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Inhaled Loxapine as a Rapid Treatment for Agitation in Patients with Personality Disorder: A Prospective Study on the Effects of Time

Marc Ferrer[1,2,3,4], Óscar Soto-Angona[1], María Soler-Artigas[2,3,5], Pol Ibáñez[3], Christian Fadeuilhe[1,2,3,4], Raúl Felipe Palma-Álvarez[1,2,3,4], Raquefet Lidai[1], Sebastian Vargas-Cáceres[1], María Ángeles Torrecilla[1], Anna López[1], Josep Antoni Ramos-Quiroga[1,2,3,4]

[1]Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Catalonia, [2]Biomedical Network Research Centre on Mental Health (CIBERSAM), Barcelona, Catalonia, [3]Group of Psychiatry, Mental Health and Addiction, Vall d'Hebron Research Institute (VHIR), Barcelona, [4]Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Barcelona, [5]Department of Genetics, Microbiology and Statistics, Faculty of Biology, Universitat de Barcelona, Barcelona, Spain

Objective: Agitation in patients diagnosed with personality disorders (PD) is one of the most frequent crises in emergency departments (ED). Although many medications have been tested, their effectiveness has been small or non-significant, 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 most of whom were women diagnosed with Borderline Personality Disorder. Subjects were treated with a single dose of IL (9.1 mg). Efficacy was assessed with the Clinical Global Impression 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 mild to severe agitation, with a quick onset of effect and persistence. 'Effect 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.
Conclusion: Results suggest that IL could be a safe and effective option to manage agitation in PD.

KEY WORDS: Psychomotor agitation; Personality disorders; Loxapine; Antipsychotic agents.

INTRODUCTION

Agitation is an excessive motor activity associated with a feeling of inner tension [1] which can progress to aggressive and violent behaviours [2]. Its prevalence ranges from 4.6% [3] to 10% [4] of all episodes consulting a Psychiatric Emergency Department (ED), while 20－50% of visits to psychiatric emergency services 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. Such clinical profile is commonly identifiable both in Borderline Personality Disorder (BPD) and Antisocial Personality Disorder (APD) [7]. As a matter of a fact, 9－27% of agitated patients consulting in the ED are diagnosed with BPD, this being the third most prevalent diagnosis that causes agitation after schizophrenia and bipolar disorder [3].

Since there is not enough evidence for specific treatment in agitated patients diagnosed with PD, general recommendations, ranging from verbal interventions fo-

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Address for correspondence: Óscar Soto-Angona
Department of Psychiatry, Hospital Universitari Vall d'Hebron, Passeig Vall d'Hebron 119-129, Barcelona 08035, Spain
E-mail: osoto@vhebron.net
ORCID: https://orcid.org/0000-0003-0234-4280

cused on behaviour control (i.e., de-escalation) to physical restraint, are applied [8,9]. Administering medication might be a useful way to calm the patient and ensure cooperativeness, allowing for a proper assessment of the underpinning cause of agitation. In this sense, pharmacological treatment should aim at calming without sedating, allowing patients to participate in their own therapy [10].

Regarding pharmacological interventions, oral and intramuscular administration of benzodiazepines and antipsychotics are the most widely used choices. However, benzodiazepines can cause excessive sedation and hypotension and might also lead to paradoxical reactions [11,12], while antipsychotics might cause extrapyramidal symptoms and cardiac conduction abnormalities. This is also the case of atypical antipsychotics, although these might show a better tolerability [13]. Antipsychotics have also shown a moderate effect on some relevant symptomatic dimensions of PD, especially anger and (to a lesser extent) cognitive-perceptual symptoms [14].

Although loxapine is classified as a typical antipsychotic, its pharmacodynamicsis closer to that of atypical antipsychotics [15]. Loxapine is widely used in some countries such as France as an intramuscular formulation for acute agitation [16]. The possibility of having an inhaled formulation that reaches the maximum blood concentration (C_{max}) 2 minutes after intake makes loxapine especially interesting to treat agitation, as it guarantees a rapid onset of the effect [17]. Furthermore, it allows for a lower dose and hence fewer side effects. In comparison with the 9.1 mg of inhaled formulation, the amount of loxapine to treat agitation when administered intramuscularly might range from 200 up to 600 mg [18]. On the other hand, patient cooperation is needed for the administration of inhaled loxapine (IL), hindering its use for severe and disorganized agitation episodes [19]. 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 [20].

