Efficacy and Safety of Loxapine in Acute Agitation:

A Systematic Review of Interventional Studies

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Abstract

Objective: To assess the efficacy and safety of loxapine in acute agitation.

Data Sources: PubMed, Cochrane database, EMBASE, PsycINFO, and ClinicalTrials.gov were searched to identify relevant articles published in English or French from inception to March 15, 2022. The term "Loxap*" was searched in titles and abstracts.

Study Selection and Data Extraction: Interventional studies that compared the effectiveness of loxapine to any other intervention (including another administration route or dosage of loxapine, other drugs, and placebo) in acute agitation were included. From the 1,435 articles initially identified, and after the assessment of 73 full texts, 7 articles were selected, encompassing 1,276 participants. Two reviewers independently extracted data of interest using a predefined form.

Results: Among included studies, 5 were double-blind, 2 were open-label, and all were randomized. The risk of bias was low for 2 studies, involving 658 participants. Four articles compared loxapine to placebo, and 3 compared it with haloperidol, aripiprazole, and droperidol. Loxapine was found to be more effective and faster regarding acute agitation control. Also, across included studies, loxapine was well-tolerated, with mildly or moderately severe adverse effects.

Conclusions: Notwithstanding methodological limitations of the included studies, this systematic review provides reassuring results regarding the use of loxapine in acute agitation. However, further studies with methodological optimizations might be of interest.

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Agitation is defined in the *DSM-5* as an "excessive motor activity associated with a feeling of inner tension."[1] It can be related to various conditions including acute intoxication/withdrawal of a psychoactive substance, drug iatrogenesis, metabolic disturbances, infectious illnesses, neurologic disorders, and mental health disorders,[2–5] which especially encompass anxiety, bipolar disorder (manic state), psychotic disorders, and personality disorders. As agitation can result in auto- or hetero-aggressive behaviors, it is necessary to intervene as quickly and effectively as possible to prevent self-harm or physical assault on other people including health care workers.[6]

The care of acute agitation includes nonpharmacologic approaches such as strategies aiming to appease patients and involving notably de-escalation.[7,8] Nevertheless, in numerous cases there is a need for pharmacologic treatments, and despite that the oral route is preferred, there is currently no consensus regarding the pharmacologic class to use.[7] Such consensual recommendations might be of interest considering the existence in countries such as France of laws governing the prescription of seclusion and restraint measures that can be considered as a last resort for severely agitated patients.[9,10] Among the medications that can be used for acute agitation, the *Société Française de Médecine d'Urgence* (SFMU), in their 2003 consensus conference on agitation, mentioned loxapine, explaining that this medication seems unanimously accepted by medical professionals in France.[11] More recently, in their 2021 Recommendations for Good Clinical Practice, they recognized loxapine as a standard for the treatment of patients with acute agitation.[12] In France, loxapine is therefore one of the most frequently used pharmacologic agents for the control of agitated individuals.[13]

Clinical Points

- Compared to other interventions (including placebo, haloperidol, aripiprazole, or droperidol), loxapine was well-tolerated and more effective regarding acute agitation control, and its action was faster than comparators.
- Loxapine use for acutely agitated patients, in combination with nonpharmacologic techniques and depending on the agitation severity including the risk of aggressive behaviors, may lower the probability of seclusion and restraint use.
- Since there is only one dosage of intramuscular injection as well as the inhaled form and considering the cardiovascular safety compared to other antipsychotics, loxapine is relatively easy to use in clinical practice. In case of insufficient efficacy, a benzodiazepine can be added.

Loxapine is commercialized in Canada and was approved by the US Food and Drug Administration for the management of agitated patients.[14,15]

With available galenic forms for oral, nasal, and intramuscular administration, loxapine is a first-generation antipsychotic that belongs to the dibenzoxazepines and is known to have sedative as well as anxiolytic effects.[16] Despite its widespread use for over 40 years in some settings, there is a scarcity of clinical trials on the efficacy and safety of this antipsychotic drug in acute agitation. In comparison, there is more research on other antipsychotic medications such as haloperidol or olanzapine, on benzodiazepines such as midazolam or lorazepam,[17] and more recently on ketamine.[18] Systematic reviews and meta-analyses have evaluated several psychotropic treatments in the control of acute agitation, but they did not include loxapine.[19,20]

Considering the high frequency of acute agitation notably in emergency and intensive care units, the frequent use of loxapine in some occidental countries, and the lack of dedicated summarizing data, we planned this systematic review. Indeed, an evaluation of loxapine effectiveness, through a systematic analysis of published literature, could contribute to good practice recommendations on agitation.

