treatment, and the calming effect could be maintained over time. Our preliminary results ~~must~~should be replicated with randomized controlled trials with larger samples, comparing IL with other drugs, and analysing the effect on psychopathological dimensions of PD that could be on the basis of agitation episodes, ~~like~~such as anger or cognitive-perceptual symptoms. Furthermore, given the lack of significant side effects and with the aim of increasing the access to IL treatment, future studies should assess IL safety and efficacy when treating agitation of PD patients in settings other than hospitals and without the supervision of healthcare professionals.

~~Considering that no specific drugs have shown superiority over others in this regard, and that results from randomized controlled trials (RCT) are lacking, the recommendation for the treatment of agitation in PD is to choose a method to achieve a fast response, of high tolerability and safety, and that allows patients' participation in their treatment. These conditions appear to be compatible with IL, although RCTs with a bigger size sample have yet to be conducted to confirm these preliminary results.~~

6 Acknowledgements:

Over the course of this investigation, M. Soler Artigas was a recipient of a contract from the Biomedical Network Research Center on Mental Health (CIBERSAM), Madrid, Spain and was also a recipient of a Juan de la Cierva Incorporación contract from the Ministry of Science, Innovation and Universities, Spain (IJC2018-035346-I).

We would like to acknowledge Alex Ruè Jiménez, from the Clinical Trials Unit of the Department of Psychiatry in Vall d'Hebron Research Institute, for his help in proofreading and ensuring correct English use.

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8 Conflict of interests

M. Ferrer has received fees from Shire, Takeda, Ferrer, Otsuka, Lundbeck, Janssen-Cilag, Eli-Lilly, Rubió, Oryzon, Almirall to act as speaker or consultant.

C. Fadeuilhe has received fees to give talks for Shire, Takeda, Ferrer, Italfarmaco and Otsuka in the last 5 years.

R.F. Palma-Álvarez has received fees to give talks for Exeltis, Lundbeck, MSD, Mundipharma and Takeda.

J.A. Ramos-Quiroga was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogui, Lundbeck, Almirall, Braingaze, Sincrolab, Medice and Rubió in the last 5 years. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli-Lilly, Lundbeck, Janssen- Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious, and Rubió.

9 Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

10 Authors Contribution

Ferrer M, Ramos-Quiroga JA and Ibañez P designed the study and obtained the ethics approval. Soto-Angona O., Lidai R., Fadeuilhe C., Palma-Álvarez RF, Vargas-Cáceres S., Torrecilla MA, and López A, gathered the clinical data and collaborated in the creation of the dataset used for the study. Soto-Angona O., Ibañez P., and Soler Artigas M., performed the statistical analysis of the results obtained. Soto-Angona O. and Ferrer M. conducted the bibliographic search, and wrote the different versions of the manuscript. All authors provided key suggestions and contributed to the discussion, proofreading and correction of the final version of this work. All authors meet all four criteria for authorship included in the ICMJE recommendations.

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서식 지정함: 스페인어(스페인)

서식 지정함: 스페인어(스페인)

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서식 지정함: 스페인어(스페인)

서식 지정함: 스페인어(스페인)

Table 1. Clinical and socio-demographic characteristics of the study sample

	Mean	SD
Age	39	9.73
	Participants (n=30)	**Percentage (%)**
Gender		
Female	20	66.7
Personality Disorder (PD)		
Borderline PD	23	76.7
Antisocial PD	3	10
Histrionic PD	4	13.3
Comorbid Disorders*		
SUD	14	46.6
Affective Disorders	10	33.3
Eating Disorders	2	6.6
ADHD	1	3.3
Dissociative disorder	1	3.3
Drug treatment**		
Antidepressants	27	90
Antipsychotics	20	66.6
Mood stabilizers	14	46.6
Benzodiazepines	17	56.6
Other	2	6.6