Despite that indications for IL include only agitation in patients diagnosed with schizophrenia and bipolar disorder [21,22], off-label use has been reported, especially for agitation in substance use disorders (SUD) and PD [23]. Evidence focusing on its use on PD is scarce and limited to a retrospective study [24] and a case series assessing the efficacy of IL for the agitation treatment of patients diagnosed with PD in different clinical settings [25].

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, focusing on its potentiality as a rapid acting and well-tolerated agent. Using a prospective design allows to study the time effect of such drug across the study period.

METHODS

Study Design and Informed Consent Statement

This is a naturalistic, unicentric and prospective 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. 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.

Participants

Thirty adult patients 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.

Inclusion criteria for this study included being aged between 18 and 65 years, presenting moderate-severe agitation according to Clinical Global Impression-Severity (CGI-S) scoring (GCI-S $\geq$ 3 and $\leq$ 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. 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.

Measurements

CGI-S [26]: 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).

Clinical Global Impression-Improvement (CGI-I) scale: a 7-point scale that assesses clinical improvement from the clinician's point of view [27]. It rates clinical improvement ranging from 1 (much improvement) to 7 (much worsening).

Excited Component of the Positive and Negative Syndrome scale (PANSS-EC) [28]: 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.

Agitation-Calmness Evaluation Scale (ACES) [29]: 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 was carried out, in which all the research staff was informed about the study, trained to properly conduct the scales involved and solve any further doubts. In addition, two additional meetings were scheduled during the study, in which the research staff refreshed the instructions.

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

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 clinician.. If patients did not respond to standard verbal interventions (de-escalation), were suitable for treatment with IL 9.1 mg and agreed to participate, informed consent was gathered and IL was administed by the clinician. Consecutive subject inclusion for the study was performed until a final sample size of n = 30 was achieved. Seven patients declined to participate during the recruitment period. We ensured that the recruitment procedures did not imply any modification in the medical treatment that the participants could receive in case they did not wish to participate.

In all cases, baseline assessment (T0) was performed within 30 minutes before the initial administration of the trial drug. Socio demographic information, as well as clinical data, was gathered. Agitation severity was assessed with the CGI-S scale, the PANSS-EC, and the ACES.

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.

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. 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.

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. For each

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

Variable	Participants (n = 30)
Age	39 ± 9.73
Gender	
Women	20 (66.7)
Personality disorder (PD)	
Borderline PD	23 (76.7)
Antisocial PD	3 (10)
Histrionic PD	4 (13.3)
Comorbid disorders[a]	
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[b]	
Antidepressants	27 (90)
Antipsychotics	20 (66.6)
Mood stabilizers	14 (46.6)
Benzodiazepines	17 (56.6)
Other	2 (6.6)

Values are presented as mean ± standard deviation ornumber (%). SUD, substance use disorders; ADHD, attention-deficit/hyperactivity disorder.
[a]A patient can be diagnosed with different comorbid disorders; [b]A patient can receive different drug treatments simultaneously.

value, the scale was dichotomised. 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 (IBM Co., Armonk, NY, USA) and R v3.6.3.

RESULTS

Patients were aged between 19 and 57 (mean = 39, standard deviation [SD] = 9.73) and were mostly women (n = 20, 66.7%). Table 1 shows the main demographic characteristics, comorbidities and baseline treatment. SUD (n = 14, 46.6%) and affective disorders (n = 10, 33.3%) where the most prevalent comorbid disorders. 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.

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 ($z = -2.985$, $p = 0.003$). ACES scale results showed a significant increase from a median of 2 ('moderate agitation') at baseline to 4 ('normal state') at T1 ($z = -4.713$, $p = 2 \times 10^{-6}$), maintaining this state of 'normality' at T3 ($z = -4.866$, $p = 0.000001$). PANSS-EC scores had a median of 21.50 at baseline, decreasing to a median of 8 at T1 ($z = -4.788$, $p = 2 \times 10^{-6}$), and to a me-