The objective of this systematic review was to evaluate the efficacy of loxapine in the care of patients with acute agitation. The PICOS approach was used to address this objective, with the following declinations: (1) Population: patients with acute agitation, regardless of the setting (emergency department, inpatient, outpatient); (2) Intervention: loxapine, regardless of route of administration (oral, intramuscular, inhaled); (3) Comparison: other loxapine dosage, other loxapine route, other medications or placebo; (4) Outcome: agitation control (in terms of time, intensity, duration); and (5) Study design: interventional studies.

METHODS

Our review's sections are displayed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement.[21] The review was registered in the International Prospective Register of Systematic Reviews (registration no. CRD42022330846).

Eligibility Criteria

Inclusion criteria were based on the PICOS approach items detailed previously. We excluded studies performed on animal models, case reports, letters to the editor, comments, duplicated papers, articles for which the full text was unavailable even after request, the least recent studies if several studies were based on the same population, and studies written in a language other than English or French.

Information Sources and Search Strategy

We systematically searched for relevant articles in PubMed/MEDLINE, EMBASE, PsycINFO (Ovid), Cochrane database, and ClinicalTrials.gov from inception to March 15, 2022. To retrieve relevant articles, the term "Loxap*" was searched in titles and abstracts with no particular filters such as time limits.

Selection Process

The results were exported to the Rayyan platform (https://www.rayyan.ai/), which is a tool dedicated to the management of articles during the systematic review process. After duplicate removal, the remaining articles were evaluated on their title and/or abstract according to our eligibility criteria. This evaluation was independently performed by 2 reviewers (C.L. and F.T.E.), with the resolution of potential discrepancies by consensus or the intervention of a third assessor (G.C.). After this first selection step, the full texts of the retained articles were searched and scrutinized, also on the basis of our inclusion criteria, independently by 2 reviewers (C.L. and F.T.E.) with the same process of discrepancy resolution. Authors of articles for which we did not have access to the full text were contacted when possible, and lack of response within 1 month led to the exclusion of the article. The reasons for exclusion were reported.

Data Collection Process

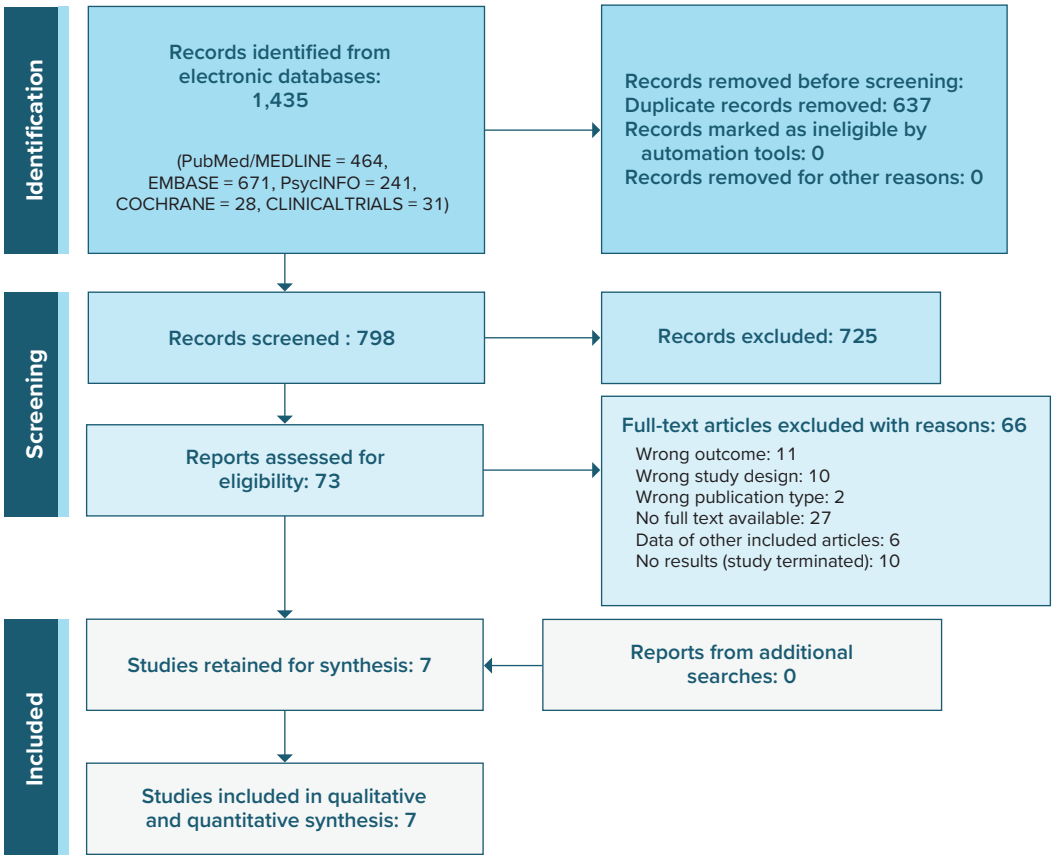
After meticulous examinations of the final selected articles, we collected our data of interest using a predefined and pretested Google form. Further, using a blind process, 2 reviewers (C.L. and F.T.E.) independently extracted data, with resolution of divergences through consensual decisions after discussions or the intervention of a third author (G.C.).

