http://dx.doi.org/10.1590/1516-4446-2018-0177
Brazilian guidelines for the management of psychomotor agitation. Part 2. Pharmacological approach

Table S1 Selected articles on the pharmacological management of psychomotor agitation

Reference	Population	Intervention	Route	Study type	Primary efficacy outcome measure	Adverse events	Level of evidence
Agid[1]	79 hospitalized patients with psychotic disorder and acute agitation	Ziprasidone (2 mg) vs. ziprasidone (20 mg)	IM	RCT	PANSS	None	2B Ziprasidone IM may be associated with more rapid improvement in psychotic symptoms.
Ahmed[2]	30 individuals acutely aggressive or agitated due to psychotic illness	Chlorpromazine (50 mg) vs. haloperidol (5 mg)	IM	Systematic review	Rapid tranquilization	Sudden, serious hypotension, status epilepticus	2A Where drugs that have been better evaluated are available, it may be best to avoid use of chlorpromazine.
Alexander[3]	200 people with agitation, aggression, or violent behavior	Haloperidol (10 mg) + promethazine (25-50 mg) vs. lorazepam (4 mg)	IM	RCT	Tranquil or asleep 15 min, 30 min, 60 min, 120 min, and 240 min after first medication	Moderate worsening of respiratory difficulty, nausea, and dizziness with lorazepam	1B Both interventions are effective for controlling violent/agitated behavior.
Allen[4]	129 agitated patients due to schizophrenia, schizophreniform, and schizoaffective disorder	Loxapine (5 mg) vs. loxapine (10 mg) vs. placebo	IN	RCT	PANSS-EC	Sedation and dysgeusia	1B Inhaled loxapine was generally safe and well-tolerated and produced rapid improvement in agitated patients with psychotic disorders.
Allen[5]	40 agitated patients with schizophrenia and nicotine dependence	Nicotine (21 mg) vs. placebo	TD	RCT	ABS and PANSS-EC	Drowsy	2B The mean ABS score for the nicotine replacement group was 33% lower at 4 hours and 23% lower at 24 hours than for the placebo group.
Andrezina[6]	448 patients with agitation associated with schizophrenia or schizoaffective disorder	Aripiprazole (9.75 mg) vs. haloperidol (7.5 mg) vs. placebo	IM	RCT	Mean change in PANSS-EC score from baseline to 2 hours after first injection	Headache, dizziness, nausea, and insomnia with aripiprazole Insomnia, headache, and extrapyramidal disorder with haloperidol	1B Aripiprazole was non-inferior to haloperidol.
Asadollahi[7]	160 agitated patients	Haloperidol (5 mg) + placebo vs. sodium valproate (20 mg/kg) + placebo	IV	RCT	ABS, ACES, and PANSS-EC at 30 min	Intense sedation and EPS with haloperidol	2B Intravenous valproate is as effective as haloperidol in reducing agitation with a better safety profile.
Baldaçara[8]	150 patients with agitation due to psychosis or bipolar disorder	Olanzapine (10 mg) vs. ziprasidone (20 mg) vs. haloperidol (5 mg) + promethazine (50 mg) vs. haloperidol (5 mg) + midazolam (15 mg) vs.	IM	RCT	OASS and OAS at 1, 2, 4, 6, and 12 hours after first medication	Sedation and EPS	2B Olanzapine, ziprasidone, haloperidol + promethazine, haloperidol + midazolam and haloperidol were effective in controlling agitation and aggression caused by mental illness

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		haloperidol (5 mg).					over 12 hours. Although all the drugs had advantages and disadvantages, haloperidol + midazolam was associated with the worst results in all the observed parameters.
