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Inhaled Loxapine for Agitation in Intoxicated Patients: A Case Series

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Objectives: Episodes of agitation are frequent in intoxicated patients who have a substance use disorder, a psychiatric disorder or both (dual diagnosis). For managing the agitation, it is necessary to act promptly in a safe environment and addressing any underlying etiology. Inhaled loxapine improves symptoms of agitation in adults with psychiatric disorders (eg, schizophrenia) within 10 minutes of administration. Recently, some reports have documented the usefulness of loxapine in dual diagnoses patients with agitation. However, the efficacy of loxapine in intoxicated patients has not been deeply addressed.

Methods: This report describes a case series of 12 patients (with addiction or dual disorder) who received inhaled loxapine for symptoms of psychomotor agitation during intoxication with different substances (eg, alcohol, cannabis, or cocaine) at 1 center in Spain.

Results: Data from 12 patients were reviewed, 5 patients were attended at the emergency room, 4 at the addiction and dual diagnosis unit, and 3 were treated during hospitalization for detoxification. All patients were under effects of substances. They had substance use disorder (including cannabis, cocaine, alcohol, hypnotics, and hallucinogens), and almost all (90%) presented 1 or more psychiatric disorders. One dose of inhaled loxapine was effective in 9 patients (75%), and in 3 patients, a second dose was required. Only mild dizziness was reported in 1 patient after the second dose.

Conclusions: The acute agitation was effectively and quickly managed with inhaled loxapine in all intoxicated patients and enabled the appropriate clinical evaluation of the agitated state and the patient's management.

Key Words: agitation, inhaled loxapine, emergency, substance use disorders, mental disorders

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Substance use disorders (SUDs) and psychiatric disorders (or even both diagnoses, namely dual diagnosis) are a frequent factor for agitation episodes in intoxicated patients.^{1–5} Substance intoxication is one of the main etiologies of psychomotor agitation according to several expert consensus.^{4,6,7} Intoxicated patients in

a state of psychomotor agitation are common users of emergency departments. Their management includes providing a safe environment, managing agitation to enable appropriate clinical evaluation of the agitated state, and addressing the underlying etiology.

To allow a safe management of the agitated patient is necessary a “quick intervention,” including nonpharmacological and pharmacological strategies.⁸ Pharmacological treatment consists in achieving patient's tranquilization and includes mainly benzodiazepines or antipsychotics, which are chosen depending on the absence or presence of psychotic symptoms.³ Low doses of neuroleptics are recommended for intoxications in agitated patients with history of alcohol and sedative use, whereas benzodiazepines are preferred if there is a suspicion of substance intoxication other than alcohol (eg, with amphetamines, cocaine, or phencyclidine).³ Nevertheless, antipsychotics are preferred over benzodiazepines for patients with a known psychiatric disorder (schizophrenia, schizoaffective disorder, bipolar disorder), because they address the underlying disease.^{3,5}

There are few data on the use of antipsychotics, other than haloperidol, for agitation secondary to intoxication in patients with underlying psychiatric pathology.^{3,5,9} New intramuscular formulations for antipsychotics provide faster effect, but they are invasive and are not well received by most of the patients.¹⁰ The most frequent complications of rapid tranquilization depend on the pharmacologic profile but also can derive from the interactions with other addictive substances or the existence of subjacent diseases.⁹ Thus, complications from sedatives reside in their long duration of action and the risk of lethality in overdose, especially when they are combined with other medications or alcohol.³ On the other hand, the use of antipsychotics may result in extrapyramidal adverse effects, QTc prolongation, arrhythmias, potential serotonin syndrome, and neuroleptic malignant syndrome.¹¹ Furthermore, antipsychotics can also reduce the seizure threshold and

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should be used with caution in patients who are prone to seizures (including patients undergoing alcohol or sedative-hypnotic withdrawal)¹² and not to mention that antipsychotics are related to metabolic syndrome.¹³ Hence, there is a need for treatments with a good safety profile and low drug interactions, with fast onset but enough duration of action, easy to administer, and nontraumatic.⁷