Data Items

Data collected for each article were as follows:

(1) Bibliometric data with the name of the first author and the year of publication.

Figure 1.
Preferred Reporting Items for Systematic Reviews and Meta-Analyses–Based Flowchart



(2) General characteristics of the studies with the phase and the registration number of the clinical trial, the country and period of the study, the study design, the setting of the study (emergency unit, psychiatric unit, intensive care unit, etc), the randomization method and tool, the study hypothesis, the statistical analysis, and the experimental design.

(3) General characteristics of study participants encompassing the main selection criteria, the sample sizes in each arm, the mean age, the sex ratio, the underlying conditions with assessment/screening tools and cutoff used, the type of agitation, the tool used to assess acute agitation, the data collection method, and the follow-up duration.

(4) Information pertaining to interventions, especially drug classes, administration routes, protocols, daily doses, and timing of drug administrations.

(5) The outcomes regarding efficacy of the interventions (time to control agitation, proportions of successfully controlled agitations, sedation scale scores, agitation scale scores, need of additional treatments for sedation, use of seclusion and/or restraint, occurrences of self-harm, frequency and severity of side effects) and safety.

Risk of Bias Assessment

The risk of bias assessment was performed using the Cochrane Risk of Bias (RoB) 2.0 tool.[22] This tool was developed in 2016 and released in August 2019 and consists of 5 domains identified as potential sources of bias. These domains include risk of bias resulting from the randomization process, risk of bias resulting from deviations from planned interventions, missing data on the outcome, risk of bias due to measurement of the outcome, and risk of bias in the selection of reported results. Two investigators performed this step (C.L. and F.T.E.) with a blind and independent evaluation, and disagreements were resolved by consensus.

From the assessment of each domain, we were able to identify the overall risk of bias for each study. A low overall risk of bias was retained when all domains had a low risk. An overall risk of bias with "some concern" was retained when there was a bias rated as "some concern" for 1 of the domains. A high risk of overall bias was retained if 1 of the domains had a high risk or if more than 1 domain had "some concerns."

Synthesis Methods

We defined the following plan to present our findings: (1) graphical illustration of the selection process with

Table 1.