Baker[9]	148 acutely agitated patients with schizophrenia, schizoaffective disorder, schizophreniform disorder, or bipolar I disorder, manic or mixed episode	Oral olanzapine in rapid initial dose escalation (up to 40 mg) vs. oral olanzapine (10 mg) + oral lorazepam as needed	PO	RCT	PANSS-EC at 24 hours	Headache and dizziness in rapid initial dose escalation group	2B Olanzapine dosing, at an expanded initial dose range of up to 40 mg/day, was superior in rapidly and effectively controlling the symptoms of agitation without over sedation.
Bieniek[10]	20 subjects treated on the psychiatric emergency service	Lorazepam IM (2 mg) vs. haloperidol IM (5 mg) + lorazepam IM (2 mg).	IM	RCT	OAS	No adverse effects were observed or reported in either treatment group	2C Repeated measures analyses of variance showed that both groups improved over time, but between-group differences were not significant.
Breier[11]	270 acutely agitated patients with schizophrenia	Olanzapine (2.5 mg) vs. olanzapine (5 mg) vs. olanzapine (7.5 mg) vs. olanzapine (10 mg) vs. haloperidol (7.5 mg) vs. placebo	IM	RCT	PANSS-EC	Hypotension with olanzapine and acute dystonia with haloperidol	2B All olanzapine groups and haloperidol group had decreased agitation compared with placebo.
Castle[12]	2,011 acutely agitated patients with schizophrenia or acute mania	Olanzapine vs. other antipsychotics	IM	Observational, multisite	PANSS-EC and CGI-S at 2, 24, and 72 hours and at 7 days following initial injection and on oral antipsychotic transition	EPSs	2C IM olanzapine provided somewhat more effective control of acute agitation than other assessed IM antipsychotics.
Chan[13]	336 agitated patients	Droperidol (5 mg) + midazolam (2.5-5 mg) vs. olanzapine (5 mg) + midazolam (2.5-5 mg) vs. placebo + midazolam (2.5-5 mg)	IV	RCT	Sedation at 5 and 10 min; need for additional medication	Need for airway management (jaw thrust, oral/nasal airway) or assisted ventilation (bag-valve-mask, intubation), oxygen desaturation, systolic blood pressure less than 90 mmHg, dystonic reactions, seizures, vomiting or aspiration, and movement disorders	1B IV droperidol or olanzapine as an adjunct to midazolam is effective and decreases the time to adequate sedation compared with midazolam alone.

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Chan[14]	49 agitated patients with schizophrenia	Olanzapine (10 mg) vs. haloperidol (7.5 mg)	IM	RCT	PANSS-EC at 2 hours	Insomnia	2B Both IM olanzapine and IM haloperidol were safe and well-tolerated.
Chouinard[15]	16 acutely agitated psychotic patients with manic or manic-like symptoms	Clonazepam (1-2 mg) vs. haloperidol (5-10 mg)	IM	RCT	Reduction of manic symptoms within 2 hours of initial treatment	None	C IM clonazepam is an effective, safe, but slower-acting alternative to IM haloperidol in the treatment of agitated psychiatric patients in need of rapid tranquilization.
Currier & Simpson[16]	60 patients in emergency treatment of psychotic agitation	Oral risperidone (2 mg) + oral lorazepam (2 mg) vs. IM haloperidol (5 mg) + IM lorazepam (2 mg).	VO, IM	RCT	PANSS, CGI, and time to sedation	No patients receiving risperidone demonstrated any side effects or adverse events, while one patient receiving IM haloperidol developed acute dystonia	2C Oral treatment with risperidone and lorazepam appears to be a tolerable and comparable alternative to IM haloperidol and lorazepam for short-term treatment of agitated psychosis in patients who accept oral medications.
Currier[17]	162 patients exhibiting agitation associated with active psychosis	Oral risperidone (2 mg) + lorazepam (2 mg) vs. IM haloperidol (5 mg) + lorazepam (2 mg)	PO, IM	RCT	PANSS at 30, 60, and 120 min after dosing.	No differences	2B A single oral dose of risperidone plus lorazepam was as effective as parenterally administered haloperidol plus lorazepam for the rapid control of agitation and psychosis.
