APPENDIX 14: CLINICAL EVIDENCE – GRADE PROFILES

Abbreviations

ABS	Agitated Behavior Scale
ACES	Agitation and Calmness Evaluation Scale
AD	antidepressant
AP	antipsychotic
BZD	benzodiazepine
CES	Coercion Experience Scale
CI	confidence interval
EPS	extrapyramidal symptoms
HAL	haloperidol
IM	intramuscular
MD	mean difference
NE	non-emergency situations
OAS	Overt Aggression Scale
OIS	optimal information size
OR	odds ratio
PANSS-EC	Positive and Negative Syndrome Scale – Excited Component
ROB	risk of bias
RR	relative risk/risk ratio
SMD	standardised mean difference
TAU	treatment as usual
TEAE	treatment emergent adverse events
WAIC	Working Alliance Inventory – client form
WAIT	Working Alliance Inventory – therapist form

1.1 NON-PHARMACOLOGICAL INTERVENTIONS

1.1.1 Pre- and immediately pre-event: inpatient settings – adults

1.1.1.1 Modifications to the environment versus an alternative management strategy

Quality assessment							Number of patients		Effect		Quality	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Modifications to the environment	An alternative management strategy	Relative (95% CI)	Absolute		
Verbal aggression (assessed with: Modified Overt Aggression Scale)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/99 (0%)	0/107 (0%)	OR 0.49 (0.26 to 0.91)	-	VERY LOW	
Aggression towards others (assessed with: Modified Overt Aggression Scale)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/99 (0%)	0/107 (0%)	OR 0.51 (0.09 to 2.78)	-	VERY LOW	
Risk of aggression (measured with: Brøset Violence Checklist; better indicated by lower values)												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	31	25	-	SMD 0.11 lower (0.64 lower to 0.42 higher)	VERY LOW	
Rates of seclusion – total private space per patient (m^2)												
1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-		OR 0.88 (0.82 to 0.94)	-	VERY LOW	
Rates of seclusion – observation bedrooms												

1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	-		OR 0.78 (0.5 to 1.22)	-	VERY LOW	
Rates of seclusion – number of patients in the building												
1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-		OR 1.01 (1 to 1.02)	-	VERY LOW	
Rates of seclusion – presence of outdoor space or garden (yes versus no)												
1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-		OR 9.09 (2.31 to 35.77)	-	VERY LOW	
Rates of seclusion – comfort												
1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-		OR 0.77 (0.61 to 0.97)	-	VERY LOW	
Rates of seclusion – personal furniture (yes versus no)												
1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	-		OR 0.81 (0.51 to 1.29)	-	VERY LOW	
Rates of seclusion – type of ventilation												
1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	-		OR 0.84 (0.49 to 1.44)	-	VERY LOW	
Rates of seclusion – presence of nursing station (yes versus no)												
1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	-		OR 1.03 (0.63 to 1.68)	-	VERY LOW	

Rates of seclusion – special safety measures											
1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-		OR 1.6 (1.09 to 2.35)	-	VERY LOW
Rates of seclusion – visibility on ward											
1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-		OR 0.69 (0.49 to 0.97)	-	VERY LOW
Rates of seclusion – violence-proof finish											
1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	-		OR 1.3 (0.59 to 2.86)	-	VERY LOW
Rates of seclusion – number of seclusion rooms (ward)											
1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-		OR 1.12 (0.89 to 1.41)	-	VERY LOW
Rates of seclusion – number of seclusion rooms (building)											
1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	-		OR 1.24 (0.9 to 1.71)	-	VERY LOW
Rates of seclusion – number of bedrooms that can be locked											
1	observational studies[4]	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	-		OR 1.25 (0.58 to 2.69)	-	VERY LOW
Experience of seclusion – treatment satisfaction (total) (better indicated by lower values)											
1	observational	serious[3]	no serious	no serious	serious[2]	none	15	16	-	MD 3.42 higher	VERY

	studies		inconsistency	indirectness						(0.95 to 5.89 higher)	LOW	
Experience of seclusion – treatment satisfaction (males) (better indicated by lower values)												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	6	9	-	MD 1.55 higher (2.42 lower to 5.52 higher)	VERY LOW	
Experience of seclusion – treatment satisfaction (females) (better indicated by lower values)												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	9	7	-	MD 5.6 higher (2.56 to 8.64 higher)	VERY LOW	
Experience of seclusion – influence of interior on behaviour (total) (better indicated by lower values)												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	15	16	-	MD 3.26 higher (0.98 to 5.54 higher)	VERY LOW	
Experience of seclusion – influence of interior on behaviour (males) (better indicated by lower values)												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	6	9	-	MD 0.83 higher (2.93 lower to 4.59 higher)	VERY LOW	
Experience of seclusion – influence of interior on behaviour (females) (better indicated by lower values)												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	9	7	-	MD 5.53 higher (2.62 to 8.44 higher)	VERY LOW	

[1] High risk of bias across all domains.
[2] Sample size did not reach optimal information size.
[3] Participants/care administrators/raters non-blind.
[4] Case-control.
[5] 95% CI includes both important effect and no effect; OIS met.

1.1.1.2 Management strategies/training programmes versus an alternative management strategy

Quality assessment							Number of patients		Effect		Quality	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Management strategies/training programmes**	**Alternative management strategy**	**Relative (95% CI)**	**Absolute**		
Rate of seclusion, restraint or room observation (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0	-	-	MD 0.09 lower (0.13 to 0.05 lower)	LOW	
Duration of seclusion-restraint (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	50	38	-	MD 0.24 lower (0.4 to 0.08 lower)	VERY LOW	
violence and aggression: physical violence (self, other) (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	0	-	-	MD 0.03 higher (0.39 lower to 0.45 higher)	VERY LOW	
Rates of restrictive intervention 'containment'												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	RD 0.23 (0.09 to 0.37)	-	MODERATE	
Rates of violence and aggression 'conflict'												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	RD 0.15 (0.05 to 0.25)	-	MODERATE	

[1] Unclear ROB across multiple, from: sequence/ allocation/ blinding/ outcome/ reporting/ other.
[2] Sample size did not reach optimal information size.
[3] 95% CI included line of no effect, OIS met.

1.1.2 Pre- and immediately pre-event: community settings – adults

1.1.2.1 Advance decisions and statements versus an alternative management strategy

Quality assessment							Number of patients		Effect		Quality	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Advance decisions and statements	An alternative management strategy	Relative (95% CI)	Absolute		
Psychiatric admission – voluntary admissions [15 months UK] (follow-up 15 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	27/159 (17%)	26/157 (16.6%)	RR 1.03 (0.63 to 1.68)	5 more per 1000 (from 61 fewer to 113 more)	LOW	
Psychiatric admission – compulsory admission under Mental Health Act (follow-up mean 15 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	3/80 (3.8%)	11/80 (13.8%)	RR 0.27 (0.08 to 0.94)	100 fewer per 1000 (from 8 fewer to 126 fewer)	MODERATE	
Psychiatric admission – all admissions [UK] (follow-up 15-18 months)												
2	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[1,2]	none	101/347 (29.1%)	116/360 (32.2%)	OR 0.86 (0.62 to 1.19)	32 fewer per 1000 (from 95 fewer to 39 more)	VERY LOW	
Psychiatric admission – involuntary admissions [UK] (follow-up 15-18 months)												
3	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[1,2]	none	74/426 (17.4%)	93/437 (21.3%)	OR 0.78 (0.55 to 1.09)	39 fewer per 1000 (from 83 fewer to 15 more)	VERY LOW	
Psychiatric admission – within 18 months – compulsory admission [18 months: white] (follow-up mean 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	-	-	Not estimable	-	LOW	

Psychiatric admission – within 18 months – compulsory admission [18 months: black/black British] (follow-up mean 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	-	-	Not estimable	-	LOW	
Psychiatric admission – within 18 months – compulsory admission [18 months: Asian/Asian British] (follow-up mean 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	-	-	Not estimable	-	LOW	
Psychiatric admission – within 18 months – compulsory admission [18 months: total] (follow-up mean 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	-	-	OR 0.9 (0.59 to 1.37)	-	LOW	
Psychiatric admissions – within 18 months [clinician versus advocate] – total admissions [18 months NE] (follow-up median 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	33/69 (47.8%)	24/70 (34.3%)	See comment	134 more per 1000 (from 31 fewer to 302 more)	LOW	
Psychiatric admissions – within 18 months [clinician versus advocate] – voluntary admissions [18 months NE] (follow-up mean 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	16/69 (23.2%)	14/70 (20%)	See comment	32 more per 1000 (from 100 fewer to 170 more)	LOW	
Psychiatric admissions – within 18 months [clinician versus advocate] – emergency admissions [18 months NE] (follow-up mean 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	12/69 (17.4%)	7/70 (10%)	See comment	74 more per 1000 (from 40 fewer to 190 more)	LOW	
Psychiatric admissions – within 18 months [clinician versus advocate] – court order admission [18 months NE]												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	11/69 (15.9%)	7/70 (10%)	See comment	59 more per 1000 (from 50 fewer to 170 more)	LOW	