Main Characteristics of the Included Studies

Study/Country/Time Period	Study Design	Participants, N	Diagnosis/Context	Intervention	Duration of Follow-Up	No. of Administrations Allowed	Agitation Scale	Mean Age, y (range)	Baseline Agitation Score (Mean)
Fruensgaard et al, 1977[23] Denmark NA	RCT, multicentric, double-blind	30 (7 male/ 23 female)	Schizophrenia, psychogenic psychosis/ NA	Loxapine IM 25–50 mg vs haloperidol IM 2.5 to 5 mg	84 h (72 h during the treatment period, 6 to 12 h after the last dose)	NA (average daily 130 mg for loxapine and 12 mg for haloperidol)	Agitation/ agression scale, BPRS, CGI	Loxapine: 41.3 (19–65), haloperidol 40.1 (19–61)	Agitation scale: NA BPRS: 56.0 loxapine, 57.7 haloperidol CGI: 3.60 loxapine, 3.73 haloperidol
Gaussares et al, 1989[24] France NA	RCT, monocentric, open-label	15 (all male)	NA/hospital department	Loxapine IM 200 mg vs droperidol IM 100 mg	3 to 5 d	2/d	Analogical scale assessing the state of agitation rated from 1 to 4	31 (20–58)	NA
Allen et al, 2011[25] United States September 2006– January 2007	RCT, multicentric, double-blind	129 (105 male/ 24 female)	Schizophrenia, schizoaffective disorder, and schizophreniform disorders/hospital and emergency departments	Loxapine inhaled 5 mg vs placebo inhaled vs loxapine inhaled 10 mg	24 h	1	PANSS-EC, CGI, BARS	41.2 (21–61)	PANSS-EC: 17.4 ± 2.23 placebo, 17.6 ± 1.94 loxapine 5 mg, 17.4 ± 2.02 loxapine 10 mg CGI: NA BARS: 4.98 ± 0.46 placebo, 4.96 ± 0.6 loxapine 5 mg and 5.00 ± 0.59 loxapine 10 mg
Lesem et al, 2011[26] United States February–June 2006	RCT, multicentric, double-blind	344 (253 male/ 91 female)	Schizophrenia, hospital and psychiatric/emergency departments	Loxapine inhaled 5 mg vs placebo inhaled vs loxapine inhaled 10 mg	24 h	3	PANSS-EC, CGI, ACES	Loxapine 5 mg: 43.2 (16–65), loxapine 10 mg: 42.2 (21–62), placebo: 43.9 (23–69)	PANSS-EC: 17.4 placebo, 17.8 loxapine 5 mg, 17.6 loxapine 10 mg; CGI-S: 3.9 placebo, 4.0 loxapine 5 mg, 4.1 loxapine 10 mg
Kwentus et al, 2012[27] United States July–November 2008	RCT, multicentric, double-blind	314 (156 male/ 158 female)	Bipolar disorder/ hospital and emergency departments	Loxapine inhaled 5 mg vs placebo inhaled vs loxapine inhaled 10 mg	24 h	3	PANSS-EC, CGI, ACES	Loxapine 5 mg: 41.2 (19–62), loxapine 10 mg: 40.5 (19–64), placebo: 40.6 (19–60)	PANSS-EC: NA CGI-I: NA ACES: 2.01 ± 0.4 placebo, 2.11 ± 0.4 loxapine
Gaudry et al, 2017[28] France, November 2011–November 2013	RCT, multicentric, double-blind	87 (66 male/ 21 female)	NA/situation of weaning from mechanical ventilation in intensive care units	Loxapine enteral (NGT) 150 mg vs placebo enteral (NGT)	48 h–14 d	NA	RASS	Loxapine: 59.6 (NA), placebo: 51 (NA)	NA
San et al, 2018[29] Czech Republic, Germany, Spain, Russia December 2014–October 2016	RCT, multicentric, open-label	357 (181 male/ 176 female)	Schizophrenia or bipolar disorder type 1/ hospital and emergency departments	Loxapine inhaled 9.1 mg vs aripiprazole 9.75 mg IM	4–24 h	2	CGI	Loxapine: 40.44 (NA), aripiprazole 40.26 (NA)	CGI-S: 4.42 loxapine, 4.31 aripiprazole

Abbreviations: ACES = Agitation-Calmness Evaluation Scale, BARS = Behavioral Activity Rating Scale, CGI = Clinical Global Impressions, BPRS = Brief Psychiatric Rating Scale, IM = intramuscular, NA = not available, NGT = nasogastric tube, PANSS-EC = Positive and Negative Syndrome Scale Excited Component, RASS = Richmond Agitation Sedation Scale, RCT = randomized clinical trial.

Table 2.
Risk of Bias of the Included Studies

Study	Domain 1: Risk of Bias Arising From the Randomization Process	Domain 2: Risk of Bias Due to Deviations From the Intended Interventions (assignment)	Domain 2: Risk of Bias Due to Deviations From the Intended Interventions (adhering)	Domain 3: Missing Outcome Data	Domain 4: Risk of Bias in Measurement of the Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
Fruensgaard et al, 1977[23]	Some concerns	Some concerns	Low	Low	Low	Low	**Some concerns**
Gaussares et al, 1989[24]	Some concerns	Some concerns	High	Low	Some concerns	Low	**High**
Allen et al, 2011[25]	High	Low	Low	Low	Low	Low	**High**
Lesem et al, 2011[26]	Low	Low	Low	Low	Low	Low	**Low**
Kwentus et al, 2012[27]	Low	Low	Low	Low	Low	Low	**Low**
Gaudry et al, 2017[28]	Some concerns	Low	Low	Low	Low	Low	**Some concerns**
San et al, 2018[29]	Some concerns	High	High	Low	Low	Low	**High**

a PRISMA-based flowchart, (2) tabular report of individual characteristics of the selected studies, (3) tabular presentation of results related to risk of bias assessment, and (4) tabular and text syntheses of results regarding efficacy and safety outcomes.

