4. Il paziente agitato o aggressivo

Question: Should haloperidol vs chlorpromazine be used in adults with aggression or agitation?

Bibliography: Leucht C, Kitzmantel M, Kane J, Leucht S, Chua WLLC. Haloperidol versus chlorpromazine for schizophrenia. Cochrane Database of Systematic Reviews 2008, Issue 1.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Haloperidol	Chlorpromazine	Relative (95% CI)	Absolute		
Global state: No clinically significant improvement - as defined by the individual studies												
4[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	30/89 (33.7%)	33/70 (47.1%)	RR 0.65 (0.36 to 1.19)	165 fewer per 1000 (from 302 fewer to 90 more)	⊕⊕OO LOW	CRITICAL
Leaving the study early												
2[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	2/109 (1.8%)	2/84 (2.4%)	RR 0.66 (0.1 to 4.18)	8 fewer per 1000 (from 21 fewer to 76 more)	⊕⊕OO LOW	CRITICAL
Extrapyramidal symptoms												
3[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3,7]	none	12/64 (18.8%)	2/45 (4.4%)	RR 3.49 (0.84 to 14.44)	111 more per 1000 (from 7 fewer to 597 more)	⊕⊕OO LOW	IMPORTANT
Hypothension												
3[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	4/64 (6.3%)	8/45 (17.8%)	RR 0.37 (0.1 to 1.41)	112 fewer per 1000 (from 160 fewer to 73 more)	⊕⊕OO LOW	IMPORTANT

[1] From Analysis 2.2 of Leucht 2008. Haloperidol dosages: 5mg (2 studies); 1-5mg (1 study); 5-30mg (1 study). Chlorpromazine dosages: 25mg (1 study); 50mg (2 studies); 25-300mg (1 study).
[2] Visual inspection of forest plot suggests some heterogeneity. I-squared=58%
[3] Less than 200 patients included in the analysis, and CI ranges from substantial benefit with haloperidol to no benefit at all.
[4] From Analysis 2.1 of Leucht 2008
[5] Less than 200 patients included in the analysis, and CI ranges from substantial benefit with haloperidol to substantial benefit with chlorpromazine.
[6] From Analysis 2.6 of Leucht 2008
[7] Less than 200 patients included in the analysis, and CI ranges from substantial benefit with chlorpromazine to no benefit at all.
[8] From Analysis 2.4 of Leucht 2008

Question: Should clotiapine vs conventional antipsychotics be used in adults with aggression or agitation?

Bibliography: Berk M, Rathbone J, Mandriota-Carpenter SL. Clotiapine for acute psychotic illnesses. Cochrane Database of Systematic Reviews 2004, Issue 4.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clotiapine	Conventional antipsychotics	Relative (95% CI)	Absolute		
Global state: No clinically significant improvement - as defined by the individual studies												
3[1]	randomised trials	no serious risk of bias	serious[2]	serious[3]	serious[4]	none	9/40 (22.5%)	15/43 (34.9%)	RR 0.82 (0.25 to 2.66)	63 fewer per 1000 (from 262 fewer to 579 more)	⊕OOO VERY LOW	CRITICAL
Leaving the study early												
3[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[6]	none	10/59 (16.9%)	5/62 (8.1%)	RR 2.26 (0.4 to 12.88)	102 more per 1000 (from 48 fewer to 958 more)	⊕OOO VERY LOW	CRITICAL

[1] From Analysis 1.1 of Berk 2004. Clotiapine dose: 40-240mg/day
[2] Visual inspection of forest plot suggests significant heterogeneity. I-squared=55%
[3] Only one study used clotiapine injections.
[4] Less than 100 patients in the analysis, and CI ranges from substantial benefit with clotiapine to substantial benefit with conventional antipsychotics.
[5] From Analysis 1.3 of Berk 2004
[6] Less than 200 patients in the analysis, and CI ranges from substantial benefit with clotiapine to substantial benefit with conventional antipsychotics.