*: A patient can be diagnosed with different comorbid disorders; **: A patient can receive different drug treatments simultaneously; SUD: Substance Use Disorders; ADHD: Attention-deficit/hyperactivity disorder

서식 지정함: 글꼴: 10 pt

서식 지정함: 영어(미국)

~~**Table 1. Clinical and socio-demographic characteristics of the study sample (*n* = 30)**~~

	~~Mean~~	~~SD~~
~~**Age**~~	~~39~~	~~9.73~~
	~~***n***~~	~~**%**~~
~~**Gender**~~		
~~Female~~	~~20~~	~~66.7~~
~~**Personality Disorder (PD)**~~		
~~Borderline PD~~	~~23~~	~~76.7~~
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*: A patient can be diagnosed with different comorbid disorders; **: A patient can receive different drug treatments simultaneously; SUD: Substance Use Disorders; ADHD: Attention-deficit/hyperactivity disorder

Table 2. Differences in the clinical assessment across the study period

Tool	Time	Scores Median (p25, p75)	Time comparison	*Z-score*	*p*-value
CGI-I					
	T1	2 (1, 2)			
	T3	1 (1, 1)	T1 vs T3	-2.985	0,0028
ACES					
	T0	2 (2, 2)	T0 vs T1	-4.713	**0,000002**
	T1	4 (4, 4.25)	T1 vs T3	-2.217	0,026617
	T3	4 (4, 6)	T0 vs T3	-4.866	**0,000001**
PANSS-EC					
	T0	21.5 (19.5, 24.25)	T0 vs T1	-4.788	**0,000002**
	T1	8 (6, 14.25)	T1 vs T3	-4.121	**0,000038**
	T3	5 (5, 7)	T0 vs T3	-4.787	**0,000002**
PANSS-EC T					
	T0	4 (5, 6)	T0 vs T1	-4.657	**0,000181**
	T1	2 (1, 3)	T1 vs T3	-3.745	**0,000001**
	T3	1 (1, 1.25)	T0 vs T3	-4.824	**0,000001**
PANSS-EC LIC					
	T0	5 (4, 5.25)	T0 vs T1	-4.669	**0,000003**
	T1	2 (2, 3)	T1 vs T3	-4.327	**0,000015**
	T3	1 (1, 2)	T0 vs T3	-4.815	**0,000001**
PANSS-EC H					
	T0	4 (3, 5)	T0 vs T1	-4.571	**0,000005**
	T1	1 (1, 2)	T1 vs T3	-2.588	**0,000181**
	T3	1 (1, 1)	T0 vs T3	-4.65	**0,000003**
PANSS-EC LoC					
	T0	3 (2.75, 4)	T0 vs T1	-4.473	**0,000008**
	T1	1 (1, 2)	T1 vs T3	-2.588	0,009654
	T3	1 (1, 1)	T0 vs T3	-4.609	**0,000004**
PANSS-EC E					
	T0	5 (4, 6)	T0 vs T1	-4.820	**0,000001**
	T1	2 (1, 3)	T1 vs T3	-3.695	**0,000220**
	T3	1 (1, 1.25)	T0 vs T3	-4.815	**0,000181**

Bold p-values: significant after Bonferroni correction; CGI-I: Clinical Global Impresion – Improvement; ACES: Agitation-Calmness Evaluation Scale; PANSS-EC: Positive and Negative Syndrome Scale – Excited Component; PANSS-EC T: PANSS-EC Tension item; PANSS-EC LIC: PANSS-EC Low Impulse Control item; PANSS-EC H: PANSS-EC Hostility item; PANSS-EC LoC: PANSS-EC Lack of Control item; PANSS-EC E: PANSS-EC Excitation item; T1: 10-minute assessment point; T3: 30-minute assessment point.