Psychiatric admissions – within 18 months [clinician versus advocate] – emergency visits [18 months NE] (follow-up mean 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	22/69 (31.9%)	22/70 (31.4%)	See comment	3 more per 1000 (from 151 fewer to 160 more)	LOW	
Psychiatric admission – within 18 months [ADs versus TAU] – total admissions [18 months NE] (follow-up mean 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	57/139 (41%)	33/73 (45.2%)	OR 0.84 (0.48 to 1.49)	43 fewer per 1000 (from 168 fewer to 99 more)	LOW	
Psychiatric admission – within 18 months [ADs versus TAU] – voluntary admissions [18 months NE] (follow-up mean 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	30/139 (21.6%)	12/73 (16.4%)	OR 1.4 (0.67 to 2.93)	52 more per 1000 (from 48 fewer to 201 more)	LOW	
Psychiatric admission – within 18 months [ADs versus TAU] – emergency admissions [18 months NE] (follow-up mean 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	19/139 (13.7%)	14/73 (19.2%)	OR 0.67 (0.31 to 1.42)	55 fewer per 1000 (from 123 fewer to 60 more)	LOW	
Psychiatric admission – within 18 months [ADs versus TAU] – court order [18 months NE] (follow-up mean 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	18/139 (12.9%)	19/73 (26%)	OR 0.42 (0.21 to 0.87)	132 fewer per 1000 (from 26 fewer to 191 fewer)	MODERATE	
Psychiatric admission – within 18 months [ADs versus TAU] – emergency visit [18 months NE] (follow-up mean 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	44/139 (31.7%)	19/73 (26%)	OR 1.32 (0.7 to 2.48)	57 more per 1000 (from 63 fewer to 206 more)	LOW	
Psychiatric admissions 'duration' – within 18 months – total number of admissions (follow-up mean 18 months; better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	267	280	-	MD 0.03 higher (0.13 lower to 0.19 higher)	LOW	

Psychiatric admissions 'duration' – within 18 months – mean days' compulsory admission [18 months UK] (follow-up mean 18 months; better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	267	280	-	MD 1.7 higher (10.49 lower to 13.89 higher)	LOW	
Psychiatric admissions 'duration' – within 18 months – mean days' admission [18 months UK] (follow-up mean 18 months; better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	267	280	-	MD 3.1 higher (9.63 lower to 15.83 higher)	LOW	
Coercive intervention – within 24 months (follow-up mean 24 months)												
1	observational studies	very serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	-	-	-	-	VERY LOW	
Working alliance (1 month) – completed PADs with improved working alliance (follow-up mean 1 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	-	Not estimable	-	MODERATE	
Working alliance (1 month) – not completed PADs with improved working alliance (follow-up mean 1 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	-	-	Not estimable	-	LOW	
Working alliance (1 month) – completed PADs with no improvement in working alliance (follow-up mean 1 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	-	-	Not estimable	-	LOW	
Working alliance (within 18 months) – WAIT (therapist) (follow-up mean 18 months; better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	267	280	-	MD 4.6 lower (13.24 lower to 4.04 higher)	LOW	
Working alliance (within 18 months) – WAIC (client) (follow-up mean 18 months; better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	267	280	-	MD 3.1 higher (9.63 lower to 15.83 higher)	LOW	

Working alliance (within 18 months) – Service Engagement Scale (follow-up mean 18 months; better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	202	228	-	MD 0.31 higher (1.05 lower to 1.67 higher)	LOW	
Working alliance (within 18 months) – perceived coercion (follow-up mean 18 months; better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1,2]	none	213	245	-	MD 0.23 lower (0.55 lower to 0.09 higher)	LOW	

[1] Sample size did not reach optimal information size.
[2] 95% CI included line of no effect, OIS met.
[3] Moderate heterogeneity (I^2 = 30-60%).
[4] Unclear/ serious ROB across multiple, from: selection/ performance/ attrition/ detection.
[5] No explanation was provided.

1.1.3 During event: inpatient settings – adults

1.1.3.1 Seclusion and restraint versus an alternative management strategy: effectiveness

Quality assessment							Number of patients		Effect		Quality	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Seclusion and restraint	An alternative management strategy	Relative (95% CI)	Absolute		
Violence and aggression (PANSS score) – randomly assigned (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	12	14	-	SMD 0.31 higher (0.47 lower to 1.08 higher)	VERY LOW	
Violence and aggression (PANSS score) – non-randomly assigned (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	48	28	-	SMD 0.42 higher (0.06 lower to 0.89 higher)	VERY LOW	
Change of intervention: seclusion versus restraint – need to change intervention early – within 1 hour												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/54 (33.3%)	7/51 (13.7%)	RR 2.43 (1.11 to 5.32)	196 more per 1000 (from 15 more to 593 more)	LOW	
Change of intervention: seclusion versus restraint – still restricted by 4 hours												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	24/54 (44.4%)	25/51 (49%)	RR 0.91 (0.6 to 1.36)	44 fewer per 1000 (from 196 fewer to 176 more)	VERY LOW	
Change of intervention: seclusion versus restraint – change because of improvements												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54/54 (100%)	42/51 (82.4%)	RR 1.21 (1.06 to 1.38)	173 more per 1000 (from 49 more to 313 more)	LOW	

Change of intervention: seclusion versus restraint – change because of deterioration												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/54 (33.3%)	0/51 (0%)	RR 34.98 (2.16 to 565.75)	-	LOW	
Change of intervention: seclusion versus restraint – not discharged by 14 days												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	39/54 (72.2%)	39/51 (76.5%)	RR 0.94 (0.75 to 1.18)	46 fewer per 1000 (from 191 fewer to 138 more)	VERY LOW	
Compliance – need to call doctor – in first 24 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,4]	none	21/54 (38.9%)	26/51 (51%)	RR 0.76 (0.5 to 1.17)	122 fewer per 1000 (from 255 fewer to 87 more)	VERY LOW	
Compliance – did not accept oral medication												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	2/54 (3.7%)	3/51 (5.9%)	RR 0.63 (0.11 to 3.62)	22 fewer per 1000 (from 52 fewer to 154 more)	VERY LOW	
Compliance – need of extra tranquilising drugs – in first 24 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	21/54 (38.9%)	22/51 (43.1%)	RR 0.9 (0.57 to 1.43)	43 fewer per 1000 (from 185 fewer to 185 more)	VERY LOW	
Adverse effects – hypertension (24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	1/54 (1.9%)	2/51 (3.9%)	RR 0.47 (0.04 to 5.05)	21 fewer per 1000 (from 38 fewer to 159 more)	VERY LOW	
Adverse effects – death												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	1/54 (1.9%)	0/51 (0%)	RR 2.84 (0.12 to 68.07)	-	VERY	

											LOW	
Adverse effects – pain in shoulder												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	1/54 (1.9%)	0/51 (0%)	RR 2.84 (0.12 to 68.07)	-	VERY LOW	

[1] Low/unclear ROB across multiple, from: selection/ performance/ attrition/ detection.
[2] Sample size did not reach optimal information size.
[3] 95% CI included line of no effect, OIS met.
[4] Unclear/ serious ROB across multiple, from: selection/ performance/ attrition/ detection.

1.1.3.2 Restrictive intervention versus alternative: experience

Quality assessment							Number of patients		Effect		Quality	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Restrictive interventions**	**An alternative management strategy**	**Relative (95% CI)**	**Absolute**		
Perceived coercion (CES) seclusion versus mechanical restraint – CES (restriction of freedom to move) (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	60	48	-	MD 1.1 lower (1.65 to 0.55 lower)	LOW	
Perceived coercion (CES) seclusion versus mechanical restraint – CES (experience of restriction of freedom to move) (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	60	48	-	MD 0.5 lower (1.09 lower to 0.09 higher)	VERY LOW	
Perceived coercion (CES) seclusion versus mechanical restraint – CES (restriction of autonomy) (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	60	48	-	MD 0.5 lower (0.99 to 0.01 lower)	VERY LOW	
Perceived coercion (CES) seclusion versus mechanical restraint – CES (experience of restriction of autonomy) (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	60	48	-	MD 0.4 lower (0.93 lower to 0.13 higher)	VERY LOW	
Perceived coercion (CES) seclusion versus mechanical restraint – CES (coercion at beginning of measure) (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	60	48	-	MD 0.4 lower (0.95 lower to 0.15 higher)	VERY LOW	

Perceived coercion (CES) seclusion versus mechanical restraint – CES (experience of coercion at the beginning of measure) (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[1,2]	none	60	48	-	MD 0.4 higher (0.17 lower to 0.97 higher)	VERY LOW	
Perceived coercion (CES) seclusion versus mechanical restraint – CES (restriction of interpersonal contact) (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	60	48	-	MD 0.2 higher (0.39 lower to 0.79 higher)	VERY LOW	
Perceived coercion (CES) seclusion versus mechanical restraint – CES (experience of restriction of interpersonal contact) (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	60	48	-	MD 0 higher (0.54 lower to 0.54 higher)	VERY LOW	
Patient rated satisfaction: seclusion versus restraint												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	47/216 (21.8%)	45/204 (22.1%)	RR 0.65 (0.36 to 1.17)	77 fewer per 1000 (from 141 fewer to 37 more)	VERY LOW	
Patient rated satisfaction: seclusion versus restraint – Not satisfied												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	13/54 (24.1%)	19/51 (37.3%)	RR 0.65 (0.36 to 1.17)	130 fewer per 1000 (from 238 fewer to 63 more)	VERY LOW	
Patient rated satisfaction: seclusion versus restraint – Unclear												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	13/54 (24.1%)	12/51 (23.5%)	RR 1.02 (0.52 to 2.03)	5 more per 1000 (from 113 fewer to 242 more)	VERY LOW	

Patient rated satisfaction: seclusion versus restraint – Satisfied											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	8/54 (14.8%)	5/51 (9.8%)	RR 1.51 (0.53 to 4.32)	50 more per 1000 (from 46 fewer to 325 more)	VERY LOW
Patient rated satisfaction: seclusion versus restraint – Refused/unable to answer											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	13/54 (24.1%)	9/51 (17.6%)	RR 1.36 (0.64 to 2.91)	64 more per 1000 (from 64 fewer to 337 more)	VERY LOW

[1] Unclear/ serious ROB across multiple, from: selection/ performance/ attrition/ detection.
[2] Sample size did not reach optimal information size.
[3] 95% CI included line of no effect, OIS met.