RESULTS

Study Selection

From the 1,435 articles initially identified, 637 duplicates were excluded, and of the 798 remaining articles, 73 were selected based on titles and abstracts. After searching and analyzing full texts (when it was possible), 7 studies were retained for our narrative synthesis.[23–29] Of note, we requested full texts for 6 articles of interest regarding our eligibility criteria, received 4 of them, and finally included 2 in our review. The different stages of the selection process are illustrated in Figure 1.

Study Characteristics

Of the 7 enrolled studies, 3 took place in the United States, 2 in France, 1 in Denmark, and 1 involved the Czech Republic, Germany, Spain, and Russia (Table 1). The studies were published between 1977 and 2018 and were all randomized controlled trials. More precisely, 5 were double-blind and 2 were open label. Only 1 of the trials was a single center study (see Table 1).

The total number of participants was 1,276, with sample sizes ranging from 15 to 357. The mean age of participants varied between 31 and 59.6 years old, with a minimum of 16 years and a maximum of 69 years, and the male to female ratio was 1.58 (783/493). Only 1 article[24] reported the mean weight of the participants, and none reported the minimum and maximum weights. Three studies[23,25,26] targeted patients with psychotic disorder, 1[27] focused on patients with bipolar disorder, and 1[29] selected patients with psychotic disorder or type 1 bipolar disorder. Also, 1 study[28] selected participants whose agitation resulted from weaning from mechanical ventilation in an intensive care unit. The other trials were conducted in hospital or emergency departments (see Table 1).

Four studies[25–28] compared loxapine to placebo, and the others compared loxapine to haloperidol, aripiprazole, or droperidol. Regarding the routes of administration, 4 trials[25–27,29] studied the inhaled route, 2[23,24] the intramuscular route, and 1[28] the enteral route via a nasogastric tube. The frequency of administration varied from 1 to 3 times per day, and 1 study[23] reported the mean daily amount of loxapine administered, which was 130 mg. The follow-up durations ranged from 24 hours (in 4 of the studies) to 14 days, and in 6 studies benzodiazepine was planned as a rescue medication.

The agitation scales used in the included studies[22–28] were the Positive and Negative Syndrome Scale–Excited Component (PANSS-EC), the Clinical Global Impressions (CGI), the Brief Psychiatric Rating Scale, the Behavioral Activity Rating Scale, the Agitation-Calmness Evaluation Scale, the Richmond Agitation Sedation Scale, an analog agitation/aggression scale, and an analog scale assessing the state of agitation and rated from 1 to 4. The CGI was the most commonly used scale (5 of the included articles[23,25–27,29]), and the mean agitation score at baseline as measured by the CGI scale ranged from 3.60 to 4.42 (see Table 1).

Risk of Bias

Our risk of bias appraisal revealed a good quality for 2 studies,[26,27] with a low risk of overall bias (Table 2). The analysis classified 2 articles as "some concern" and 3 articles[24,25,29] as high risk of overall bias. Although all studies were described as randomized, many did not provide details regarding the randomization method used. In addition, for 2 articles[28,29] there were some significant differences between the intervention groups at baseline, suggesting an issue during the randomization process. Two studies[24,29] were conducted in an open-label design. The risk of bias due to deviations from the intended interventions (effects of assignment and adherence to the intervention) was consequently high.

Table 3.