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)			0.0028
	T3	1 (1, 1)	T1 vs. T3	−2.985	
ACES	T0	2 (2, 2)	T0 vs. T1	−4.713	0.000002[a]
	T1	4 (4, 4.25)	T1 vs. T3	−2.217	0.026617
	T3	4 (4, 6)	T0 vs. T3	−4.866	0.000001[a]
PANSS-EC	T0	21.5 (19.5, 24.25)	T0 vs. T1	−4.788	0.000002[a]
	T1	8 (6, 14.25)	T1 vs. T3	−4.121	0.000038[a]
	T3	5 (5, 7)	T0 vs. T3	−4.787	0.000002[a]
PANSS-EC T	T0	4 (5, 6)	T0 vs. T1	−4.657	0.000181[a]
	T1	2 (1, 3)	T1 vs. T3	−3.745	0.000001[a]
	T3	1 (1, 1.25)	T0 vs. T3	−4.824	0.000001[a]
PANSS-EC LIC	T0	5 (4, 5.25)	T0 vs. T1	−4.669	0.000003[a]
	T1	2 (2, 3)	T1 vs. T3	−4.327	0.000015[a]
	T3	1 (1, 2)	T0 vs. T3	−4.815	0.000001[a]
PANSS-EC H	T0	4 (3, 5)	T0 vs. T1	−4.571	0.000005[a]
	T1	1 (1, 2)	T1 vs. T3	−2.588	0.000181[a]
	T3	1 (1, 1)	T0 vs. T3	−4.65	0.000003[a]
PANSS-EC LoC	T0	3 (2.75, 4)	T0 vs. T1	−4.473	0.000008[a]
	T1	1 (1, 2)	T1 vs. T3	−2.588	0.009654
	T3	1 (1, 1)	T0 vs. T3	−4.609	0.000004[a]
PANSS-EC E	T0	5 (4, 6)	T0 vs. T1	−4.820	0.000001[a]
	T1	2 (1, 3)	T1 vs. T3	−3.695	0.000220[a]
	T3	1 (1, 1.25)	T0 vs. T3	−4.815	0.000181[a]

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.

[a]Significant after Bonferroni correction.

dian of 5 ($z = -4.787$, $p = 2 \times 10^{-6}$) 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.

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 remained stable over the study period. The scores of systolic arterial tension (SAT), diastolic arterial tension (DAT) and cardiac frequency remained at physiological levels (Table 3).

In all scales except for the ACES, time was significantly associated ($p < 0.05$) with a reduction in the score. For the ACES, on the other hand, increased over time. In addition, we observed that the odds of moving through the different values of the scale as time passed were not constant. Results suggest (for all scales except for the ACES) greater effects of time for higher values of the scales, implying a faster change between higher values than between lower values (see Fig. 1 and, for more details, see Supplementary Table 1 [available online]). 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.

DISCUSSION

Results of our study show that a single dose of 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. Since agitated PD patients represent roughly 9−27% of agitated emergency episodes [30] 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 minutes assessment point, a very interesting fact considering a fast decrease of symptoms is the main goal of the pharmacological treatment of agitation when non-pharmacological strategies do not work [6]. In this regard, the IL administration

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

Parameter	Time	Median (p25, p75)	χ^2	*df*	*p* value
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)			
O_2SAT	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; O_2SAT, oxygen saturation; CF, cardiac frequency.