1.1.4 Post-event: inpatient settings – adults

1.1.4.1 Post-incident management versus treatment as usual

Quality assessment							Number of patients		Effect		Quality	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Post-incident (seclusion) review**	**TAU**	**Relative (95% CI)**	**Absolute**		
Trauma experienced by service user (Impact of Event Scale – Revised) – total (better indicated by lower values)												
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	0	-	-	SMD 0.12 higher (0.59 lower to 0.83 higher)	VERY LOW	

[1] Low/unclear ROB across multiple, from: selection/ performance/ attrition/ detection.
[2] Sample size did not reach optimal information size.
[3] 95% CI included line of no effect, OIS met.

1.2 RAPID TRANQUILLISATION

1.2.1 During event: inpatient and emergency settings – adults

1.2.1.1 Intramuscular (IM) BZD versus placebo

Quality assessment							Number of patients		Effect		Quality	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM BZD	Placebo	Relative (95% CI)	Absolute		
Global impression: 1. No improvement – short term (follow-up 15-60 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33/51 (64.7%)	37/51 (72.5%)	RR 0.89 (0.69 to 1.16)	80 fewer per 1000 (from 225 fewer to 116 more)	LOW	
Global impression: 1. No improvement – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/51 (35.3%)	29/51 (56.9%)	RR 0.62 (0.4 to 0.97)	216 fewer per 1000 (from 17 fewer to 341 fewer)	LOW	
Global impression: 2. Need for additional medication – medium term (follow-up mean 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27/51 (52.9%)	27/51 (52.9%)	RR 1 (0.69 to 1.44)	0 fewer per 1000 (from 164 fewer to 233 more)	LOW	
Global impression: 3. Sedation – medium term (follow-up mean 1-24 hours)												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[2]	none	18/119 (15.1%)	8/124 (6.5%)	RR 2.16 (1.06 to 4.09)	75 more per 1000 (from 4 more to 199 more)	LOW	
Behaviour: 1. Average change score (ABS, high = worse) – medium term (follow-up mean 1-24 hours; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	51	50	-	SMD 0.60 lower (1 to 0.21 lower)	LOW	

Adverse effects: 1. Extrapyramidal symptoms – medium term (follow-up mean 1-24 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/120 (0.83%)	4/123 (3.3%)	RR 0.34 (0.05 to 2.1)	21 fewer per 1000 (from 31 fewer to 36 more)	LOW	
Adverse effects: 2. Use of medication for EPS – medium term (follow-up mean 1-24 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/51 (2%)	3/51 (5.9%)	RR 0.33 (0.04 to 3.1)	39 fewer per 1000 (from 56 fewer to 124 more)	LOW	
Adverse effects: 3. Specific – dizziness – medium term (follow-up mean 1-24 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/120 (11.7%)	5/123 (4.1%)	RR 2.75 (0.8 to 9.47)	71 more per 1000 (from 8 fewer to 344 more)	LOW	
Adverse effects: 3. Specific – nausea – medium term (follow-up mean 1-24 hours)												
2	randomised trials	serious[1]	serious[3]	no serious indirectness	serious[2]	none	4/120 (3.3%)	4/123 (3.3%)	RR 1.02 (0.01 to 72.79)	1 more per 1000 (from 32 fewer to 1000 more)	VERY LOW	
Adverse effects: 3. Specific – vomiting – medium term (follow-up mean 1-24 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/120 (2.5%)	2/123 (1.6%)	RR 1.39 (0.18 to 10.55)	6 more per 1000 (from 13 fewer to 155 more)	LOW	
Adverse effects: 3. Specific – headache – medium term (follow-up mean 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/69 (4.3%)	9/72 (12.5%)	RR 0.35 (0.1 to 1.23)	81 fewer per 1000 (from 112 fewer to 29 more)	LOW	
Adverse effects: 3. Specific – insomnia – medium term (follow-up mean 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/69 (1.4%)	6/72 (8.3%)	RR 0.17 (0.02 to 1.41)	69 fewer per 1000 (from 82 fewer to 34 more)	LOW	
Adverse effects: 3. Specific – somnolence – medium term (follow-up mean 1-24 hours)												
1	randomised	serious[1]	no serious	no serious	serious[2]	none	5/69	4/72	RR 1.3 (0.37	17 more per 1000 (from		

	trials		inconsistency	indirectness			(7.2%)	(5.6%)	to 4.66)	35 fewer to 203 more)	LOW	
Adverse effects: 3. Specific – sedation – medium term (follow-up mean 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/69 (11.6%)	1/72 (1.4%)	RR 8.35 (1.07 to 65.01)	102 more per 1000 (from 1 more to 889 more)	LOW	

[1] Generally unclear risk of bias and funded by manufacturer.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] One study shows positive effect and one study shows negative effect and I squared value significant.

1.2.1.2 IM BZD versus IM antipsychotic (AP)

Quality assessment							**Number of patients**		**Effect**		**Quality**	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IM BZD**	**IM AP**	**Relative (95% CI)**	**Absolute**		
Global impression: 1. No improvement – versus haloperidol – medium term (follow-up 1-24 hours)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36/76 (47.4%)	46/82 (56.1%)	RR 0.87 (0.56 to 1.36)	73 fewer per 1000 (from 247 fewer to 202 more)	LOW	
Global impression: 2. Need for additional medication – versus haloperidol – medium term (follow-up mean 1-24 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31/73 (42.5%)	39/77 (50.6%)	RR 0.87 (0.7 to 1.09)	66 fewer per 1000 (from 152 fewer to 46 more)	LOW	
Global impression: 2. Need for additional medication – versus olanzapine – medium term (follow-up mean 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27/51 (52.9%)	26/99 (26.3%)	RR 2.02 (1.33 to 3.07)	268 more per 1000 (from 87 more to 544 more)	LOW	
Global impression: 3. Sedation – versus haloperidol – short term (follow-up mean 15-60 minutes)												
1	randomised	serious[1]	no serious	no serious	serious[2]	none	9/23	7/21	RR 1.17 (0.53	57 more per 1000 (from		

	trials		inconsistency	indirectness			(39.1%)	(33.3%)	to 2.59)	157 fewer to 530 more)	LOW	
Global impression: 3. Sedation – versus haloperidol – medium term (follow-up 1-24 hours)												
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	49/172 (28.5%)	45/222 (20.3%)	RR 1.33 (0.94 to 1.87)	67 more per 1000 (from 12 fewer to 176 more)	LOW	
Global impression: 3. Sedation – versus olanzapine – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/51 (9.8%)	13/99 (13.1%)	RR 0.75 (0.28 to 1.98)	33 fewer per 1000 (from 95 fewer to 129 more)	LOW	
Global impression: 3. Sedation – versus aripiprazole – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/68 (19.1%)	18/150 (12%)	RR 1.59 (0.83 to 3.06)	71 more per 1000 (from 20 fewer to 247 more)	LOW	
Behaviour: 1. Average change/endpoint score (ABS, high = worse) – versus haloperidol – medium term (follow-up 1-24 hours; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	35	-	SMD 0.20 higher (0.28 lower to 0.69 higher)	LOW	
Behaviour: 1. Average change/endpoint score (ABS, high = worse) – versus olanzapine – medium term (follow-up 1-24 hours; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	51	98	-	SMD 0.47 higher (0.13 to 0.81 higher)	LOW	
Behaviour: 2. Average change score (OAS, high = worse) – versus haloperidol – medium term (follow-up 1-24 hours; better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	22	24	-	SMD 0.15 higher (0.43 lower to 0.73 higher)	LOW	
Adverse effects: 1. Extrapyramidal symptoms (follow-up 1-24 hours)												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/235 (1.3%)	38/367 (10.4%)	RR 0.15 (0.06 to 0.4)	88 fewer per 1000 (from 62 fewer to 97 fewer)	LOW	