Main Results of the Narrative Synthesis

Study	Efficacy Criteria	Time of Outcomes Assessment	Definition of Responders	Proportion of Responders	Decrease in Agitation Scale Score	Rapidity for the Control of Agitation	Time to Need a Second Dose or Other Tranquilizers	Main Result
Fruensgaard et al, 1977[23]	Sedation scale scored from 0 to 4, "severity of agitation/excitation and aggressive behavior" scale scored from 0 to 4, BPRS, CGI	At 0 and after the first and second dose at 30 minutes, 1 h, 2h, 4h, and 6h CGI: D1, D2, D3	No. of patients sedated (yes/no) after the first injection	Loxapine (78.7%) > haloperidol (60.0%)* with earlier onset of action of loxapine (as early as 2 h after the first injection)* and significant effect in the "acute schizophrenia" subgroup	BPRS and CGI: no significant differences. For agitation: tendency for better control of agitation/excitation (psychomotor) and aggression with loxapine compared to haloperidol	Loxapine > haloperidol from 2 h after the first injection* (sedation scale)	NA	Significantly stronger and more rapid sedative effect with loxapine; tendency to better control of psychomotor agitation
Gaussares et al, 1989[24]	Time at onset of the "aggressolytic" effect, analogical scales rated from 1 to 4 assessing the state of motor, psychomotor, and psychic agitation; evaluation of the patient's behavior via the presence or absence of 3 criteria	D1, D2, D3, D4, D5 at 15 minutes, 30 minutes, and 3 h after the first injection and at 15 minutes, 30 minutes, and 3 h after the second injection	NA	NR	Loxapine > droperidol at second injection D1 and D2*; then = (motor agitation), loxapine > droperidol at 30 minutes from first injection D1*; confirmed at 3 h second injection (psychomotor agitation), loxapine > droperidol at D2* then = (psychic agitation)	Loxapine > droperidol from 15 minutes after the first injection*	NA, but "aggressolytic" effect persisting longer with loxapine than with droperidol (D4)	Control of agitation significantly faster and longer lasting compared to droperidol; cumulative effect of injections allowing to have effect on psychic agitation
Allen et al, 2011[25]	PANSS-EC, CGI, BARS, time for administration of other tranquilizers (lorazepam)	PANSS-EC: at 0, 10, 20, 30, 45, 60, and 90 minutes and 2, 4, and 24 h CGI-I: at 0 and 2 h BARS: at 0, 10, 20, 30, 45, 60, and 90 minutes and 2, 4, and 24 h	CGI-I score at 2 h of 1 "very much improved" or 2 "much improved"	Loxapine 10 mg (63%) > loxapine 5 mg (49%) > placebo (21%)*	Loxapine 10 mg > placebo at 2 h (PANSS-EC)*; loxapine 10 mg > placebo at 2 h (BARS)*; loxapine 10 mg > placebo (CGI-I, not significant)	Loxapine10 mg > placebo from 20 minutes (PANSS-EC)*	Time to need for lorazepam (rescue medication): loxapine 5 mg and loxapine10 mg > placebo*; need for lorazepam (rescue medication) for placebo (33%) > loxapine 10 mg (15%) > loxapine 5 mg (11%)*	Significantly better and faster agitation control with loxapine 10 mg
Lesem et al, 2011[26]	PANSS-EC, CGI-I, ACES	PANSS-EC: at 10, 20, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 h after the first dose CGI-I: at 2 h ACES: at 2 h	CGI-I score at 2 h of 1 "very much improved" or 2 "much improved"	Loxapine 5 mg (56,8%) and loxapine10 mg (66,9%) > placebo (35,6%)*	Loxapine 5 mg and loxapine 10 mg > placebo at 2 h (PANSS-EC)*; loxapine 5 gm and loxapine 10 mg > placebo at 2 h (CGI-I)*	Loxapine 5 mg and loxapine10 mg > placebo from 10 minutes (PANSS-EC)*	Time to second dose: loxapine10 mg > placebo*; need for lorazepam (rescue medication) for 18 participants in the placebo group, 7 in the loxapine 5 mg group and 6 in the loxapine 10 mg group	Significantly better and faster control of agitation with loxapine; continuous treatment effect over the 24-h evaluation period
Kwentus et al, 2012[27]	PANSS-EC, CGI-I, ACES, need and time before second dose of product	PANSS-EC: at 0, 10, 20, 30, and 45 minutes and 1, 1.5, 2, 4, and 24 h after the first dose CGI-I: at 0 and 2 h	CGI-I score at 2 h of 1 "very much improved" or 2 "much improved"	Loxapine 5 mg (66.3%) and loxapine 10 (74.3%) > placebo (27.6%)*	Loxapine10 mg > loxapine 5 mg > placebo at 2 h (PANSS-EC and CGI)*	Loxapine 5 mg and loxapine10 mg > placebo from 10 minutes*	Loxapine 5 mg and loxapine 10 mg > placebo (time to second dose)*	Significantly better and faster control of agitation with loxapine; dose effect relation

(continued)

Table 3.
(continued)

Study	Efficacy Criteria	Time of Outcomes Assessment	Definition of Responders	Proportion of Responders	Decrease in Agitation Scale Score	Rapidity for the Control of Agitation	Time to Need a Second Dose or Other Tranquilizers	Main Result
Gaudry et al, 2017[28]	RASS	RASS: at 0, 30, 60, and 90 minutes; 4 h; and then every 4 h	NR	NR	Loxapine > placebo at 4 h*	NA	Tendency to increase the total dose of administration in the placebo group compared to the loxapine group	Significantly better agitation control with loxapine
San et al, 2018[29]	CGI-I, number of patients who received a second dose/rescue medication, TSQM	CGI S: 30 minutes before the first dose, then between 4 h and 24 h after the first dose (or after resolution of agitation): 10 ± 2, 20 ± 2, 30 ± 2, 50 ± 2, 60 ± 5, 90 ± 5, and 120 ± 5 minutes TSQM: at 2 h and 24 h (or after resolution of agitation) after the first dose	CGI-I score of 1 "very much improved" or 2 "much improved"	Loxapine (14%) > aripiprazole (3.9%) from 10 minutes*	NA	Median theoretical time to CGI-I response: loxapine (50 minutes) > aripiprazole (60 minutes)* Schizophrenia subgroup: loxapine (50 minutes) > aripiprazole (60 minutes)* TB1 subgroup: loxapine (30 minutes) > aripiprazole (50 minutes)	Need for a second dose for aripiprazole (9.6%) > loxapine (6.7%); rescue medication for loxapine (n = 1) (150 minutes after dose 1) > aripiprazole (n = 0)	Loxapine significantly superior in terms of proportion of responders and rapidity of agitation control