서식 지정함: 글꼴: 10 pt

~~**Table 2. Differences in the clinical assessment across the study period**~~

~~Tool~~	~~Time~~	~~Scores Median (p25, p75)~~	~~Time comparison~~	~~*Z*~~	~~*p* value~~
~~CGI-I~~					
	~~T1~~	~~2 (1, 2)~~			
	~~T3~~	~~1 (1, 1)~~	~~T1 vs T3~~	~~-2.985~~	~~0,0028~~
~~ACES~~					
	~~T0~~	~~2 (2, 2)~~	~~T0 vs T1~~	~~-4.713~~	~~**0,000002**~~
	~~T1~~	~~4 (4, 4.25)~~	~~T1 vs T3~~	~~-2.217~~	~~0,026617~~
	~~T3~~	~~4 (4, 6)~~	~~T0 vs T3~~	~~-4.866~~	~~**0,000001**~~
~~PANSS-EC~~					
	~~T0~~	~~21.5 (19.5, 24.25)~~	~~T0 vs T1~~	~~-4.788~~	~~**0,000002**~~
	~~T1~~	~~8 (6, 14.25)~~	~~T1 vs T3~~	~~-4.121~~	~~**0,000038**~~

	T3	5 (5, 7)	T0 vs T3	-4.787	**0,000002**
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	T0	4 (5, 6)	T0 vs T1	-4.657	**0,000181**
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	T0	3 (2.75, 4)	T0 vs T1	-4.473	**0,000008**
	T1	1 (1, 2)	T1 vs T3	-2.588	0,009654
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Bold p-values: significant after Bonferroni correction; PANSS-EC T: PANSS-EC Tension item; PANSS-EC LIC: PANSS-EC Low-Impulse Control item; PANSS-EC H: PANSS-EC Hostility item; PANSS-EC LoC: PANSS-EC Lack-of-Control item; PANSS-EC E: PANSS-EC Excitation item; T1: 10-minute assessment point; T3: 30-minute assessment point.

Table 3. Differences in hemodynamic parameters and oxygen saturation ACROSS the study period

Parameter	Time	Median (p25, p75)	X^2	*df*	*p*
SAT	T-1	122 (110.75, 136)	30.28	4	<0.001
	T0	123.5 (117, 136.5)			
	T1	122.5 (108.75, 129)			
	T2	121 (108, 129)			
	T3	122.5 (108.75, 129)			
DAT	T-1	86 (77.75, 91.75)	39.88	4	<0.001
	T0	86 (78, 92.25)			
	T1	78.50 (72, 85)			
	T2	79 (71.75, 86.25)			
	T3	78 (65.75, 82)			
CF	T-1	83.5 (77.5, 100)	23.55	4	<0.001
	T0	85 (77.75, 100)			
	T1	79.50 (74.5, 88.25)			
	T2	80 (70.50, 85)			
	T3	79 (71, 85)			
O2SAT	T-1	98 (97.75, 99)	0.99	3	0.80
	T0	98 (97.5, 99)			
	T1	98 (97.75, 99)			
	T2	98 (97.75. 99)			
	T3	98 (97.75, 99)			

T-1: Assessment point during the patient's admission in the Psychiatric Emergency Department; T0: Baseline assessment point; T1: 10-minute assessment point; T3: 30-minute assessment point; SAT: Systolic arterial tension; DAT: Diastolic arterial tension; O2SAT: Oxygen saturation; CF: cardiac frequency.

~~**Table 3. Differences in hemodynamic parameters and oxygen saturation ACROSS the study period**~~

~~Parameter~~	~~Time~~	~~Median (p25, p75)~~	~~X^2~~	~~*df*~~	~~*p*~~
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	~~T3~~	~~122.5 (108.75, 129)~~			
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	~~T1~~	~~78.50 (72, 85)~~			
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서식 있음: 왼쪽, 탭: 5.59 글자, 왼쪽 + 6.3 글자, 가운데

Table 2. Differences in the clinical assessment across the study period

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Supplementary Table

Results for the mixed-effects logistic regression models are presented per scale and per value. The column "comparison" presents the values where the dichotomisation of the scale was done. Note that the model could not be fit for all values of each scale given the limited sample size available.