Question: Should clotiapine vs lorazepam be used in adults with aggression or agitation?

Bibliography: Berk M, Rathbone J, Mandriota-Carpenter SL. Clotiapine for acute psychotic illnesses. Cochrane Database of Systematic Reviews 2004, Issue 4.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clotiapine	Lorazepam	Relative (95% CI)	Absolute		
Global state: No clinically significant improvement - as defined by the individual studies (Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency[2]	serious[3]	very serious[4]	none	30	30	-	MD 3.36 lower (8.09 lower to 1.37 higher)	⊕OOO VERY LOW	CRITICAL
Leaving the study early												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency[2]	serious[3]	very serious[6]	none	1/30 (3.3%)	1/30 (3.3%)	RR 1 (0.07 to 15.26)	0 fewer per 1000 (from 31 fewer to 475 more)	⊕OOO VERY LOW	CRITICAL

[1] From Analysis 2.1 of Berk 2004
[2] Only one study into this analysis.
[3] Outcome measured three days after beginning of treatment
[4] Less than 100 patients in the analysis, and CI ranges from substantial benefit with clotiapine to no benefit at all.
[5] From Analysis 2.2 of Berk 2004
[6] Less than 100 patients in the analysis, and CI ranges from substantial benefit with clotiapine to sbstantial benefit with lorazepam.

Question: Should zuclopenthixol vs haloperidol be used in adults with aggression or agitation?

Bibliography: Gibson RC, Fenton M, da Silva Freire Coutinho E, Campbell C. Zuclopenthixol acetate for acute schizophrenia and similar serious mental illnesses. Cochrane Database of Systematic Reviews 2004, Issue 3.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zuclopenthixol	Haloperidol	Relative (95% CI)	Absolute		
Global state: Requiring supplementary medication												
3[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	33/69 (47.8%)	21/65 (32.3%)	RR 1.49 (0.97 to 2.3)	158 more per 1000 (from 10 fewer to 420 more)	⊕⊕OO LOW	CRITICAL
Leaving the study early												
3[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	7/279 (2.5%)	7/243 (2.9%)	RR 0.85 (0.31 to 2.31)	4 fewer per 1000 (from 20 fewer to 38 more)	⊕⊕OO LOW	CRITICAL
Extrapyramidal symptoms: dystonia												
3[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	12/132 (9.1%)	15/110 (13.6%)	RR 0.68 (0.34 to 1.36)	44 fewer per 1000 (from 90 fewer to 49 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] From Analysis 1.2 of Gibson 2004
[2] Visual inspection of forest plot suggests significant heterogeneity. I-squared=79%
[3] Less than 200 patients in the analysis. CI ranges from substantial benefit for haloperidol to no difference between haloperidol and zuclopenthixol.
[4] From Analysis 1.12 of Gibson 2004. In one study zuclopenthixol was compared with chlorpromazine.
[5] Very low total number of events in both treatment arms. CI ranges from substantial benefit with zuclopenthixol to substantial benefit with haloperidol.
[6] From Analysis 1.9 of Gibson 2004
[7] Less than 200 patients in the analysis. CI ranges from substantial benefit for zuclopenthixol to no difference between haloperidol and zuclopenthixol.

Question: Should benzodiazepines vs antipsychotics be used in adults with aggression or agitation?

Bibliography: Gillies D, Beck A,McCloud A, Rathbone J. Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database of Systematic Reviews 2005, Issue 4.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzodiazepines	Antipsychotics	Relative (95% CI)	Absolute		
Global state: Sedation - medium term												
6[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	23/138 (16.7%)	36/186 (19.4%)	RR 0.76 (0.48 to 1.21)	46 fewer per 1000 (from 101 fewer to 41 more)	⊕⊕⊕O MODERATE	CRITICAL
Extrapyramidal symptoms												
5[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/171 (2.3%)	30/220 (13.6%)	RR 0.17 (0.06 to 0.43)	113 fewer per 1000 (from 78 fewer to 128 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] From Analysis 2.2 of Gillies 2005. Haloperidol (5-10mg im) in all studies but one (olanzapine 10-25mg). Lorazepam 2-5mg in three studies, diazepam, flunitrazepam and clonazepam in one study each.
[2] CI ranges from substantial benefit of antipsychotics to no difference between benzodiazepines and antipsychotics.
[3] From Analysis 2.16 of Gillies 2005

Question: Should benzodiazepines plus antipsychotics vs benzodiazepines be used in adults with aggression or agitation?