*Significant difference.
Abbreviations: ACES = Agitation-Calmness Evaluation Scale, BARS = Behavioral Activity Rating Scale, BPRS = Brief Psychiatric Rating Scale, CGI-I = Clinical Global Impressions–Improvement, CGI-S = Clinical Global Impressions–Severity, NA = not available, NR = not relevant, PANSS-EC = Positive and Negative Syndrome Scale Excited Component, RASS = Richmond Agitation Sedation Scale, TSQM = Treatment Satisfaction Questionnaire for Medication.

Results of Syntheses

Five studies[23,25–27,29] assessed the proportion of treatment responders, and for 4 of them, the definition of a responder was a 2-hour CGI-I score of 1 ("very much improved") or 2 ("much improved") (Table 3). The fifth[23] defined a responder as a sedated patient (yes/no) after the first injection. It should be noted that for the oldest article,[23] the efficacy outcome was sedation and not reduction in agitation. All the studies that assessed treatment responders showed a significantly higher proportion in the loxapine group. This superiority of loxapine was significant as early as 2 hours versus haloperidol, and as early as 10 minutes versus aripiprazole. Two studies[23,29] performed subgroup analyses, and the effect of loxapine was significantly greater in patients with a diagnosis of schizophrenia, but no significant difference was found in bipolar disorder patients.

Loxapine significantly decreased the agitation scale score in 5 of the 6 articles[23–28] that appraised this outcome, and while focusing on the time needed to reach efficacy, loxapine was significantly faster (see Table 3). The times at which the agitation scale score was significantly lower in the loxapine group were 10 minutes (for inhaled loxapine compared with placebo), 15 minutes, 20 minutes, and 2 hours (for loxapine compared with haloperidol). The delay between the first administration and a second dose or rescue medication (lorazepam) was significantly longer in the inhaled loxapine group compared with placebo. The 7 included articles hence concluded that loxapine is significantly more effective and faster in controlling acute agitation.

Two studies[26,28] comparing loxapine to placebo reported no significant differences in the frequency of adverse events, and the other articles reported no statistical analyses on this outcome. The most commonly reported side effects were extrapyramidal syndromes, dizziness, and symptoms reflecting anticholinergic effects. In the articles that studied the inhaled route of administration,[25–27,29] dysgeusia was also reported as a frequent side effect. Overall, the adverse events were considered by the authors to be minor or of moderate severity, with a resolution using dedicated treatment (benztropine for extrapyramidal syndromes). Of the 703 participants who received inhaled loxapine, 3 experienced bronchospasms, with 1 requiring intervention with albuterol. Loxapine does not appear to induce more important sedation levels compared to haloperidol or aripiprazole. Although the sedation rating scales were disparate,

the included articles noted moderate sedation levels. Nevertheless, 2 participants experienced severe sedation after administration of inhaled loxapine 10 mg, and 1 participant died within 6 days after inhaled loxapine 10 mg. The cause of death was not reported and was considered by the investigators to be unrelated to treatment. No articles specified that QT interval measurements were performed, and no cardiac adverse events were reported.

The satisfaction of patients toward pharmacologic treatments was assessed in some studies, and we found that loxapine was significantly superior to droperidol ("feeling relaxed") and to aripiprazole ("very" or "extremely satisfied").

DISCUSSION

General Interpretation of the Results in the Context of Other Evidence

In this systematic review, we included 7 articles that were all randomized trials and encompassed a total of 1,276 participants. Our syntheses revealed that loxapine, while administrated for acute agitation and compared with other drugs, was associated with a greater proportion of responders, as well as a greater and faster decrease in agitation intensity. Also, loxapine was not associated with a greater frequency of adverse events and resulted in patient satisfaction with improvement.

