

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, 1977²³	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, 1989²⁴	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, 2011²⁵	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)	Loxapine 10 mg > placebo from 20 minutes (PANSS-EC)*	Time to need for lorazepam (rescue medication): loxapine 5 mg and loxapine 10 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, 2011²⁶	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 loxapine 10 mg (66.9%) > placebo (35.6%)*	Loxapine 5 mg and loxapine 10 mg > placebo at 2 h (PANSS-EC)*; loxapine 5 mg and loxapine 10 mg > placebo at 2 h (CGI-I)*	Loxapine 5 mg and loxapine 10 mg > placebo from 10 minutes (PANSS-EC)*	Time to second dose: loxapine 10 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, 2012²⁷	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%)*	Loxapine 10 mg > loxapine 5 mg > placebo at 2 h (PANSS-EC and CGI)*	Loxapine 5 mg and loxapine 10 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
Gaudry et al, 2017²⁸	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, 2018²⁹	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.