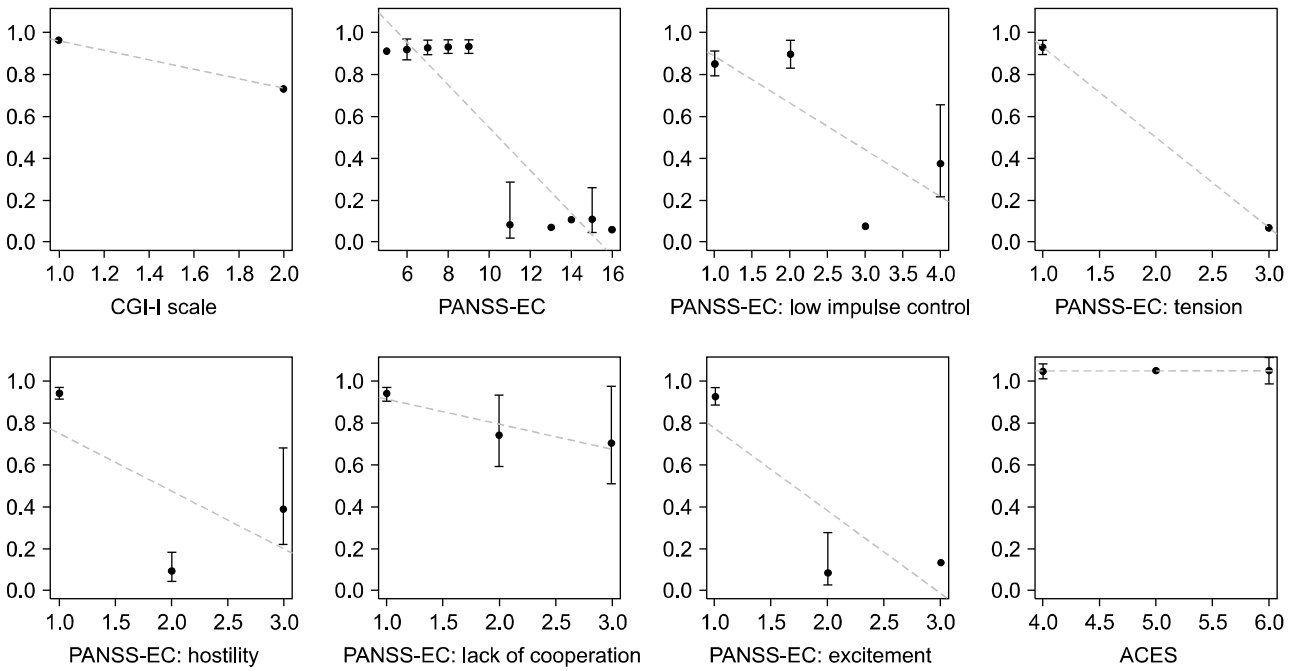

Fig. 1. Odds ratios with 95% confidence intervals per scale and value are presented. A grey dashed line representing the line of best fit is also included for each scale.
CGI-I, Clinical Global Impresion-Improvement; ACES, Agitation-Calmness Evaluation scale; PANSS-EC, Positive and Negative Syndrome Scale-Excited Component.

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 [17]. 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 point 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 be in line with the recommendations of treating agitation without sedating and would allow a higher implication of patients in their therapy [10]. Regarding safety issues, oxygen saturation maintained high levels across the study time with no episodes of bronchoconstriction, and heart rate and blood pressure remained within 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 [31,32]. 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 [11-13]. 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 se-

curity in off-label usessuch as substance intoxications and dual disorders [19-21], which have showed similarly good results in tolerability and safety. It is important to note that the results of our study are in line with the recent publication of Patrizi *et al.* [24] 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 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, treating acute agitated patients in the ED adds the advantage that the data was 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.

Some study limitations 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, 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, there is not a gold-standard drug to perform a direct comparison. Second, results of the mixed effect logistic regression models must be interpreted with caution, as there are not enough data to obtain robust estimates or even to estimate confidence intervals, even though our data appear to support a maintained efficacy trend over time, especially in highest severity agitations. 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, limiting the generalization of the study results to other PD. However, our findings can be clinically relevant considering that BPD, together with APD, are the PDs with the highest association with agitation [6].

According to the results of our prospective, naturalistic study, IL could be a safe and effective option to treat agitation of PD in hospital EDs, especially for those patients diagnosed with BPD. 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 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, 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.

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■ Conflicts of Interest

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

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

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■ Author Contributions

Marc Ferrer, Josep Antoni Ramos-Quiroga, and Pol Ibáñez designed the study and obtained the ethics approval. Óscar Soto-Angona, Raquefet Lidai, Christian Fadeuilhe, Raúl Felipe Palma-Álvarez, Sebastian Vargas-Cáceres, María Ángeles Torrecilla, and Anna López, gathered the clinical data and collaborated in the creation of the dataset used for the study. Óscar Soto-Angona, Pol Ibáñez, and María Soler-Artigas performed the statistical analysis of the results obtained. Óscar Soto-Angona and Marc Ferrer 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.

■ ORCID

Marc Ferrer https://orcid.org/0000-0002-1283-8578
Óscar Soto-Angona https://orcid.org/0000-0003-0234-4280
María Soler-Artigas https://orcid.org/0000-0002-3213-1107
Pol Ibáñez https://orcid.org/0000-0003-0714-8908
Christian Fadeuilhe https://orcid.org/0000-0001-5821-347X
Raúl Felipe Palma-Álvarez https://orcid.org/0000-0002-6428-9865
Raquefet Lidai https://orcid.org/0000-0003-4476-1226
Sebastian Vargas-Cáceres https://orcid.org/0000-0001-6113-0392
María Ángeles Torrecilla https://orcid.org/0000-0001-5811-2695
Anna López https://orcid.org/0000-0003-3932-9674
Josep Antoni Ramos-Quiroga https://orcid.org/0000-0003-1622-0350

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