Bibliography: Gillies D, Beck A,McCloud A, Rathbone J. Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database of Systematic Reviews 2005, Issue 4.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Benzodiazepines plus antipsychotics**	**Benzodiazepines**	**Relative (95% CI)**	**Absolute**		
Global state: Need for additional medication - medium term												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	27/41 (65.9%)	26/42 (61.9%)	RR 1.02 (0.79 to 1.32)	12 more per 1000 (from 130 fewer to 198 more)	⊕⊕OO LOW	CRITICAL

[1] From Analysis 3.1 of Gillies 2005

[2] Less than 100 patients in the analysis. CI ranges from substantial benefit of the combination to substantial benefit of benzodiazepines alone.

Question: Should benzodiazepines plus antipsychotics vs antipsychotics be used in adults with aggression or agitation?

Bibliography: Gillies D, Beck A,McCloud A, Rathbone J. Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database of Systematic Reviews 2005, Issue 4.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Benzodiazepines plus antipsychotics**	**Antipsychotics**	**Relative (95% CI)**	**Absolute**		
Global state: Need for additional medication - medium term												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency[2]	no serious indirectness	very serious[3]	none	27/32 (84.4%)	31/35 (88.6%)	RR 0.95 (0.79 to 1.15)	44 fewer per 1000 (from 186 fewer to 133 more)	⊕⊕OO LOW	CRITICAL
Extrapyramidal symptoms												
2[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	7/46 (15.2%)	16/49 (32.7%)	RR 0.45 (0.22 to 0.94)	180 fewer per 1000 (from 20 fewer to 255 fewer)	⊕⊕⊕O MODERATE	IMPORTANT

[1] From Analysis 4.1 of Gillies 2005
[2] Only one study in this analysis
[3] Less than 100 patients in the analysis. CI ranges from benefit of the combination to benefit of antipsychotics alone.
[4] From Analysis 4.6 of Gillies 2005
[5] Less than 100 patients in the analysis

Question: Should midazolam vs propofol be used in adults with aggression or agitation?[1,2]

Bibliography: Hohl et al. Safety and Clinical Effectiveness of Midazolam versus Propofol for Procedural Sedation in the Emergency Department: A Systematic Review Academic Emergency Medicine 2008; 15:1–8. Nobay F, Simon BC, Levitt MA, Dresden GM. A prospective, double-blind, randomized trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients. Academy of Emergency Medicine 2004;11: 744-9. Isbister GK, Calver LA, Page CB, Stokes B, Bryant JL, Downes MA. Randomized controlled trial of intramuscular droperidol versus midazolam for violence and acute behavioral disturbance: the DORM study. Annals of Emergency Medicine 2010; 56: 392-401.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Midazolam**	**Propofol**	**Relative (95% CI)**	**Absolute**		
Efficacy: procedural sedation												
4[3]	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	no serious imprecision	none	-[5]	-	Not estimable	-	⊕⊕⊕O MODERATE	CRITICAL

[1] There is also one additional RCT comparing midazolam with haloperidol and lorazepam (Nobay 2004). 27 patients received lorazepam, 42 patients received haloperidol, and 42 patients received midazolam. The mean (SD) time to sedation was 32.2 (SD 20) minutes for patients receiving lorazepam, 28.3 (SD 25) minutes for haloperidol, and 18.3 (SD 14) minutes for midazolam.