Adverse effects: 1. Extrapyramidal symptoms – versus haloperidol – medium term (follow-up 1-24 hours)											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/115 (1.7%)	22/118 (18.6%)	RR 0.13 (0.04 to 0.43)	162 fewer per 1000 (from 106 fewer to 179 fewer)	LOW
Adverse effects: 1. Extrapyramidal symptoms – versus olanzapine – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/51 (2%)	8/99 (8.1%)	RR 0.24 (0.03 to 1.89)	61 fewer per 1000 (from 78 fewer to 72 more)	LOW
Adverse effects: 1. Extrapyramidal symptoms – versus aripiprazole – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/69 (0%)	8/150 (5.3%)	RR 0.13 (0.01 to 2.17)	46 fewer per 1000 (from 53 fewer to 62 more)	LOW
Adverse effects: 2. Use of medication for extrapyramidal symptoms (follow-up 24 hours)											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/151 (3.3%)	20/284 (7%)	RR 0.42 (0.17 to 1.03)	41 fewer per 1000 (from 58 fewer to 2 more)	LOW
Adverse effects: 2. Use of medication for extrapyramidal symptoms – versus haloperidol – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/31 (12.9%)	9/35 (25.7%)	RR 0.5 (0.17 to 1.47)	129 fewer per 1000 (from 213 fewer to 121 more)	LOW
Adverse effects: 2. Use of medication for extrapyramidal symptoms – versus olanzapine – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[2]	none	1/51 (2%)	8/99 (8.1%)	RR 0.24 (0.03 to 1.89)	61 fewer per 1000 (from 78 fewer to 72 more)	LOW
Adverse effects: 2. Use of medication for extrapyramidal symptoms – versus aripiprazole – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/69 (0%)	3/150 (2%)	RR 0.31 (0.02 to 5.89)	14 fewer per 1000 (from 20 fewer to 98 more)	LOW
Adverse effects: 3. Specific – versus haloperidol – ataxia – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/31 (6.5%)	1/35 (2.9%)	RR 2.26 (0.22 to 23.71)	36 more per 1000 (from 22 fewer to 649 more)	LOW

Adverse effects: 3. Specific – versus haloperidol – apnoea – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/42 (0%)	1/42 (2.4%)	RR 0.33 (0.01 to 7.96)	16 fewer per 1000 (from 24 fewer to 166 more)	LOW
Adverse effects: 3. Specific – versus haloperidol – dizziness – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/31 (9.7%)	3/35 (8.6%)	RR 1.13 (0.25 to 5.19)	11 more per 1000 (from 64 fewer to 359 more)	LOW
Adverse effects: 3. Specific – versus aripiprazole – dizziness – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/69 (10.1%)	11/150 (7.3%)	RR 1.38 (0.56 to 3.42)	28 more per 1000 (from 32 fewer to 177 more)	LOW
Adverse effects: 3. Specific – versus olanzapine – dizziness – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/51 (13.7%)	9/99 (9.1%)	RR 1.51 (0.6 to 3.82)	46 more per 1000 (from 36 fewer to 256 more)	LOW
Adverse effects: 3. Specific – versus haloperidol – dry mouth – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/31 (16.1%)	3/35 (8.6%)	RR 1.88 (0.49 to 7.24)	75 more per 1000 (from 44 fewer to 535 more)	LOW
Adverse effects: 3. Specific – versus haloperidol – heart rate – high – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	0/22 (0%)	2/24 (8.3%)	RR 0.22 (0.01 to 4.29)	65 fewer per 1000 (from 82 fewer to 274 more)	LOW
Adverse effects: 3. Specific – versus haloperidol – hypotensive – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/42 (0%)	1/42 (2.4%)	RR 0.33 (0.01 to 7.96)	16 fewer per 1000 (from 24 fewer to 166 more)	LOW
Adverse effects: 3. Specific – versus olanzapine – nausea – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/51 (7.8%)	1/99 (1%)	RR 7.76 (0.89 to 67.67)	68 more per 1000 (from 1 fewer to 673 more)	LOW

Adverse effects: 3. Specific – versus aripiprazole – nausea – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/69 (0%)	22/150 (14.7%)	RR 0.05 (0 to 0.78)	139 fewer per 1000 (from 32 fewer to 147 fewer)	LOW
Adverse effects: 3. Specific – versus haloperidol – speech disorder – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/31 (6.5%)	4/35 (11.4%)	RR 0.56 (0.11 to 2.87)	50 fewer per 1000 (from 102 fewer to 214 more)	LOW
Adverse effects: 3. Specific – versus haloperidol – tremor – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/22 (0%)	5/24 (20.8%)	RR 0.1 (0.01 to 1.69)	187 fewer per 1000 (from 206 fewer to 144 more)	LOW
Adverse effects: 3. Specific – versus olanzapine – vomiting – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/51 (5.9%)	0/99 (0%)	RR 13.46 (0.71 to 255.7)	-	LOW
Adverse effects: 3. Specific – versus aripiprazole – vomiting – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/69 (0%)	8/150 (5.3%)	RR 0.13 (0.01 to 2.17)	46 fewer per 1000 (from 53 fewer to 62 more)	LOW
Adverse effects: 3. Specific – versus aripiprazole – headache – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/69 (4.3%)	24/150 (16%)	RR 0.27 (0.08 to 0.87)	117 fewer per 1000 (from 21 fewer to 147 fewer)	LOW
Adverse effects: 3. Specific – versus aripiprazole – insomnia – medium term (follow-up 1-24 hours)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/69 (1.4%)	13/150 (8.7%)	RR 0.17 (0.02 to 1.25)	72 fewer per 1000 (from 85 fewer to 22 more)	LOW
Adverse effects: 3. Specific – versus aripiprazole – somnolence – medium term (follow-up 1-24 hours)											
1	randomised	serious[1]	no serious	no serious	serious[2]	none	5/69	12/150	RR 0.91 (0.33	7 fewer per 1000 (from 54	

	trials		inconsistency	indirectness			(7.2%)	(8%)	to 2.47)	fewer to 118 more)	LOW	
Adverse effects: 3. Specific – versus aripiprazole – sedation – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/69 (11.6%)	8/150 (5.3%)	RR 2.17 (0.85 to 5.55)	62 more per 1000 (from 8 fewer to 243 more)	LOW	

[1] Generally unclear risk of bias and funded by manufacturer.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Generally unclear risk of bias and funding not reported.

1.2.1.3 IM BZD + AP versus same BZD

Quality assessment							Number of patients		Effect		Quality	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IM BZD + AP**	**Same BZD**	**Relative (95% CI)**	**Absolute**		
Global impression: 1. No improvement – + haloperidol – short term (15-60 minutes) (follow-up 15-60 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/9 (0%)	5/11 (45.5%)	RR 0.11 (0.01 to 1.74)	405 fewer per 1000 (from 450 fewer to 336 more)	VERY LOW	
Global impression: 1. No improvement – + haloperidol – medium term (1-24 hours) (follow-up 1-24 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	27/42 (64.3%)	28/41 (68.3%)	RR 0.96 (0.7 to 1.3)	27 fewer per 1000 (from 205 fewer to 205 more)	LOW	
Global impression: 2. Need for additional medication – + haloperidol – medium term (follow-up 1-24 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	27/41 (65.9%)	26/42 (61.9%)	RR 0.93 (0.34 to 2.55)	43 fewer per 1000 (from 409 fewer to 960 more)	LOW	
Global impression: 3. Sedation – + haloperidol – short term (follow-up 15-60 minutes)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	18/24 (75%)	9/23 (39.1%)	RR 1.92 (1.1 to 3.35)	360 more per 1000 (from 39 more to 920 more)	LOW	
Global impression: 3. Sedation – + haloperidol – medium term (follow-up 1-24 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	26/56 (46.4%)	30/54 (55.6%)	RR 0.85 (0.53 to 1.35)	83 fewer per 1000 (from 261 fewer to 194 more)	LOW	
Behaviour: 1. Average endpoint score (ABS, high = worse) – + haloperidol – medium term (follow-up 1-24 hours; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	32	31	-	SMD 0.18 lower (0.67 lower to 0.32 higher)	LOW	

Adverse effects: 1. Extrapyramidal symptoms – + haloperidol – medium term (follow-up 1-24 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	2/41 (4.9%)	1/42 (2.4%)	RR 1.94 (0.18 to 20.3)	22 more per 1000 (from 20 fewer to 460 more)	LOW	
Adverse effects: 2. Use of medication for EPS – + haloperidol – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	3/32 (9.4%)	4/31 (12.9%)	RR 0.73 (0.18 to 2.99)	35 fewer per 1000 (from 106 fewer to 257 more)	LOW	
Adverse effects: 3. Specific – + haloperidol – ataxia – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	3/32 (9.4%)	2/31 (6.5%)	RR 1.45 (0.26 to 8.11)	29 more per 1000 (from 48 fewer to 459 more)	LOW	
Adverse effects: 3. Specific – + haloperidol – dizziness – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	2/32 (6.3%)	3/31 (9.7%)	RR 0.65 (0.12 to 3.61)	34 fewer per 1000 (from 85 fewer to 253 more)	LOW	
Adverse effects: 3. Specific – + haloperidol – dry mouth – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	3/32 (9.4%)	5/31 (16.1%)	RR 0.58 (0.15 to 2.23)	68 fewer per 1000 (from 137 fewer to 198 more)	LOW	
Adverse effects: 3. Specific – + haloperidol – speech disorder – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	3/32 (9.4%)	2/31 (6.5%)	RR 1.45 (0.26 to 8.11)	29 more per 1000 (from 48 fewer to 459 more)	LOW	

[1] Generally unclear risk of bias and funded by manufacturer.
[2] Very small sample with wide CIs crossing the line of no effect.
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[4] Generally unclear risk of bias and funding not reported.