Daniel[18]	448 agitated patients with schizophrenia or schizoaffective	Aripiprazole (9.75 mg) vs. haloperidol (6.5 mg) vs. placebo	IM	RCT	PANSS-EC at 24 hours	Nausea and vomiting occurred more frequently in patients receiving aripiprazole; extrapyramidal symptom-related adverse events were lower for aripiprazole	2B Acutely agitated patients with schizophrenia or schizoaffective disorder treated with aripiprazole IM or haloperidol IM demonstrated similar effective and safe transition to their respective oral formulations.
Daniel[19]	79 agitated psychotic patients	Ziprasidone (20 mg) vs. ziprasidone (2 mg)	IM	RCT	BARS at 24 hours	None	2B Ziprasidone IM 20 mg substantially and significantly reduced the symptoms of acute agitation in patients with psychotic disorders. Ziprasidone 20 mg IM was very well-tolerated and produced no dystonia or akathisia.
De Filippis[20]	201 agitated patients with schizophrenia or bipolar disorder	Aripiprazole (9.75 mg)	IM	Open-label trial	PANSS-EC, ACES, and CGI 30, 60, 90, 120 min, and 24 hours	None	2C Aripiprazole was effective and safe in reducing acute agitation in patients

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							with bipolar disorder or schizophrenia.
Dorevitch[21]	28 actively psychotic inpatients	Haloperidol (5 mg) vs. flunitrazepam (1 mg)	IM	RCT	OAS 15, 30, 45, 60, 90, and 120 min	None	2B Flunitrazepam and haloperidol administered intramuscularly were similarly effective in controlling agitated or aggressive behavior in acute psychotic inpatients.
Escobar[22]	278 patients with acute psychosis and agitation	Olanzapine alone (mean dosage 12 mg) vs. olanzapine in combination. Reintervention or not (clonazepam, clorazepate, clotiapine, diazepam, fluphenazine, lorazepam, oxcarbazepine, risperidone, ziprasidone, and zuclopenthixol)	PO	Observational, prospective	PANSS-EC and ACES	Bradycardia, dry mouth, sedation, hypertension, hypotension, and orthostatic hypotension	2C The utilization of olanzapine alone decreased agitation in psychotic patients in emergency room settings. Incidence of adverse events was low, and it was well-tolerated.
Fang[23]	205 agitation-exhibiting schizophrenic inpatients at six hospitals	Risperidone OS (2-6 mg) + clonazepam (0-8 mg) vs. IM haloperidol (10-20 mg) per day	PO, IM	RCT	PANSS-EC at 2, 4, and 24 hours	Extrapyramidal symptoms were lower with oral treatment than with IM treatment	2B Risperidone OS in combination with clonazepam is an effective treatment comparable with IM haloperidol, and is well-tolerated for acute agitation in patients with schizophrenia.
Gault[24]	11 trials of agitated patients from multiple settings such as the emergency department, inpatient psychiatric unit, or a psychiatric emergency services facility	Risperidone 2 mg + lorazepam 2 mg Oral risperidone 3 mg Oral olanzapine 10-20 mg olanzapine ODT 10-20 mg olanzapine + BZDs.	PO, IM	Structure review	Change in scales scores in the first minutes or hours.	Similar than IM formulations	2A Oral risperidone or olanzapine or ODT risperidone or olanzapine with or without oral lorazepam were as effective as IM formulations.
Gillies[25]	21 trials with a total of n=1,968 participants; acute psychotic illness, especially when associated with agitated or violent behavior, can require urgent pharmacological tranquillization or sedation	Oral alprazolam (1 mg) + IM haloperidol (5 mg) IM haloperidol (5 mg) IM clonazepam (1-2 mg) + IM procyclidine placebo IM haloperidol (5-10 mg) + procyclidine IM clonazepam (3.5 mg) + olanzapine (5-30 mg) IM haloperidol (5-20 mg)	PO, IM, IV	Systematic review	Global impression, adverse effects, satisfaction, cost-effectiveness	Respiratory depression, ataxia, excessive sedation, memory impairment and paradoxical disinhibition	1A There is no strong evidence to support or refute the use of BZDs (with or without antipsychotics or in combination with other drugs) if the situation has deteriorated to such an extent that emergency drugs are needed.