[2] There is also a RCT (Isbister 2010) comparing midazolam with droperidol and the combination. From 223 emergency department patients with violent and acute behavioral disturbance, 91 patients were included; 33 received droperidol, 29 received midazolam, and 29 received the combination. There was no difference in the median duration of the violent and acute behavioral disturbance: 20 minutes (interquartile range [IQR] 11 to 37 min) for droperidol, 24 minutes (IQR 13 to 35 minutes) for midazolam, and 25 minutes (IQR 15 to 38 minutes) for the combination.

[3] From Hohl 2008. 4 RCTs, 232 patients.

[4] The study population is different from our study population. In this review included patients who received procedural sedation (PS) for orthopedic reductions, cardioversion and chest tube insertions. Additionally, midazolam was given IV and not IM. Finally, the comparison group received propofol, an agent not used for psychiatric indications.

[5] Efficacy of midazolam: 89.9% (95% CI = 83.2% to 94.6%). Efficacy of propofol: 92.8% (95% CI = 87.5% to 96.8%)

Question: Should haloperidol plus promethazine vs lorazepam be used in adults with aggression or agitation?[1]

Bibliography: Huf G, Alexander J, AllenMH, Raveendran NS.Haloperidol plus promethazine for psychosis-induced aggression. Cochrane Database of Systematic Reviews 2009, Issue 3.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Haloperidol plus promethazine	Lorazepam	Relative (95% CI)	Absolute		
Efficacy: NOT tranquil or asleep by 30 minutes												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	5/100 (5%)[4]	19/100 (19%)	RR 0.26 (0.1 to 0.68)	141 fewer per 1000 (from 61 fewer to 171 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Efficacy: NOT asleep												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	31/100 (31%)	78/100 (78%)	RR 0.40 (0.29 to 0.54)	468 fewer per 1000 (from 359 fewer to 554 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse effects												
1[6]	randomised trials	no serious risk of bias	no serious inconsistency[3]	no serious indirectness	serious[7]	none	0/100 (0%)[8]	1/100 (1%)	RR 0.33 (0.01 to 8.09)	7 fewer per 1000 (from 10 fewer to 71 more)	⊕⊕⊕O MODERATE	CRITICAL
Extrapyramidal side-effects												
1[9]	randomised trials	no serious risk of bias	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	0/100 (0%)	0/100 (0%)	Not estimable	-	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] Haloperidol IM: dose up to 10 mg + promethazine IM: dose up to 50 mg. Lorazepam IM: dose up to 4 mg.
[2] From Analysis 1.1 of Huf 2009
[3] Only one study included in this analysis
[4] Time until tranquil or asleep: haloperiol plus promethazine: 29.7 (35.6) minutes. Lorazepam: 47.8 (46.7).
[5] From Analysis 1.3 of Huf 2009
[6] From Analysis 1.5 of Huf 2009
[7] CI ranges from substantial benefit with haloperidol plus promethazine to substantial benefit with lorazepam.
[8] A single person, with a history of bronchial asthma, in the lorazepam group who complained of moderate worsening of respiratory difficulty.
[9] From Analysis 1.6 of Huf 2009

Question: Should haloperidol plus promethazine vs midazolam be used in adults with aggression or agitation?[1]