1.2.1.4 IM BZD + AP versus same AP

Quality assessment							Number of patients		Effect		Quality	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IM BZD + AP**	**SAME AP**	**Relative (95% CI)**	**Absolute**		
Global impression: 1. no improvement – +/versus haloperidol – medium term (1-24 hours) (follow-up 1-24 hours)												
2	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	33/62 (53.2%)	25/65 (38.5%)	RR 3 (0.13 to 67.48)	769 more per 1000 (from 335 fewer to 1000 more)	LOW	
Global impression: 2. need for additional medication – +/versus haloperidol – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	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)	LOW	
Global impression: 3. sedation – +/versus haloperidol – short term (follow-up 15-60 minutes)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	18/24 (75%)	7/21 (33.3%)	RR 2.25 (1.18 to 4.3)	417 more per 1000 (from 60 more to 1000 more)	LOW	
Global impression: 3. sedation – +/versus haloperidol – medium term (follow-up 1-24 hours)												
3	randomised trials	serious[3]	serious[1]	no serious indirectness	serious[2]	none	38/86 (44.2%)	22/86 (25.6%)	RR 1.67 (0.67 to 4.12)	171 more per 1000 (from 84 fewer to 798 more)	VERY LOW	
Behaviour: 1. average endpoint score (ABS, high = worse) – +/versus haloperidol – medium term (follow-up 1-24 hours; better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	32	35	-	SMD 0.02 higher (0.46 lower to 0.5 higher)	LOW	

Behaviour: 2. average endpoint score (OAS, high = worse) – +/versus haloperidol – short term (follow-up 15-60 minutes; better indicated by lower values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	SMD 0.48 higher (0.03 lower to 1 higher)	LOW	
Behaviour: 2. average endpoint score (OAS, high = worse) – +/versus haloperidol – medium term (follow-up 1-24 hours; better indicated by lower values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	SMD 0.66 higher (0.14 to 1.18 higher)	LOW	
Adverse effects: 1. extrapyramidal symptoms – +/versus haloperidol – medium term (follow-up 1-24 hours)												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	5/62 (8.1%)	12/65 (18.5%)	RR 0.45 (0.17 to 1.22)	102 fewer per 1000 (from 153 fewer to 41 more)	LOW	
Adverse effects: 2. use of medication for EPS – +/versus haloperidol – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	4/32 (12.5%)	9/35 (25.7%)	RR 0.49 (0.17 to 1.43)	131 fewer per 1000 (from 213 fewer to 111 more)	LOW	
Adverse effects: 3. specific – +/versus haloperidol – ataxia – medium term (follow-up mean 1-24 hours)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	3/32 (9.4%)	1/35 (2.9%)	RR 3.28 (0.36 to 29.97)	65 more per 1000 (from 18 fewer to 828 more)	LOW	
Adverse effects: 3. specific – +/versus haloperidol – dizziness – medium term (follow-up 1-24 hours)												
1	observational studies	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	2/32 (6.3%)	3/35 (8.6%)	RR 0.73 (0.13 to 4.09)	23 fewer per 1000 (from 75 fewer to 265 more)	LOW	
Adverse effects: 3. specific – +/versus haloperidol – dry mouth – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	3/32 (9.4%)	3/35 (8.6%)	RR 1.09 (0.24 to 5.04)	8 more per 1000 (from 65 fewer to 346 more)	LOW	

Adverse effects: 3. specific – +/versus haloperidol – hypotension – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	5/30 (16.7%)	0/30 (0%)	RR 11 (0.64 to 190.53)	-	LOW	
Adverse effects: 3. specific – +/versus haloperidol – speech disorder – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	3/32 (9.4%)	4/35 (11.4%)	RR 0.82 (0.2 to 3.39)	21 fewer per 1000 (from 91 fewer to 273 more)	LOW	

[1] Studies found contrasting results. High, significant I^2 value.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Generally unclear risk of bias and funded by manufacturer.
[4] Generally unclear or high risk of bias and funding not reported.
[5] Generally unclear risk of bias and funding not reported.

1.2.1.5 IM BZD + AP versus different IM AP

Quality assessment							Number of patients		Effect		Quality	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IM BZD + AP**	**DIFFERENT IM AP**	**Relative (95% CI)**	**Absolute**		
Global impression: 1. no improvement – +haloperidol versus olanzapine – medium term (1-24 hours) (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/30 (40%)	0/30 (0%)	RR 25 (1.55 to 403.99)	-	LOW	
Global impression: 1. no improvement – +haloperidol versus ziprasidone – medium term (1-24 hours) (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/30 (40%)	3/30 (10%)	RR 4 (1.25 to 12.75)	300 more per 1000 (from 25 more to 1000 more)	LOW	

Global impression: 2. need for additional medication – not reported												
0	-	-[3]	-	-	-[2]	none	27/41 (65.9%)	26/42 (61.9%)	-	-		
Global impression: 3. sedation – +haloperidol versus olanzapine – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/30 (40%)	1/30 (3.3%)	RR 12 (1.66 to 86.59)	367 more per 1000 (from 22 more to 1000 more)	LOW	
Global impression: 3. sedation – +haloperidol versus ziprasidone – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/30 (40%)	3/30 (10%)	RR 4 (1.25 to 12.75)	300 more per 1000 (from 25 more to 1000 more)	LOW	
Behaviour: 1. average change score (OAS, high = worse) – +haloperidol versus olanzapine – short term (follow-up 15-60 minutes; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	SMD 0.96 higher (0.42 to 1.49 higher)	LOW	
Behaviour: 1. average change score (OAS, high = worse) – +haloperidol versus olanzapine – medium term (follow-up 1-24 hours; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	SMD 0.91 higher (0.38 to 1.45 higher)	LOW	
Behaviour: 1. average change score (OAS, high = worse) – +haloperidol versus ziprasidone – short term (follow-up 15-60 minutes; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	SMD 0.55 higher (0.03 to 1.06 higher)	LOW	
Behaviour: 1. average change score (OAS, high = worse) – +haloperidol versus ziprasidone – medium term (follow-up 1-24 hours; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	SMD 0.96 higher (0.43 to 1.5 higher)	LOW	

Adverse effects: 1. side effects – +risperidone versus clozapine – medium term (follow-up 1-24 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/40 (0%)	4/36 (11.1%)	RR 0.18 (0.02 to 1.48)	91 fewer per 1000 (from 109 fewer to 53 more)	LOW	
Adverse effects: 1. side effects – +risperidone versus haloperidol – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/20 (0%)	9/20 (45%)	RR 0.05 (0 to 0.85)	427 fewer per 1000 (from 67 fewer to 450 fewer)	LOW	
Adverse effects: 2. extrapyramidal symptoms – +haloperidol versus olanzapine – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/30 (10%)	0/30 (0%)	RR 7 (0.38 to 129.93)	-	LOW	
Adverse effects: 2. extrapyramidal symptoms – +haloperidol versus ziprasidone – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/30 (10%)	0/30 (0%)	RR 7 (0.38 to 129.93)	-	LOW	
Adverse effects: 3. specific – +haloperidol versus olanzapine – hypotension – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/30 (16.7%)	1/30 (3.3%)	RR 5 (0.62 to 40.28)	133 more per 1000 (from 13 fewer to 1000 more)	LOW	
Adverse effects: 3. specific – +haloperidol versus ziprasidone – hypotension – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/30 (16.7%)	6/30 (20%)	RR 0.83 (0.28 to 2.44)	34 fewer per 1000 (from 144 fewer to 288 more)	LOW	

[1] Generally unclear risk of bias and funding not reported.