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		IV diazepam (30-40 mg) IV haloperidol (20-35 mg) IM flunitrazepam (1 mg) IM lorazepam (2-4 mg) + IM haloperidol (5-10 mg) IV midazolam (4 mg) IV droperidol (4 mg) IM midazolam (15 mg) + haloperidol (5 mg) IM haloperidol (5 mg) + promethazine (50 mg) IM olanzapine (10 mg) IM ziprasidone (20 mg)					
Hsu[26]	42 inpatients from an acute care psychiatric ward	IM olanzapine (10 mg) vs. oral disintegrating tablet olanzapine (10 mg) vs. OS risperidone (3 mg) vs. IM haloperidol (7.5 mg).	PO, IM	RCT	PANSS-EC, ACES, and CGI-S at 24 hours	Drowsiness	2C There is no significant difference in effectiveness among IM olanzapine, orally disintegrating olanzapine tablets, and oral risperidone solution.
Hatta[27]	87 patients scoring ≥ 15 on PANSS-EC (acute psychotic agitation)	Initial doses of olanzapine ODT and risperidone OS were 10 and 3 mg Mean ± SD doses of olanzapine ODT and risperidone OS were 10.4±3.3 and 3.3±2.6 mg	PO	Pseudorandomized, open-label, flexible-dose, multicenter study	PANSS-EC and CGI at 6 hours	Extrapyramidal symptoms change in heart rate On one physiological parameter (i.e., tachycardia) olanzapine ODT might be superior to risperidone OS	2B Olanzapine ODT and risperidone OS treatments yielded similar improvements in acutely agitated patients who accepted oral medication.
Huf[28] (version 3)		Haloperidol (up to 10 mg) Haloperidol (2.5-10 mg) + promethazine (25-50 mg) Midazolam (up to 15 mg) Haloperidol (2.5-5 mg) +midazolam (7.5-15 mg) Lorazepam (up to 4 mg) Olanzapine (5-10 mg) Ziprasidone (10-20 mg)	IM	Systematic review	Being tranquil	Excessive sedation, respiratory depression with midazolam and lorazepam, haloperidol more EPS	1A All treatments evaluated in the review were effective. More swift haloperidol + promethazine and midazolam. The study did not detect an advantage in the use of haloperidol monotherapy.
Huf[29]	316 patients with agitation or dangerous behavior	Haloperidol (5-10 mg) vs. haloperidol (5-10 mg) + promethazine (50 mg)	IM	Pragmatic, RCT	Tranquil or asleep by 20 min; secondary outcomes were asleep by 20 min; tranquil or asleep by 40, 60, and 120 min.	Dystonia, seizure	1B Haloperidol + promethazine is a better option than haloperidol alone in terms of speed of onset of action and safety.
Isbister[30]	91 patients with violent and acute behavioral	Droperidol (10 mg) vs. midazolam (5 mg) vs.	IM	RCT	Duration of the violent and acute behavioral	Abnormal QT with droperidol	2B IM droperidol and midazolam resulted

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	disturbance	droperidol (10 mg) + midazolam (5 mg)			disturbance	Over sedation with midazolam	in a similar duration of violent and acute behavioral disturbance, but more additional sedation was required with midazolam. Midazolam caused more adverse effects because of over sedation, and there was no evidence of QT prolongation associated with droperidol compared with midazolam.