Bibliography: Huf G, Alexander J, AllenMH, Raveendran NS.Haloperidol plus promethazine for psychosis-induced aggression. Cochrane Database of Systematic Reviews 2009, Issue 3. Mantovani C, Labate CM, Sponholz A Jr, de Azevedo Marques JM, Guapo VG, de Simone Brito dos Santos ME, Pazin-Filho A, Del-Ben CM. Are low doses of antipsychotics effective in the management of psychomotor agitation? A randomized, rated-blind trial of 4 intramuscular interventions. Journal of Clinical Psychopharmacology 2013; 33: 306-312.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Haloperidol plus promethazine	Midazolam	Relative (95% CI)	Absolute		
Efficacy: NOT tranquil or asleep by 30 minutes												
1[2,3]	randomised trials	no serious risk of bias	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	49/150 (32.7%)	17/151 (11.3%)	RR 2.90 (1.75 to 4.8)	214 more per 1000 (from 84 more to 428 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Efficacy: NOT asleep												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	107/150 (71.3%)[6]	58/151 (38.4%)	RR 1.86 (1.48 to 2.33)	330 more per 1000 (from 184 more to 511 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse effects												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency[4]	no serious indirectness	serious[8]	none	1/150 (0.67%)[9]	1/151 (0.66%)	RR 1.01 (0.06 to 15.95)	0 more per 1000 (from 6 fewer to 99 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Haloperidol IM: dose up to 10 mg + promethazine IM: dose up to 50 mg. Midazolam IM: dose up to 15 mg.
[2] From Analysis 1.1 of Huf 2009
[3] There is one additional study carried out by Mantovani and colleagues (2013) who compared haloperidol 2,5mg plus promethazine 25 versus haloperidol 2,5mg plus midazolam 7.5mg for the management of psychomotor agitation. Although this randomized trial enrolled a limited number of patients, it found that levels of tranquilization with the combination haloperidol 2,5mg plus promethazine 25 mg was lower than the treatment effect obtained with the combination haloperidol 2,5mg plus midazolam 7.5mg. The study concluded that low doses of haloperidol combined with midazolam can be effective in reducing psychomotor agitation without increasing the risk of extrapyramidal effects.
[4] Only one study in this analysis
[5] From Analysis 1.3 of Huf 2009
[6] Time until asleep: haloperidol plus promethazine: 37.4 (42.9) minutes; lorazepam: 80.6 (64.3) minutes.
[7] From Analysis 1.5 of Huf 2009
[8] CI ranges from substantial benefit with haloperidol plus promethazine to substantial benefit with midazolam.
[9] Two serious adverse effects occurred within the first 30 minutes. One aggressive person who also suffered from epilepsy was given haloperidol (5 mg) and promethazine (50 mg) and had a seizure 15

minutes after the drugs were administered.With benzodiazepines the person settled and recovered fully. One person with alcohol, and perhaps cocaine-induced aggression, was given midazolam(15mg). Respiratory rate immediately fell and the person became cyanosed, but recovered fully after flumazenil (0.25 mg IM) was given and did not suffer further aggressive episodes during the stay.

Question: Should haloperidol plus promethazine vs haloperidol be used in adults with aggression or agitation?[1]

Bibliography: Huf G, Alexander J, AllenMH, Raveendran NS.Haloperidol plus promethazine for psychosis-induced aggression. Cochrane Database of Systematic Reviews 2009, Issue 3.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Haloperidol plus promethazine	Haloperidol	Relative (95% CI)	Absolute		
Efficacy: NOT tranquil or asleep by 20 minutes												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	48/160 (30%)	72/156 (46.2%)	RR 0.65 (0.49 to 0.87)	162 fewer per 1000 (from 60 fewer to 235 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Efficacy: NOT asleep by 20 minutes												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	132/160 (82.5%)	145/156 (92.9%)	RR 0.89 (0.82 to 0.96)	102 fewer per 1000 (from 37 fewer to 167 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse effects												
1[5]	randomised trials	no serious risk of bias	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	1/153 (0.65%)[6]	11/145 (7.6%)	RR 0.09 (0.01 to 0.66)	69 fewer per 1000 (from 26 fewer to 75 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Haloperidol IM: dose up to 10 mg + IM promethazine: dose up to 50 mg. Haloperidol IM alone: dose up to 10 mg.
[2] From Analysis 2.1 of Huf 2009
[3] Only one study in this analysis
[4] From Analysis 2.2 of Huf 2009
[5] From Analysis 2.3 of Huf 2009
[6] Haloperidol on its own caused a greater incidence of acute dystonia with 10 people in this group experiencing this distressing side effect compared with none in the haloperidol plus promethazine group (1 RCT, n=298, RR 0.05 CI 0.00 to 0.76, NNH 16 CI 15 to 62). The other adverse effect recorded was seizure and here one person in each group suffered a seizure after receiving treatment.