In terms of efficacy and safety, our findings are respectively different and similar to that of Popovic and colleagues.[30] Those authors performed a comprehensive and systematic literature review with the aim to examine the efficacy and tolerability of the various formulations of loxapine. They concluded that available data suggest that the antipsychotic efficacy of loxapine is similar to the efficacy of other typical or atypical antipsychotics, with an adverse effects profile comparable to that of the typical antipsychotics at high doses for chronic treatment.[30] Nevertheless, their review differs from our study in that they focused their searches in PubMed/MEDLINE; targeted agitation and aggression in patients affected with schizophrenia, bipolar disorder, and other psychiatric conditions; and did not exclusively consider the "acute" feature of agitation. The findings pertaining to our narrative syntheses seem to confirm results of observational studies comparing loxapine to other antipsychotic drugs for acute agitation, especially in emergency departments.[30,31] For instance, Ruch et al[31] compared 61 agitated or aggressive patients that received inhaled loxapine to 29 that received non-parenteral treatment as usual and found a 6-fold faster and more robust symptom control with loxapine. McDowell and colleagues,[32] while comparing 54 agitated patients that received inhaled loxapine to 225 and 127 patients managed with ziprasidone and haloperidol, respectively, found that inhaled loxapine may be a more effective and rapid treatment option.

The place of loxapine in other diagnoses such as personality disorders, intoxication, or somatic diseases has not been evaluated mainly because these conditions were exclusion criteria in included trials. However, a recently published naturalistic, unicentric, prospective study[33] of 30 personality disorder subjects with acute agitation attending emergency departments suggested that inhaled loxapine could be a safe and effective therapeutic option. Regarding agitation in intoxicated patients, there are observational studies reporting the effective and quick management of acute agitation with inhaled loxapine, with the possibility of appropriate subsequent clinical evaluation.[34] Articles on other psychiatric diagnoses, such as case reports on children with autistic disorders, suggest that loxapine is effective in treating agitation but need to be confirmed in clinical trials.[35]

Since its introduction in the 1970s, loxapine has gradually become part of the prescribing habits of practitioners in France or North American countries, especially for the management of acute agitation.[14,15] This prevalence might be explained by its relative ease of use in emergency situations. Indeed, the existence of only 1 dosage of intramuscular injection ampoule, as well as 1 dosage of some commercialized inhaled form, and 2 dosages for oral loxapine, allows a fast action and limits the risk of administration errors. This systematic review allowed us to determine the place of this treatment in the current scientific literature and to highlight the lack of evidence.

Limitations

The data suggest that loxapine is an effective, rapid, and well-tolerated treatment for the control of acute agitation. Although this is the first systematic review investigating the effect of loxapine in acute agitation, the interpretation of our findings should take into consideration some limitations. First, we had high heterogeneity in terms of treatment arms and outcome assessments. Indeed, across studies, there is wide variability in the agitation rating scales used, which for instance did not allow us to perform a meta-analysis. It must be noted that the CGI, which was the most commonly used assessment tool in the included studies, is not specific to agitation as is the PANSS-EC for example.[36,37] Some of the authors justified this choice by the greater ease of use, that it was for all types of practitioners (no need of specialized knowledge), and the short time needed for scoring, making this scale more applicable in clinical practice.[29] Other limitations are the lack of studies comparing each route of administration with others (especially inhaled versus oral or intramuscular route), as well as the relatively low number of available articles. Indeed, the choice to select only interventional studies highlighted the current lack of high-level evidence. Only 2 articles were of good quality with a low overall risk of bias but still involved 658 participants, representing more than half of the total population. The

risk of bias analysis highlighted higher risks in the area of randomization. The generalization of our findings is also hampered by the lack of data on populations such as adolescents and the elderly and the predominance of published studies in the United States and Europe. In addition, it should be noted that almost all of the studies in this review have links with pharmaceutical companies manufacturing loxapine. More specifically, there were 3 studies sponsored by Alexza Pharmaceuticals, 2 linked to Lederlè Laboratories through supply or affiliation of 1 of the authors, and 1 sponsored by Ferrer Internacional.

Implications of the Results for Practice, Policy, and Future Research

Despite the mentioned limitations, this review provides reassuring evidence regarding continuation of loxapine use in clinical practice for the management of acute agitation. The use of a common scale, instead of a visual analog, could contribute to standardized practices and avoid some escalations in treatment. Indeed, such a scale could guide decisions with progressively increasing strategies ("calming room," oral treatment, injectable treatment, seclusion and restraint) and adjustments depending on the patient's agitation score. In terms of future research, it could be interesting to perform interventional studies extended to other age groups or other profiles of underlying mental health disorders and with methodological optimization notably regarding randomization processes.

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