Katagiri[31]	90 agitated patients with schizophrenia	Olanzapine (10 mg) vs. placebo	IM	RCT	PANSS-EC at 2 hours	Orthostatic hypotension, somnolence, blood urine	2B The efficacy of IM olanzapine 10 mg in patients with exacerbation of schizophrenia with acute psychotic agitation was greater than IM placebo in the primary efficacy measure, PANSS-EC.
Kinon[32]	100 acutely agitated inpatients who were diagnosed with schizophrenia, schizophreniform, or schizoaffective disorder	Olanzapine (10 mg) vs. haloperidol (10 mg) on the first day Lorazepam was adjunctive	PO	RCT	PANSS, CGI, OASS, and side effects. Patients were assessed in the first 24 hours and then for 3 weeks	EPSs; asthenia, dry mouth, somnolence, and tachycardia in those patients who received adjunctive lorazepam; hypotension, nausea, or confusion for lorazepam	2B Oral olanzapine is as efficacious as oral haloperidol in reducing acute agitation in patients with schizophrenia. Significant within-group improvement was demonstrated in PANSS. Agitation scores for both groups as early as 1 hour after initiating therapy.
Knott[33]	153 agitated patients due to psychiatric illness or substance abuse	Droperidol (2.5-5 mg) vs. midazolam (2.5-5 mg)	IV	RCT	Sedation	Hypoventilation with midazolam	2B There is no difference in onset of adequate sedation of agitated patients using midazolam or droperidol. Patients sedated with midazolam may have an increased need for active airway management.
Kwentus[34]	314 agitated patients with bipolar disorder	Loxapine (5 mg) vs. loxapine (10 mg) vs. placebo	IN	RCT	PANSS-EC	EPS and hypotension	1B IN loxapine provided a rapid, non-injection, well-tolerated acute treatment for agitation in patients with bipolar I disorder.
Lesem[35]	117 agitated psychotic patients	Ziprasidone (10 mg) vs. ziprasidone (2 mg)	IM	RCT	BARS	Akathisia	2B Ziprasidone 10 mg IM is rapidly effective and well-tolerated in the short-term management of the agitated psychotic patient.

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Lesem[36]	344 agitated patients with schizophrenia	Loxapine (5 mg) vs. loxapine (10 mg) vs. placebo	IN	RCT	PANSS-EC	Sedation, dysgeusia, and dizziness EPS with loxapine 10 mg	2B IN loxapine provided a rapid, well-tolerated acute treatment for agitation in people with schizophrenia.
Lim[37]	124 patients with psychotic agitation at the emergency room or inpatient ward	ODT risperidone (2-6 mg) vs. IM haloperidol (5-15 mg)	PO, IM	RCT	PANSS-EC and CGI-S	Risperidone ODT: somnolence, headache, EPS, dizziness, and insomnia IM haloperidol: EPS, somnolence, headache, and dizziness	1B Risperidone orodispersible tablet was as effective and tolerable as IM administration of haloperidol.
MacDonald[38]	105 patients with agitation with (D/A+) or without (D/A-) alcohol or another drugs intoxication.	Haloperidol alone vs. haloperidol + any BZD vs. olanzapine alone vs. olanzapine + any BZD The most common doses in our sample were haloperidol 5 mg and olanzapine10 mg; lorazepam 2 mg was the most frequently prescribed BZD.	IM	Observational, retrospective	CGI and additional medication intervention at 3 hours	Compared to the use of antipsychotic alone, addition of a BZD to either antipsychotic increased the ratings of post-intervention sedation	4C The haloperidol-BZD combination was the most frequently prescribed treatment in both groups, although alcohol (+) status biased clinicians toward using haloperidol alone. Overall, D/A(+) and D/A(−) patients responded to the initial intervention at similar rates, although D/A(+) patients were rated as more agitated and had more post-treatment sedation than D/A(−) patients. In D/A(+) patients, haloperidol + BZD and IM olanzapine performed better than haloperidol alone.