	Comparison	OR	OR_LB_CI	OR_UB_CI	z value	Pr (>|z|)
CGI-I Scale	1|2	0.96102047	0.953288963	0.96881469	-9.647462585	5.04E-22
	2|3	0.73103853	0.730100437	0.731977847	-478.2033916	< 2.2e-16
PANSS-EC	5|6	0.91462735	0.913548698	0.915707282	-148.2224565	< 2.2e-16
	6|7	0.91940892	0.870672186	0.970873748	-3.023707923	0.002496974
	7|8	0.92884148	0.893096499	0.966017114	-3.686772126	0.000227117
	8|9	0.93439328	0.902649418	0.967253498	-3.848065239	0.000119054
	9|10	0.93358759	0.90271362	0.965517505	-4.005185974	6.20E-05
	11|13	0.07955742	0.022355333	0.283126312	-3.908339633	9.29E-05
	13|14	0.06729299	0.067208814	0.067377278	-4225.747331	< 2.2e-16
	14|15	0.10695281	0.106875236	0.107030457	-6037.757069	< 2.2e-16
	15|16	0.10783649	0.044401989	0.261896135	-4.919459016	8.68E-07
	16|17	0.0600129	0.059958875	0.060066975	-6122.166845	< 2.2e-16
PANSS-EC LIC	1|2	0.85019507	0.791479109	0.913266892	-4.444898492	8.79E-06
	2|3	0.89547170	0.832997665	0.962631248	-2.992170133	0.002770018
	3|4	0.07559302	0.075534502	0.075651592	-6535.411697	< 2.2e-16
	4|5	0.37524493	0.214250893	0.657214358	-3.427977175	0.000608097
PANSS-EC T	1|2	0.93218466	0.898240739	0.967411313	-3.710683543	0.0002067
	3|4	0.07285812	0.07279949	0.072916806	-6376.500146	< 2.2e-16
PANSS-EC H	1|2	0.94243187	0.913935388	0.971816878	-3.784931818	0.000153751
	2|3	0.09152631	0.045952622	0.182297905	-6.801895368	1.03E-11
	3|4	0.38759583	0.221354047	0.678688888	-3.316089991	0.000912864
PANSS-EC LoC	1|2	0.94028949	0.909285966	0.972350142	-3.59913087	0.000319282
	2|3	0.74228935	0.590864905	0.932520253	-2.560189356	0.010461514
	3|4	0.70492765	0.508852993	0.976555126	-2.102663559	0.03549519
PANSS-EC E	1|2	0.92501535	0.885484681	0.966310805	-3.497914824	0.000468911
	2|3	0.08118711	0.023733143	0.277727519	-4.001643778	6.29E-05
	3|4	0.13349264	0.133374846	0.133610554	-4470.59517	< 2.2e-16
ACES	4|5	1.04637844	1.013496232	1.080327499	2.782938086	0.005386908
	5|6	1.04773433	1.046851971	1.048617442	108.4782611	< 2.2e-16
	6|7	1.04806640	0.986010745	1.114027609	1.507594941	0.131658228

CGI-I: Clinical Global Impresion – Improvement; PANSS-EC: Positive and Negative Syndrome Scale – Excited Component; PANSS-EC T: PANSS-EC Tension item; PANSS-EC LIC: PANSS-EC Low Impulse Control item; PANSS-EC H: PANSS-EC Hostility item; PANSS-EC LoC: PANSS-EC Lack of Control item; PANSS-EC E: PANSS-EC Excitation item; ACES: Agitation-Calmness Evaluation Scale;