Question: Should haloperidol plus promethazine vs olanzapine be used in adults with aggression or agitation?[1]

Bibliography: Huf G, Alexander J, AllenMH, Raveendran NS.Haloperidol plus promethazine for psychosis-induced aggression. Cochrane Database of Systematic Reviews 2009, Issue 3. Mantovani C, Labate CM, Sponholz A Jr, de Azevedo Marques JM, Guapo VG, de Simone Brito dos Santos ME, Pazin-Filho A, Del-Ben CM. Are low doses of antipsychotics effective in the management of psychomotor agitation? A randomized, rated-blind trial of 4 intramuscular interventions. Journal of Clinical Psychopharmacology 2013; 33: 306-312.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Haloperidol plus promethazine	Olanzapine	Relative (95% CI)	Absolute		
Efficacy: NOT tranquil or asleep by 15 minutes												
1[2,3]	randomised trials	no serious risk of bias	no serious inconsistency[4]	no serious indirectness	serious[5]	none	14/150 (9.3%)[6]	19/150 (12.7%)	RR 0.74 (0.38 to 1.41)	33 fewer per 1000 (from 79 fewer to 52 more)	⊕⊕⊕O MODERATE	CRITICAL
Efficacy: NOT asleep by 15 minutes												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	64/150 (42.7%)	85/150 (56.7%)	RR 0.75 (0.6 to 0.95)	142 fewer per 1000 (from 28 fewer to 227 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Efficacy: NOT asleep by 30 minutes												
1[7]	randomised trials	no serious risk of bias	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	36/150 (24%)	55/150 (36.7%)	RR 0.65 (0.46 to 0.93)[8]	128 fewer per 1000 (from 26 fewer to 198 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Serious adverse effects												
1[9]	randomised trials	no serious risk of bias	no serious inconsistency[4]	no serious indirectness	serious[10]	none	1/150 (0.67%)[11]	3/150 (2%)	RR 0.33 (0.04 to 3.17)	13 fewer per 1000 (from 19 fewer to 43 more)	⊕⊕⊕O MODERATE	CRITICAL

[1] Haloperidol IM: dose up to 10mg + promethazine IM: dose up to 50 mg. Olanzapine IM: dose up to 10 mg.

[2] From Analysis 3.1 of Huf 2009

[3] One additional study was carried out by Mantovani and colleagues (2013) who compared olanzapine 10 mg versus haloperidol 2,5mg plus promethazine 25 mg for the management of psychomotor agitation. Although this randomized trial enrolled a limited number of patients, it found that levels of tranquilization with the combination haloperidol 2,5mg plus promethazine 25 mg was lower than the treatment effect obtained with olanzapine.

[4] Only one study in this analysis.

[5] CI ranges from substantial benefit with haloperidol plus promethazine to no difference at all.
[6] After one hour: haloperidol plus promethazine: 1/150 NOT asleep; olanzapine: 9/150 Not asleep = RR 0.11 (0.01 to 0.87) in favour of the combination.
[7] From Analysis 3.3 of Huf 2009
[8] Similar differences after 1, 2 and 4 hours in favour of haloperidol plus promethazine.
[9] From Analysis 3.6 of Huf 2009
[10] CI ranges from substantial benefit with aloperidol plus promethazine to substantial benefit with olanzapine.
[11] Only one person suffered a serious adverse effect in the haloperidol plus promethazine group (dehydration) and three people in the olanzapine group (two akathisia, one nausea).

Question: Should olanzapine vs haloperidol be used in adults with aggression or agitation?