MacDonald[39]	146 agitated patients	Haloperidol (5 mg) vs. haloperidol (5 mg) + lorazepam (2 mg) vs. olanzapine (10 mg) vs. olanzapine (10 mg) + lorazepam (2 mg)	IM	Multicenter retrospective study	Additional medication and adverse effects at 3 hours CGI-S.	Sedation	2C Haloperidol monotherapy is less effective at least in requiring additional medication than olanzapine with or without a BZD or haloperidol plus a BZD. Moreover, these later three regimens seemed comparable.
Man & Chen[40]	30 acutely psychotic patients	Haloperidol IM (5 mg) vs. chlorpromazine IM (50 mg)	IM	CT	BPRS	Hypotension	4C Haloperidol 5 mg IM or chlorpromazine 50 mg IM, administered at 30-min intervals brought about rapid amelioration of the severe unmanageable symptoms of hostility, agitation, assaultiveness, and mania in acutely psychotic patients. However,

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							haloperidol appeared to be a much safer drug than chlorpromazine because of the lack of severe hypotensive reaction for hypersensitivity.
Mantovani[41]	100 agitated patients in an emergency psychiatric service	Haloperidol (2.5 mg) + promethazine (25 mg) vs. haloperidol (2.5 mg) + midazolam (7.5 mg) vs. ziprasidone (10 mg) vs. olanzapine (10 mg)	IM	RCT	ACES and PANSS-EC	EPS A higher risk for the development of extrapyramidal symptoms within the following 24 hours was observed with haloperidol + promethazine	2B Low doses of haloperidol combined with midazolam can be as effective as olanzapine in reducing psychomotor agitation without increasing the risk of extrapyramidal effects.
Martel[42]	144 patients with acute undifferentiated agitation	Droperidol (5 mg) vs. ziprasidone (20 mg) vs. midazolam (5 mg)	IM	RCT	Altered Mental Status scale	Akathisia with droperidol and ziprasidone	2B Acutely agitated ED patients sedated with droperidol or ziprasidone required rescue medications to achieve adequate sedation less frequently than those sedated with midazolam. The onset of adequate sedation is delayed with ziprasidone, relative to the other agents.
Nobay[43]	111 violent and severely agitated patients	Midazolam (5 mg) vs. lorazepam (2 mg) vs. haloperidol (5 mg)	IM	RCT	Thomas Combativeness Scale	Hypotension and apnea with haloperidol	2B Midazolam has a significantly shorter time to onset of sedation and a more rapid time to arousal than lorazepam or haloperidol. The efficacies of all three drugs appear to be similar.
Normann[44]	191 schizophrenic patients were treated upon admission to hospital	Risperidone orally disintegrating tablets.	ODT	Multi-center, prospective, open-label observational trial	PANSS at 2, 24 and 48 hours after initiation of therapy	None	2B Oral treatment of acutely exacerbated schizophrenic patients with fast orally disintegrating risperidone tablets, alone or in combination with BZDs, was associated with a rapid onset of action and a significant and clinically relevant improvement of acute symptoms.
Perrin[45]	1,945 agitated patients with schizophrenia and bipolar mania	Olanzapine vs. other psychotropic medications	IM	Naturalistic, observational	CGI-S	EPS	2C No differences between groups.

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Pratts[46]	120 subjects with acute agitation	Asenapine SL (10 mg) vs. placebo	SL	RCT	PANSS-EC score at 2 hours	None	1B Sublingual asenapine was efficacious in the treatment of agitation. NNT for response vs. placebo was 3 (95%CI 2-4).
Preval[47]	119 agitation in psychoses or alcohol intoxication	Ziprasidone (20 mg) vs. haloperidol vs. haloperidol + lorazepam vs. chlorpromazine vs. lorazepam	IM	Observational	BARS	Dystonic reaction with ziprasidone	4C IM ziprasidone appears effective for severe agitation, including agitation associated with alcohol or substance intoxication, and may reduce time in restraints.