[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

1.2.1.6 IM BZD + AP versus IM AP + AP

Quality assessment							Number of patients		Effect		Quality	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IM BZD + AP**	**IM AP + AP**	**Relative (95% CI)**	**Absolute**		
Global impression: 1. no improvement – not reported												
0	-	-	-	-	-	none	-	-	-	-		
Global impression: 2. need for additional medication – not reported												
0	-	-	-	-	-	none	-	-	-	-		
Behaviour: 1. average endpoint score (OAS, high = worse) – + haloperidol versus clothiapine + haloperidol – medium term (1-24 hours) (follow-up 1-24 hours; better indicated by lower values)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	SMD 0.13 lower (0.64 lower to 0.37 higher)	LOW	
Adverse effects – not reported												
0	-	-	-	-	-	none	-	-	-	-		

[1] Generally unclear risk of bias and funding not reported.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

1.2.1.7 IM BZD versus IM AP + IM antihistamine (promethazine)

Quality assessment							Number of patients		Effect		Quality	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IM BZD**	**IM AP + antihistamines**	**Relative (95% CI)**	**Absolute**		
Global impression: 1. No improvement – versus haloperidol + promethazine – immediate term (0-15 minutes) (follow-up 0-15 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	70/100 (70%)	39/100 (39%)	RR 1.79 (1.36 to 2.37)	308 more per 1000 (from 140 more to 534 more)	LOW	
Global impression: 1. No improvement – versus haloperidol + promethazine – short term (15-60 minutes) (follow-up 15-60 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	42/100 (42%)	17/100 (17%)	RR 2.47 (1.51 to 4.03)	250 more per 1000 (from 87 more to 515 more)	LOW	
Global impression: 1. No improvement – versus haloperidol + promethazine – medium term (1-24 hours) (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26/100 (26%)	12/100 (12%)	RR 2.17 (1.16 to 4.05)	140 more per 1000 (from 19 more to 366 more)	LOW	
Global impression: 2. Need for additional medication – versus haloperidol + promethazine – immediate term (follow-up 0-15 minutes)												
1	-	-	-	-	-	-	-	-	not pooled	not pooled	-	
Global impression: 2. Need for additional medication – versus haloperidol + promethazine – short term (follow-up 15-60 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/100 (1%)	0/100 (0%)	RR 3 (0.12 to 72.77)	-	LOW	
Global impression: 2. Need for additional medication – versus haloperidol + promethazine – medium term (follow-up 1-24 hours)												
1	randomised	serious[1]	no serious	no serious	serious[2]	none	4/100	3/100	RR 1.33 (0.31	10 more per 1000 (from 21 fewer to 144		

	trials		inconsistency	indirectness			(4%)	(3%)	to 5.81)	more)	LOW	
Global impression: 3. Sedation (tranquil or asleep) – versus haloperidol + promethazine – immediate term (follow-up 0-15 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	78/100 (78%)	89/100 (89%)	RR 0.88 (0.77 to 0.99)	107 fewer per 1000 (from 9 fewer to 205 fewer)	LOW	
Global impression: 3. Sedation (tranquil or asleep) – versus haloperidol + promethazine – short term (follow-up 15-60 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	81/100 (81%)	95/100 (95%)	RR 0.85 (0.77 to 0.95)	142 fewer per 1000 (from 48 fewer to 219 fewer)	LOW	
Global impression: 3. Sedation (tranquil or asleep) – versus haloperidol + promethazine – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	88/100 (88%)	97/100 (97%)	RR 0.91 (0.84 to 0.98)	87 fewer per 1000 (from 19 fewer to 155 fewer)	LOW	
Global impression: 3. Sedation (tranquil or asleep) – versus haloperidol + promethazine – short term (follow-up 15-60 minutes)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	134/151 (88.7%)	101/150 (67.3%)	RR 1.32 (1.16 to 1.49)	215 more per 1000 (from 108 more to 330 more)	LOW	
Global impression: 3. Sedation (tranquil or asleep) – versus haloperidol + promethazine – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	141/151 (93.4%)	124/150 (82.7%)	RR 1.13 (1.04 to 1.23)	107 more per 1000 (from 33 more to 190 more)	LOW	
Adverse effects: 1. Specific – versus haloperidol + promethazine – airway management – medium term (follow-up 1-24 hours)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/251 (0.8%)	0/250 (0%)	RR 2.99 (0.31 to 28.54)	-	LOW	

Adverse effects: 1. Specific – versus haloperidol + promethazine – nausea – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/100 (1%)	0/100 (0%)	RR 3 (0.12 to 72.77)	-	LOW	
Adverse effects: 1. Specific – versus haloperidol + promethazine – seizure – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/151 (0%)	1/150 (0.67%)	RR 0.33 (0.01 to 8.06)	4 fewer per 1000 (from 7 fewer to 47 more)	LOW	

[1] Participants and outcome assessors were non-blinded.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

1.2.1.8 IM BZD + AP versus IM AP + IM antihistamine (promethazine)

Quality assessment							**Number of patients**		**Effect**		**Quality**	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IM BZD + AP**	**IM AP + ANTIHISTAMINES**	**Relative (95% CI)**	**Absolute**		
Global impression: 1. no improvement – +haloperidol versus haloperidol + promethazine – medium term (1-24 hours) (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/30 (40%)	0/30 (0%)	RR 25 (1.55 to 403.99)	-	LOW	
Global impression: 2. need for additional medication – not reported												
0	-	-	-	-	-		27/41 (65.9%)	26/42 (61.9%)	-	-		
Global impression: 3. sedation – +haloperidol versus haloperidol + promethazine – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/30 (40%)	1/30 (3.3%)	RR 12 (1.66 to 86.59)	367 more per 1000 (from 22 more to 1000 more)	LOW	

Behaviour: 1. average endpoint score (OAS, high = worse) – + haloperidol versus haloperidol + promethazine – short term (follow-up 15-60 minutes; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	SMD 0.85 lower (1.38 to 0.32 lower)	LOW	
Behaviour: 1. average endpoint score (OAS, high = worse) – + haloperidol versus haloperidol + promethazine – medium term (follow-up 1-24 hours; better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	SMD 0.48 higher (0.03 lower to 1 higher)	LOW	
Adverse effects: 1. extrapyramidal symptoms – +haloperidol versus haloperidol + promethazine – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/30 (10%)	5/30 (16.7%)	RR 0.6 (0.16 to 2.29)	67 fewer per 1000 (from 140 fewer to 215 more)	LOW	
Adverse effects: 2. specific – +haloperidol versus haloperidol + promethazine – hypotension – medium term (follow-up 1-24 hours)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/30 (16.7%)	3/30 (10%)	RR 1.67 (0.44 to 6.36)	67 more per 1000 (from 56 fewer to 536 more)	LOW	

[1] Participants and outcome assessors were non-blinded.

[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

1.2.1.9 IM HAL versus placebo

Quality assessment							Number of patients		Effect		Quality	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IM HAL**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Repeated need for tranquillisation – needing additional injection during 24 hours (agitation only)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	124/411 (30.2%)	145/249 (58.2%)	RR 0.52 (0.42 to 0.65)	280 fewer per 1000 (from 204 fewer to 338 fewer)	LOW	
Global outcome: 1. not improved – not marked improvement												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/29 (58.6%)	11/11 (100%)	RR 0.61 (0.44 to 0.84)	390 fewer per 1000 (from 160 fewer to 560 fewer)	LOW	
Global outcome: 1. not improved – not any improvement												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/29 (10.3%)	4/11 (36.4%)	RR 0.28 (0.08 to 1.07)	262 fewer per 1000 (from 335 fewer to 25 more)	LOW	
Global outcome: 2. need for benzodiazepine during 24 hours – need for benzodiazepine during 24 hours												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	53/411 (12.9%)	67/249 (26.9%)	RR 0.5 (0.3 to 0.81)	135 fewer per 1000 (from 51 fewer to 188 fewer)	LOW	
Specific behaviour – agitation: 2a. Average score – by about 2 hours – change score – ABS (high = worse) (better indicated by lower values)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	280	194	-	SMD 0.65 lower (0.95 to 0.35 lower)	MODERATE	

Specific behaviour – agitation: 2a. Average score – by about 2 hours – change score – PANSS-EC (high = worse) (better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	224	133	-	SMD 0.59 lower (1.04 to 0.14 lower)	LOW	
Specific behaviour – agitation: 2b. Average score – by about 24 hours – change score – ABS (high = worse) (better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	40	45	-	SMD 0.59 lower (1.02 to 0.15 lower)	LOW	
Specific behaviour – agitation: 2b. Average score – by about 24 hours – change score – PANSS-EC (high = worse) (better indicated by lower values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	40	45	-	SMD 0.38 lower (0.81 lower to 0.05 higher)	LOW	
Adverse effects: 1. General – one or more drug-related adverse effects during 24 hours												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	111/245 (45.3%)	42/150 (28%)	RR 1.64 (1.22 to 2.2)	179 more per 1000 (from 62 more to 336 more)	MODERATE	
Adverse effects: 1. General – increased severity of adverse effects after second injection												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	82/185 (44.3%)	12/88 (13.6%)	RR 3.25 (1.88 to 5.63)	307 more per 1000 (from 120 more to 631 more)	LOW	
Adverse effects: 1. General – overall adverse events during 72 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	90/185 (48.6%)	24/88 (27.3%)	RR 1.78 (1.23 to 2.59)	213 more per 1000 (from 63 more to 434 more)	LOW	
Adverse effects: 2. General – serious – death												
1	randomised trials					none	0/185 (0%)	0/88 (0%)	not pooled	not pooled		