Bibliography: Belgamwar RB, Fenton M. Olanzapine IM or velotab for acutely disturbed/agitated people with suspected serious mental illnesses. Cochrane Database of Systematic Reviews 2005, Issue 2.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Olanzapine	Haloperidol	Relative (95% CI)	Absolute		
Global effect: Did not respond - by 2 hours												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	97/313 (31%)	49/166 (29.5%)	RR 1 (0.73 to 1.38)	0 fewer per 1000 (from 80 fewer to 112 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse event: EPS - akathisia - by 5 days												
1[3]	randomised trials	no serious risk of bias	no serious inconsistency[4]	serious[2]	no serious imprecision	none	22/122 (18%)	41/116 (35.3%)	RR 0.51 (0.32 to 0.8)	173 fewer per 1000 (from 71 fewer to 240 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Adverse event: EPS - requiring anticholinergic medication												
2[5]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	no serious imprecision	none	7/316 (2.2%)	29/166 (17.5%)	RR 0.20 (0.09 to 0.44)	140 fewer per 1000 (from 98 fewer to 159 fewer)	⊕⊕⊕O MODERATE	CRITICAL

[1] From Analysis 2.1 of Belgamwar 2005. Haloperidol IM 7.5mg; olanzapine IM 10mg.
[2] Mild agitation patients only.
[3] From Analysis 2.5 of Belgamwar 2005
[4] Only one study in this analysis.
[5] From Analysis 2.6 of Belgamwar 2005

Question: Should olanzapine vs benzodiazepines be used in adults with aggression or agitation?

Bibliography: Belgamwar RB, Fenton M. Olanzapine IM or velotab for acutely disturbed/agitated people with suspected serious mental illnesses. Cochrane Database of Systematic Reviews 2005, Issue 2.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Olanzapine	Benzodiazepines	Relative (95% CI)	Absolute		
Global effect: Did not respond - by 2 hours												
2[1]	randomised trials	no serious risk of bias	serious[2]	serious[3]	no serious imprecision	none	68/236 (28.8%)	37/119 (31.1%)	RR 0.92 (0.66 to 1.3)	25 fewer per 1000 (from 106 fewer to 93 more)	⊕⊕OO LOW	CRITICAL
Adverse event: Any treatment emergent adverse event - by 24 hours												
1[4]	randomised trials	no serious risk of bias	no serious inconsistency[5]	serious[3]	serious[6]	none	35/99 (35.4%)	29/51 (56.9%)	RR 0.62 (0.43 to 0.89)	216 fewer per 1000 (from 63 fewer to 324 fewer)	⊕⊕OO LOW	CRITICAL

[1] From Analysis 3.2 of Belgamwar 2005. Lorazepam 1.2 mg IM. Olanzapine 10 mg IM.
[2] Visual inspection of forest plot suggests significant heterogeneity. I-squared = 82%.
[3] Mild patient population only.
[4] From Analysis 3.9 of Belgamwar 2005
[5] Only one study in this analysis.
[6] Less than 200 patients in this analysis.

Question: Should haloperidol vs aripiprazole be used for adults with aggression or agitation?

Bibliography: Powney MJ, Adams CE, Jones H.Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation). Cochrane Database of Systematic Reviews 2012, Issue 11.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Haloperidol	Aripiprazole	Relative (95% CI)	Absolute		
needing additional injection												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[3]	none	78/242 (32.2%)	95/231 (41.1%)	RR 0.78 (0.62 to 0.99)	90 fewer per 1000 (from 4 fewer to 156 fewer)	⊕⊕OO LOW	CRITICAL
one or more drug related adverse effects												
2[4]	randomised trials	no serious risk of bias	no serious inconsistency	serious[2]	serious[5]	none	111/245 (45.3%)	89/232 (38.4%)	RR 1.18 (0.95 to 1.46)	69 more per 1000 (from 19 fewer to 176 more)	⊕⊕OO LOW	CRITICAL

[1] Analysis 2.1 of Powney 2012.
[2] Mild patient populations only. Haloperidol was administered orally, intramuscularly or intravenously.
[3] Confidence interval ranges from substantial benefit with haloperidol to almost no difference.
[4] Analysis 2.7 of Powney 2012
[5] Confidence interval ranges from substantial benefit with aripiprazole to no difference.

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