As a new alternative, inhaled loxapine has demonstrated to reduce mild to moderate agitation in 10 minutes in patients with schizophrenia or bipolar disorder.^{14–16} Response rates observed with inhaled loxapine were similar to those observed with the intramuscular administration of other antipsychotics.¹⁷ Inhaled loxapine may have a role in the treatment of substance-induced agitation, but data on the use of inhaled loxapine in intoxicated patients are lacking.¹⁸ Recently, a case series of 14 agitated patients with dual diagnosis has been described; 4 patients presented an intoxication state and were treated with inhaled loxapine (9.1 mg) for symptoms of agitation. Inhaled loxapine

was rapid, effective, and well accepted in all patients presenting with acute agitation and facilitated the cooperation of the patient and an adequate management of the disease.¹⁹ Although, it is important to point out that inhaled loxapine was used as off-label in that report, as has been used in other diagnoses such as borderline personality disorder.²⁰

The current report aims to extend the experience with inhaled loxapine to 12 intoxicated patients attending the emergency service and the addiction and dual diagnosis unit at 1 center in Spain. All patients had a SUD, and almost all patients had an underlying psychiatric disorder. Inhaled loxapine was used to treat agitation.

CASES

Cases include 12 patients in an intoxicated state and were treated with inhaled loxapine; those patients were attended at the emergency room (ER) (n = 5), at the addiction and dual

TABLE 1. Patient Characteristics and Treatment Response

Patient No.	Age, y/Sex	Type of Substance Intoxication	SUD	Urine Toxicological Testing	Other Diagnoses	Previous Hospitalizations
1	25/M	Cocaine	Cocaine use	Not performed	Bipolar I and anxiety disorders	Several hospitalizations because of poor treatment adherence and decompensation
2	40/M	Cocaine, cannabis, and alcohol	Cocaine, cannabis, alcohol, amphetamine, nicotine, and hypnotics use	Positive for THC	Paranoid schizophrenia	Several hospitalizations
3	23/M	Alcohol and cannabis Alcohol	Alcohol and cannabis use	Not performed	Paranoid schizophrenia	None
4	42/M		Alcohol and nicotine use	Not performed	Antisocial personality and anxiety disorders	None
5	44/M	Cannabis	Cocaine, cannabis, and nicotine; sporadic use of LSD	Not performed	Drug-induced psychotic disorder (with familiar history)	None
6	44/M	Cocaine and cannabis	Cocaine, cannabis, speed, and nicotine	Positive for cocaine and THC	Bipolar disorder I, obsessive/ compulsive disorder at childhood	One hospitalization for delirium and several for detoxification
7	38/M	Cocaine, cannabis, and alcohol	Cocaine, cannabis, nicotine, and alcohol	Positive for THC, cocaine, and alcohol	Personality disorder not specified	Several hospitalizations for detoxification
8	46/M	Alcohol	Alcohol, nicotine	Not performed	Cyclothymic disorder	None
9	35/F	Cannabis	Cannabis, nicotine	Positive for THC	Bipolar disorder I	None
10	42/M	Alcohol	Alcohol, nicotine	Not performed	Borderline personality disorder	Hospitalization for detoxification
11	41/F	Alcohol	Alcohol sustained remission (>2 y)	Not performed	Borderline personality disorder	None
12	39/M	Ayahuasca	Cocaine, nicotine, and hallucinogens	Not performed	ADHD and induced psychosis	None

ADHD indicates attention deficit and hyperactivity disorder; F, female; IM, intramuscular; M, male; NR, not reported; THC, tetrahydrocannabinol.

diagnosis unit (n = 4), or during hospitalization for detoxification (n = 3) at the Hospital of Vall de Hebron in Barcelona, Spain, from December 2014 to April 2016.