Raveendran[48]	300 adults with agitated or violent behavior	Haloperidol (10 mg) + promethazine (25-50 mg) vs. olanzapine (10 mg)	IM	RCT	Tranquil or asleep at 15 and 240 min	Hypotension, seizure, dystonia	1B IM olanzapine and IM haloperidol plus promethazine were effective at rapidly tranquilizing or sedating agitated or violent patients with mental illness, but the combination resulted in fewer additional medical interventions within four hours of intervention.
Resnick & Burton[49]	27 acutely agitated patients	Droperidol IM (5 mg) vs. haloperidol IM (5 mg)	IM	RCT	BPRS at 30 min	None	2C At 30 min following treatment, 81% of the patients treated with haloperidol but only 36% treated with droperidol required a second injection.
Richards[50]	202 agitated patients due to psychosis or drug abuse (methamphetamine toxicity was present in most patients)	Droperidol (2.5-5 mg) vs. lorazepam (2-4 mg)	IV	RCT	Sedation and adverse reactions at 0, 5, 10, 15, 30, and 60 min	Reduction in pulse, systolic blood pressure, respiratory rate, and temperature over 60 min	2B Droperidol produces a more rapid and better sedation than lorazepam at the doses used in this study in agitated patients requiring chemical restraint. Lorazepam is more likely to require repeat dosing than droperidol.
Rosen[51]	46 agitated patients	Droperidol (5 mg) vs. placebo	IV	RCT	Agitation levels and GCS at 5 and 10 min after medication	EPS	2B We conclude that droperidol is effective in sedating combative patients in the prehospital setting.
Suzuki[52]	122 agitated patients with schizophrenia	Olanzapine (5-10 mg) vs. haloperidol (2.5-5 mg) vs. levomepromazine (25 mg)	IM	Observational	PANSS-EC, ACES, and BARS	EPS, hypotension, hypertension, somnolence, dizziness, paralytic ileus, and ketoacidosis	2C The results of this study suggest the possibility that the anti-agitation effects of IM olanzapine and IM levomepromazine are more rapid than

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							those of IM haloperidol.
Taylor[53]	361 agitated patients	Midazolam (5 mg) plus droperidol (5 mg) vs. droperidol (10 mg) vs. olanzapine (10 mg)	IV	RCT	Proportion of patients adequately sedated within 10 min of the first dose administration Secondary outcomes: adequate sedation, the need for another sedative less than 60 min after achieving sedation, another sedative from 60 min after sedation until ED discharge, sedation medication failure (alternate medications required), ECG QTc interval, and adverse events	Airway obstruction, oxygen desaturation, hypotension, prolonged QTc in all groups Bradycardia and hypoventilation with droperidol and olanzapine	2B Midazolam-droperidol combination therapy is superior, in the doses studied, to either droperidol or olanzapine monotherapy for IV sedation of the acutely agitated ED patient. No differences at 60 min.
Tran-Johnson[54]	357 patients with acute agitation with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder	Aripiprazole (9.75) vs. haloperidol (7.5 mg)	IM	RCT	PANSS-EC and ACES from baseline to 2 hours after first injection	Headache and extrapyramidal symptoms most frequently in haloperidol group	2B IM aripiprazole 9.75 mg is a rapidly effective and well-tolerated alternative to IM haloperidol for the control of agitation, without over sedation, in patients with schizophrenia, schizo-affective disorder, or schizophreniform disorder.
TREC Collaborative Group[55]	301 aggressive or agitated people	Haloperidol (5-10 mg) + promethazine (50 mg) vs. midazolam (7.5-15 mg)	IM	RCT	Patients tranquil or asleep by 40, 60, and 120 min	Respiratory depression with midazolam and seizure with haloperidol + promethazine	1B Both treatments were effective.