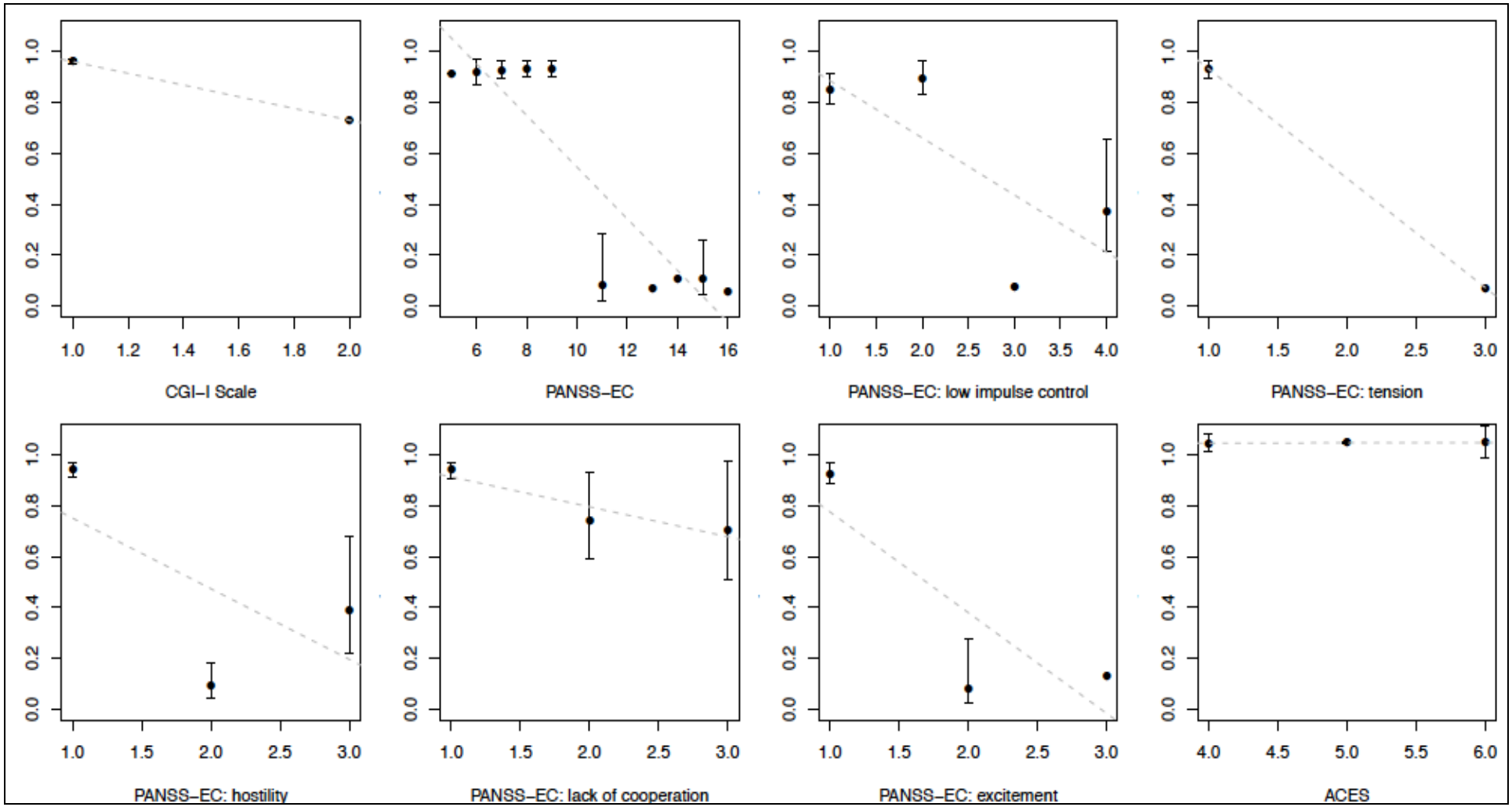

FIGURE. Odds ratios with 95% confidence intervals per scale and value are presented. A grey dashed line representing the line of best fit is also included for each scale.