All patients presented a SUD, namely nicotine (n = 9; 75.0%), alcohol (n = 7; 58.3%), cannabis (n = 6; 50.0%), cocaine (n = 6; 50.0%), and others (amphetamines [n = 2; 16.7%], hypnotics [n = 1; 8.3%], and hallucinogens [n = 1; 8.3%]). Almost all (9/10; 90%) presented 1 or more psychiatric disorders according to *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*, including personality disorder (n = 4; 33.3%), bipolar I disorder (n = 3; 25%), schizophrenia (n = 2; 16.7%), psychotic disorder (n = 1; 8.3%), cyclothymic disorder (n = 1; 8.3%), or anxiety disorder (n = 2; 16.7%). Patients presented at the center in a state of substance intoxication due to alcohol (n = 7; 58.3%), cannabis (n = 6; 50.0%), cocaine (n = 4; 33.3%), or ayahuasca (n = 1; 8.3%), which was confirmed by urine toxicological testing in 4 patients (Table 1). One dose of inhaled loxapine was effective

in 9 patients (75%) within 5 to 15 minutes after administration (<5 minutes in 8 patients; 66.7%). In 3 patients (no. 1, no. 3, and no. 6), a second dose was required between 2 and 4 hours after the first one. Clonazepam treatment was started concomitantly with loxapine for the agitation episode, because of the appearance of abstinence or anxiety, in 2 patients (no. 7 and no. 12). A third patient (no. 4) required physical restraint and rescue medication (intramuscular haloperidol and levomepromazine). No other rescue medication was needed during the acute episodes of agitation. Only mild dizziness was reported in 1 patient after the second dose. A daily dose of loxapine was effective for the treatment of daily agitation episodes during the first 5 days of hospitalization in 1 patient (no. 2).

Vital signs and other parameters were monitored during the medical intervention according to the hospital protocol for agitation. No alterations were detected on vital signs or other hemodynamic parameters.

Loxapine Administration (Cause)	Loxapine Dosage/ Effectiveness	Adverse Effects	Second Dose/Rescue Medication	Usual Treatment	Other Drugs Used in Agitation
Agitation episode	Two doses within 4 h, effective in 5 min	NR	A second dose of loxapine was administrated	Desvenlafaxine	No
Agitation episode hesitant to be hospitalized (clinical decompensation) and daily agitation episodes within first 5 d of hospitalization	One dose effective in <10 min; daily dose effective	NR	Not required	Levomepromazine, fluphenazine, biperiden, haloperidol, valproate, and naltrexone	No
Episode of psychomotor agitation	Two doses within 2 h with progressive lowering of alteration and increased cooperation	Mild dizziness after the second dose	A second dose of loxapine was administrated	Venlafaxine, pregabalin, clonazepam, and aripiprazole	No
Agitation with high psychomotor restlessness and verbal heterogeneous behavior	One dose, effective in 15 min	NR	Because of a new crisis, physical restraint and rescue medication (IM haloperidol and levomepromazine) were required	Topiramate, quetiapine, escitalopram, clonazepam, zolpidem, and olanzapine	No
Agitation in context of psychotic symptoms and disorganized behavior	One dose, effective in <5 min	NR	Not required	Not usual treatment	No
Agitation in context of psychotic symptoms	Two doses within 4 h, effective in <5 min	NR	A second dose of loxapine was administrated because of new disorganized behavior episode	Olanzapine, lithium, clonazepam, quetiapine, and paliperidone	No
Agitation in context of craving and disorganized behavior	One dose, effective in <5 min	NR	Not required	Sertraline and disulfiram	Clonazepam
Psychomotor agitation	One dose, effective in 15 min	NR	Not required	None (withdrew treatment 2 y ago)	No
Agitation in context of manic symptoms and disorganized behavior	One dose, effective in <5 min	NR	Not required	Valproate and aripiprazole	No
Agitation episode	One dose, effective in <5 min	NR	Not required	Venlafaxine, clonazepam, and quetiapine	No
Episode of psychomotor agitation	One dose, effective in <5 min	NR	Not required	Valproate, quetiapine, and disulfiram	No
Agitation in context of psychotic symptoms and moderate anxiety	One dose, effective in <5 min	NR	Not required	None	Clonazepam