Veser[56]	30 patients presenting to the emergency department with acute agitation and/or psychosis	Oral risperidone (2 mg) + IM lorazepam (2 mg) vs. oral haloperidol (5 mg) + IM lorazepam (2 mg) vs. oral placebo + IM lorazepam (2 mg)	Risperidone and haloperidol PO, lorazepam IM	RCT	BRPS and PANSS at 30 and 90 min after medication was administered	None	2B There were no statistically significant differences among the groups at any point. Lorazepam alone was as effective as lorazepam plus haloperidol or lorazepam + risperidone.
Walther[57]	43 severely agitated patients at acute care	Oral haloperidol (15 mg) vs. oral olanzapine (10	PO	Prospective, randomized,	PANSS at 2 and 24 hours after baseline	EPS	2B All drugs were effective for rapid

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	psychiatric units	mg) vs. oral risperidone (2-6 mg)		rater-blinded, controlled design within a naturalistic treatment regimen			tranquilization within 2 hours.
Wright[58]	285 hospitalized patients with schizophrenia	Olanzapine (10 mg) vs. haloperidol (7.5 mg) vs. placebo	IM	RCT	Agitated Behavior Scale, Agitation Calmness Evaluation Scale, PANSS	Less EPSs with olanzapine compared to haloperidol	2B Both IM olanzapine and IM haloperidol reduced agitation significantly more than IM placebo.
Yap[59]	92 patients with methamphetamine-related acute agitation	Midazolam (5 mg) + droperidol (5 mg) vs. droperidol (10 mg) vs. olanzapine (10 mg)	IV	RCT	Proportion of patients sedated adequately at 10 min after the initial dose administration and within 60 min	Oxygen desaturation and airway obstruction in all groups Bradycardia with olanzapine Prolonged QTc with midazolam + droperidol and olanzapine	2B A midazolam-droperidol combination appears to provide more rapid sedation of patients with methamphetamine-related acute agitation than droperidol or olanzapine alone. At 60 min the groups had similar results.
Zhang[60]	376 agitated patients with schizophrenia	Ziprasidone (10-40 mg) vs. haloperidol (5-20 mg)	IM	RCT	BARS	Dizziness and somnolence, nausea, increased blood pressure, and hematemesis with ziprasidone EPS and rash with haloperidol; peak measured QTc interval greater than or equal to 450 milliseconds.	2B Chinese study, ziprasidone had a favorable tolerability profile and comparable efficacy and safety compared to haloperidol
Zimbroff[61]	301 patients experiencing acute agitation with bipolar I disorder, manic, or mixed episodes	Aripiprazole (9.75) vs. aripiprazole (15 mg) vs. lorazepam (2 mg) vs. placebo	IM	RCT	PANSS-EC and ACES from baseline to 2 hours after first injection	Over sedation with lorazepam and aripiprazole (15 mg)	2B Aripiprazole (9.75) and (15 mg) are effective and well-tolerated for acute agitation in bipolar disorder, although the low incidence of over sedation suggests a risk-benefit profile for IM aripiprazole (9.75 mg).

95%CI = 95% confidence interval; ABS = Agitated Behavior Scale; ACES = Agitation Calmness Evaluation Scale; BARS = Barnes Akathisia Rating Scale; BPRS = Brief Psychiatric Rating Scale; BZD = benzodiazepine; CT = clinical trial ; D/A(-) = drug and alcohol-negative ; D/A(+) = drug and alcohol-positive; ECG = electrocardiogram; ED = emergency department; EPS = extrapyramidal side effects; IM = intramuscular; IN = inhaled; IV = intravenous; NNT = number needed to treat; OAS = Overt Aggression Scale; OASS = Overt Agitation Severity Scale; ODT = orally dispersive tablet; OS = oral solution; PANSS-EC = Positive and Negative Syndrome Scale Excited Component; PO = from the Latin *per orem*; RCT = randomized controlled trial; SD = standard deviation; SL = sublingual; TD = transdermal.

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