Adverse effects: 2. General – serious – rated as serious												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/60 (0%)	1/62 (1.6%)	RR 0.34 (0.01 to 8.29)	11 fewer per 1000 (from 16 fewer to 118 more)	LOW	
Adverse effects: 2. General – serious – tonic clonic seizure												
1	randomised trials					none	0/60 (0%)	0/57 (0%)	not pooled	not pooled		
Adverse effects: 3. Specific – arousal level – insomnia during 24 hours (only reported if occurred in ≧ 5%)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/185 (11.9%)	8/88 (9.1%)	RR 1.31 (0.61 to 2.82)	28 more per 1000 (from 35 fewer to 165 more)	LOW	
Adverse effects: 3. Specific – arousal level – 'over' sedated												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	40/214 (18.7%)	5/99 (5.1%)	RR 3.04 (1.27 to 7.26)	103 more per 1000 (from 14 more to 316 more)	LOW	
Adverse effects: 3. Specific – arousal level – somnolence during 24 hours												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24/400 (6%)	6/215 (2.8%)	RR 2.26 (0.96 to 5.32)	35 more per 1000 (from 1 fewer to 121 more)	LOW	
Adverse effects: 4a. Specific – cardiac: i. Miscellaneous outcomes – dizziness during 24 hours (only reported if occurred in ≧ 5%)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/242 (4.5%)	6/150 (4%)	RR 1.3 (0.47 to 3.59)	12 more per 1000 (from 21 fewer to 104 more)	LOW	
Adverse effects: 4a. Specific – cardiac: i. Miscellaneous outcomes – hypotension during 24 hours												
2	randomised	serious[1]	no serious	no serious	serious[2]	none	1/69	0/56	RR 1.2 (0.05	-		

	trials		inconsistency	indirectness			(1.4%)	(0%)	to 27.44)		LOW	
Adverse effects: 4a. Specific – cardiac: i. Miscellaneous outcomes – QTc[4] abnormality												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/60 (5%)	1/62 (1.6%)	RR 3.1 (0.33 to 28.98)	34 more per 1000 (from 11 fewer to 451 more)	LOW	
Adverse effects: 4a. Specific – cardiac: i. Miscellaneous outcomes – sinus tachycardia during 24 hours (only reported if occurred in ≥ 5%)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/60 (5%)	1/62 (1.6%)	RR 3.1 (0.33 to 28.98)	34 more per 1000 (from 11 fewer to 451 more)	LOW	
Adverse effects: 4a. Specific – cardiac: i. Miscellaneous outcomes – tachycardia during 24 hours (only reported if occurred in ≥ 5%)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/60 (1.7%)	1/62 (1.6%)	RR 1.03 (0.07 to 16.15)	0 more per 1000 (from 15 fewer to 244 more)	LOW	
Adverse effects: 5b. Specific – movement disorders: i. Average change score (Barnes Akathisia Scale, high = worse) (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	120	48	-	SMD 0.12 higher (0.22 lower to 0.45 higher)	LOW	
Adverse effects: 5c. Specific – movement disorders: ii. Average change score (Simpson-Angus Scale, high = worse) (better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	120	47	-	SMD 0.54 higher (0.2 to 0.89 higher)	LOW	

[1] Risk of bias generally unclear and funding not reported.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Risk of bias generally unclear and trial funded by manufacturer.
[4] The corrected QT interval (the period from the start of the Q wave to the end of the T wave; duration of ventricular electrical activity).

1.2.1.10 IM HAL versus other IM AP

Quality assessment							Number of patients		Effect		Quality	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IM HAL**	**Other IM AP**	**Relative (95% CI)**	**Absolute**		
Repeated need for rapid tranquillisation: needing additional injection												
9	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	220/636 (34.6%)	264/782 (33.8%)	RR 1.04 (0.87 to 1.25)	14 more per 1000 (from 44 fewer to 84 more)	LOW	
Repeated need for rapid tranquillisation: needing additional injection – versus aripiprazole												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	78/242 (32.2%)	95/231 (41.1%)	RR 0.79 (0.62 to 1)	86 fewer per 1000 (from 156 fewer to 0 more)	LOW	
Repeated need for rapid tranquillisation: needing additional injection – versus chlorpromazine												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	15/15 (100%)	14/15 (93.3%)	RR 1.07 (0.89 to 1.28)	65 more per 1000 (from 103 fewer to 261 more)	VERY LOW	
Repeated need for rapid tranquillisation: needing additional injection – versus droperidol												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	13/16 (81.3%)	4/11 (36.4%)	RR 2.23 (0.99 to 5.06)	447 more per 1000 (from 4 fewer to 1000 more)	LOW	
Repeated need for rapid tranquillisation: needing additional injection – versus olanzapine												
4	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	84/316 (26.6%)	130/472 (27.5%)	RR 1.02 (0.73 to 1.42)	6 more per 1000 (from 74 fewer to 116 more)	LOW	

Repeated need for rapid tranquillisation: needing additional injection – versus zuclopenthixol acetate												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	15/32 (46.9%)	7/38 (18.4%)	RR 2.54 (1.19 to 5.46)	284 more per 1000 (from 35 more to 822 more)	LOW	
Repeated need for rapid tranquillisation: needing additional injection – versus thiothixene												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	15/15 (100%)	14/15 (93.3%)	RR 1.07 (0.89 to 1.28)	65 more per 1000 (from 103 fewer to 261 more)	LOW	
Global outcome: 1. need for additional benzodiazepine – versus olanzapine												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	25/166 (15.1%)	25/177 (14.1%)	RR 0.62 (0.07 to 5.07)	54 fewer per 1000 (from 131 fewer to 575 more)	LOW	
Global outcome: not improved												
10	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	68/359 (18.9%)	124/481 (25.8%)	RR 0.73 (0.46 to 1.18)	70 fewer per 1000 (from 139 fewer to 46 more)	LOW	
Global outcome: not improved – versus chlorpromazine												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	3/54 (5.6%)	10/35 (28.6%)	RR 0.16 (0.05 to 0.48)	240 fewer per 1000 (from 149 fewer to 271 fewer)	LOW	
Global outcome: not improved – versus loxapine												
3	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	12/62 (19.4%)	15/59 (25.4%)	RR 0.82 (0.42 to 1.62)	46 fewer per 1000 (from 147 fewer to 158 more)	LOW	

Global outcome: not improved – versus perphenazine												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	1/23 (4.3%)	2/21 (9.5%)	RR 0.46 (0.04 to 4.68)	51 fewer per 1000 (from 91 fewer to 350 more)	LOW	
Global outcome: not improved – versus thiothixene												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	2/24 (8.3%)	0/20 (0%)	RR 4.2 (0.21 to 82.72)	-	LOW	
Global outcome: not improved – versus olanzapine												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	50/196 (25.5%)	97/346 (28%)	RR 1.04 (0.74 to 1.42)	11 more per 1000 (from 73 fewer to 118 more)	LOW	
Adverse effects: 1a. General (aripiprazole) – one or more drug-related adverse effects during 24 hours												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	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)	LOW	
Adverse effects: 1a. General (aripiprazole) – increased severity of adverse effects after second injection												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	82/185 (44.3%)	58/175 (33.1%)	RR 1.34 (1.03 to 1.74)	113 more per 1000 (from 10 more to 245 more)	LOW	
Adverse effects: 1a. General (aripiprazole) – overall adverse events during 72 hours												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	90/185 (48.6%)	64/175 (36.6%)	RR 1.33 (1.04 to 1.7)	121 more per 1000 (from 15 more to 256 more)	LOW	
Adverse effects: 1b. 'Serious' (aripiprazole) – any												
2	observational	serious[3]	no serious	no serious	serious[4]	none	4/245	7/232	RR 0.55 (0.1	14 fewer per 1000 (from 27 fewer to 65		

	studies		inconsistency	indirectness			(1.6%)	(3%)	to 3.16)	more)		
Adverse effects: 1b. 'Serious' (aripiprazole) – tonic clonic seizure												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	0/60 (0%)	1/57 (1.8%)	RR 0.32 (0.01 to 7.62)	12 fewer per 1000 (from 17 fewer to 116 more)	LOW	
Adverse effects: 1b. 'Serious' (aripiprazole) – death												
1	randomised trials					none	0/185 (0%)	0/175 (0%)	not pooled	not pooled		
Adverse effects: any serious or specific antiepileptics (chlorpromazine) – allergy – haematological – leukopenia – mild												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	1/25 (4%)	0/25 (0%)	RR 3 (0.13 to 70.3)	-	LOW	
Adverse effects: any serious or specific antiepileptics (chlorpromazine) – allergy – hepatic – glutamic pyruvic transaminase elevated												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	0/25 (0%)	1/25 (4%)	RR 0.33 (0.01 to 7.81)	27 fewer per 1000 (from 40 fewer to 272 more)	LOW	
Adverse effects: any serious or specific antiepileptics (chlorpromazine) – allergy – skin irritation – local												
1	randomised trials					none	0/15 (0%)	0/15 (0%)	not pooled	not pooled		
Adverse effects: any serious or specific antiepileptics (chlorpromazine) – anticholinergic – dry mouth												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	4/29 (13.8%)	1/10 (10%)	RR 1.38 (0.17 to 10.93)	38 more per 1000 (from 83 fewer to 993 more)	VERY LOW	
Adverse effects: any serious or specific antiepileptics (chlorpromazine) – arousal – drowsy but asleep												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	1/29 (3.4%)	6/10 (60%)	RR 0.06 (0.01 to 0.42)	564 fewer per 1000 (from 348 fewer to 594	LOW	

										fewer)		
Adverse effects: any serious or specific antiepileptics (chlorpromazine) – arousal – drowsy but awake												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	12/29 (41.4%)	0/10 (0%)	RR 9.17 (0.59 to 142.1)	-	VERY LOW	
Adverse effects: any serious or specific antiepileptics (chlorpromazine) – cardiovascular – hypotension												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	3/44 (6.8%)	3/25 (12%)	RR 0.59 (0.1 to 3.33)	49 fewer per 1000 (from 108 fewer to 280 more)	LOW	
Adverse effects: any serious or specific antiepileptics (chlorpromazine) – central nervous system – seizures												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/15 (0%)	1/15 (6.7%)	RR 0.33 (0.01 to 7.58)	45 fewer per 1000 (from 66 fewer to 439 more)	VERY LOW	
Adverse effects: any serious or specific antiepileptics (chlorpromazine) – movement disorders – extrapyramidal adverse effects												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	6/44 (13.6%)	1/25 (4%)	RR 2.07 (0.28 to 15.15)	43 more per 1000 (from 29 fewer to 566 more)	LOW	
Adverse effects: 1. General and serious (olanzapine) – one or more drug-related adverse effects												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	1/24 (4.2%)	1/25 (4%)	RR 1.04 (0.07 to 15.73)	2 more per 1000 (from 37 fewer to 589 more)	LOW	
Adverse effects: 1. General and serious (olanzapine) – treatment emergent adverse events – all												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	7/24 (29.2%)	9/25 (36%)	RR 0.81 (0.36 to 1.83)	68 fewer per 1000 (from 230 fewer to 299 more)	LOW	