DISCUSSION

To date, there are scarce clinical data on the use of inhaled loxapine in intoxicated patients because usually intoxication or having a positive drug screening was exclusion criteria in clinical trials that evaluated inhaled loxapine as treatment for agitation. The current study constitutes a report on the effectiveness and safety of inhaled loxapine in patients presenting with agitation during substance-related intoxication.

Inhaled loxapine was well received by the patient and reduced the perception of coercion or forced medication, enabling the patient's cooperation. In most cases, only 1 dose was needed to calm the patients, which was effective within minutes in a considerable proportion of them. A 66.7% (n = 8) of patients did not require an additional dose (n = 3, 25%) or rescue medication (n = 1) within 24 hours. These rates are comparable with those reported in the clinical trials with inhaled loxapine in patients with schizophrenia (60.9%) or bipolar disorders (61.5%).^{15,16} A regimen with a benzodiazepine was initiated, concomitantly with inhaled loxapine, in 2 cases. After control of acute agitation symptoms, patients received regular treatment immediately, and in these 2 cases, clonazepam was deemed the most appropriate treatment for their underlying disorder. The advantages of inhaled loxapine over the antipsychotic medication used traditionally reside in the route of administration, which is equivalent to the intravenous and faster than the intramuscular one but has better tolerability and is more patient friendly. Inhaled loxapine was well tolerated in these case series, and there were no reporting of respiratory signs/symptoms.

The most prevalent substances used were alcohol, cannabis, and cocaine use (apart from tobacco), and these were the most consumed substances causing intoxication. There is plenty of published literature on the abuse of cocaine,²¹ alcohol,²² or cannabis²³ as correlated to agitation episodes in patients with SUD and dual diagnosis and represent a major public health problem and a cause of concern in the emergency and outpatient facilities.²⁴

For a better management of the patient, it is important to determine what specific substances the patient have been consuming, and the use of urine (or blood) toxicology screening tests is an important aid at the ER.²⁵ However, the results of the test screening are not always a determining factor, and the substance might not be detectable through the routine analysis.² In the current study, the substance intoxication was detectable in 4 cases, but it was not assessed in the other 8 cases because of several reasons (the patient referred active consumption at admission, or the urine sampling was not feasible). Specific clinical signs and symptoms are also helpful, particularly psychomotor agitation is frequent in patients with stimulant intoxication (induced by cocaine or amphetamine) or alcohol-intoxicated patients, and in these patients, the use of a neuroleptic is recommended.

This article should be analyzed focusing in limitations, especially because it is a small case series and the use of inhaled loxapine as off-label in some cases. Nevertheless, the use of some medications as off-label in psychiatry and SUD is frequent²⁶ and inhaled loxapine has been administered as off-label in some reports, for example in borderline personality disorder²⁰ and in dual diagnoses patients.²¹ Finally, effectiveness was not evaluated with a standard instrument but only with clinical assessment (considering tranquilization and use of additional medication or doses).

Conclusively, inhaled loxapine would have a role in agitation related to substance intoxication, especially in dual diagnosis patients, improving cooperation and outcomes at the ER. Therefore, we may comment (and recommend) that this medication is a useful tool in drug users who are agitated and intoxicated at the same time. Although, usual contraindications of this medication have

always to be taken into consideration (eg, respiratory diseases). These case series are illustrative of the real world at the emergency and psychiatric services and substantiate the effectiveness and safety of inhaled loxapine for treating agitation, enabling the appropriate clinical evaluation of the agitated state and the adequate management of the intoxicated patients attended at our hospital. Studies with a higher sample of intoxicated patients who consume different and multiple types of drugs are needed to better characterize the potential interactions of loxapine.

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