Adverse effects: 1. General and serious (olanzapine) – overall serious adverse effects												
1	randomised trials					none	0/25 (0%)	0/24 (0%)	not pooled	not pooled		
Adverse effects: 1. General and serious (olanzapine) – death												
1	randomised trials					none	0/24 (0%)	0/25 (0%)	not pooled	not pooled		
Adverse effects: 1. General (perphenazine) – one or more adverse effect												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	10/23 (43.5%)	7/21 (33.3%)	RR 1.3 (0.61 to 2.8)	100 more per 1000 (from 130 fewer to 600 more)	LOW	
Adverse effects: 1. General (perphenazine) – clinically significant laboratory changes												
1	randomised trials					none	0/23 (0%)	0/21 (0%)	not pooled	not pooled		
Adverse effects: 1. General (ziprasidone) – one or more drug-related adverse effects – by 72 hours												
3	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[4]	none	195/345 (56.5%)	125/394 (31.7%)	RR 1.69 (1.23 to 2.33)	219 more per 1000 (from 73 more to 422 more)	VERY LOW	
Adverse effects: 1. General (ziprasidone) – severe adverse effect – by 72 hours												
1	randomised trials	[1]				none	0/187 (0%)	0/189 (0%)	not pooled	not pooled		
Adverse effects: 1. General (ziprasidone) – one or more drug-related adverse effects – by 7 days												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	25/42 (59.5%)	41/90 (45.6%)	RR 1.31 (0.93 to 1.83)	141 more per 1000 (from 32 fewer to 378 more)	LOW	

Adverse effects: 1. General (loxapine) – one or more drug-related adverse effect												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	8/15 (53.3%)	10/15 (66.7%)	RR 0.8 (0.44 to 1.45)	133 fewer per 1000 (from 373 fewer to 300 more)	LOW	
Adverse effects: 1. General – one or more adverse effects (thiothixene)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	24/39 (61.5%)	14/35 (40%)	RR 1.42 (0.97 to 2.09)	168 more per 1000 (from 12 fewer to 436 more)	LOW	

[1] Risk of bias generally unclear and funded by manufacturer.
[2] High and significant I squared value.
[3] Risk of bias generally unclear and funding not reported.
[4] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[5] Very small sample with wide CIs crossing the line of no effect.

1.2.1.11 IM HAL + IM antihistamine (promethazine) versus HAL

Quality assessment							**Number of patients**		**Effect**		**Quality**	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IM HAL + antihistamine**	**HAL**	**Relative (95% CI)**	**Absolute**		
Tranquil or asleep: 1. Not tranquil or asleep – by 20 minutes												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	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)	LOW	
Tranquil or asleep: 1. Not tranquil or asleep – by 40 minutes												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34/160 (21.3%)	40/156 (25.6%)	RR 0.83 (0.56 to 1.24)	44 fewer per 1000 (from 113 fewer to 62 more)	LOW	

Tranquil or asleep: 1. Not tranquil or asleep – by 1 hour											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24/160 (15%)	31/156 (19.9%)	RR 0.75 (0.46 to 1.23)	50 fewer per 1000 (from 107 fewer to 46 more)	LOW
Tranquil or asleep: 1. Not tranquil or asleep – by 2 hours											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/160 (10.6%)	30/156 (19.2%)	RR 0.55 (0.32 to 0.96)	87 fewer per 1000 (from 8 fewer to 131 fewer)	LOW
Tranquil or asleep: 3. Not asleep – by 20 minutes											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	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)	LOW
Tranquil or asleep: 3. Not asleep – by 40 minutes											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	106/160 (66.3%)	104/156 (66.7%)	RR 0.99 (0.85 to 1.16)	7 fewer per 1000 (from 100 fewer to 107 more)	LOW
Tranquil or asleep: 3. Not asleep – by 1 hour											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	86/160 (53.8%)	81/156 (51.9%)	RR 1.04 (0.84 to 1.28)	21 more per 1000 (from 83 fewer to 145 more)	LOW
Tranquil or asleep: 3. Not asleep – by 2 hours											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	66/160 (41.3%)	64/156 (41%)	RR 1.01 (0.77 to 1.31)	4 more per 1000 (from 94 fewer to 127 more)	LOW
Adverse effects: 1. Any serious adverse effect – by 24 hours											
1	randomised	serious[1]	no serious	no serious	serious[2]	none	1/153	11/145	RR 0.09 (0.01	69 fewer per 1000 (from 26 fewer to 75	

	trials		inconsistency	indirectness			(0.65%)	(7.6%)	to 0.66)	fewer)	LOW	
Adverse effects: 2. Acute dystonia – by 24 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/153 (0%)	10/145 (6.9%)	RR 0.05 (0 to 0.76)	66 fewer per 1000 (from 17 fewer to 69 fewer)	LOW	
Adverse effects: 3. Seizure – by 24 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/153 (0.65%)	1/145 (0.69%)	RR 0.95 (0.06 to 15.01)	0 fewer per 1000 (from 6 fewer to 97 more)	LOW	
Global effect: 1. Additional tranquillising drugs – by 2 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	5/157 (3.2%)	11/154 (7.1%)	RR 0.45 (0.16 to 1.25)	39 fewer per 1000 (from 60 fewer to 18 more)	LOW	
Global effect: 5. Other episode of aggression – within 24 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25/154 (16.2%)	20/144 (13.9%)	RR 1.17 (0.68 to 2.01)	24 more per 1000 (from 44 fewer to 140 more)	LOW	

[1] Risk of bias generally unclear and funding not reported.

[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

1.2.1.12 IM HAL + IM antihistamine (promethazine) versus IM olanzapine

Quality assessment							Number of patients		Effect		Quality	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IM HAL + antihistamine**	**IM olanzapine**	**Relative (95% CI)**	**Absolute**		
Tranquil or asleep: 1. Not tranquil or asleep – by 15 minutes												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	14/150 (9.3%)	19/150 (12.7%)	RR 0.74 (0.38 to 1.41)	33 fewer per 1000 (from 79 fewer to 52 more)	LOW	
Tranquil or asleep: 1. Not tranquil or asleep – by 30 minutes												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	6/150 (4%)	10/150 (6.7%)	RR 0.6 (0.22 to 1.61)	27 fewer per 1000 (from 52 fewer to 41 more)	LOW	
Tranquil or asleep: 1. Not tranquil or asleep – by 1 hour												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1/150 (0.67%)	9/150 (6%)	RR 0.11 (0.01 to 0.87)	53 fewer per 1000 (from 8 fewer to 59 fewer)	LOW	
Tranquil or asleep: 1. Not tranquil or asleep – by 2 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	4/150 (2.7%)	9/150 (6%)	RR 0.44 (0.14 to 1.41)	34 fewer per 1000 (from 52 fewer to 25 more)	LOW	
Tranquil or asleep: 1. Not tranquil or asleep – by 4 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	5/150 (3.3%)	6/150 (4%)	RR 0.83 (0.26 to 2.67)	7 fewer per 1000 (from 30 fewer to 67 more)	LOW	

Tranquil or asleep: 3. Not asleep – by 15 minutes											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	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)	LOW	
Tranquil or asleep: 3. Not asleep – by 30 minutes											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	36/150 (24%)	55/150 (36.7%)	RR 0.65 (0.46 to 0.93)	128 fewer per 1000 (from 26 fewer to 198 fewer)	LOW	
Tranquil or asleep: 3. Not asleep – by 1 hour											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	30/150 (20%)	51/150 (34%)	RR 0.59 (0.4 to 0.87)	139 fewer per 1000 (from 44 fewer to 204 fewer)	LOW	
Tranquil or asleep: 3. Not asleep – by 2 hours											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	14/150 (9.3%)	59/150 (39.3%)	RR 0.24 (0.14 to 0.41)	299 fewer per 1000 (from 232 fewer to 338 fewer)	LOW	
Tranquil or asleep: 3. Not asleep – by 4 hours											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	38/150 (25.3%)	62/150 (41.3%)	RR 0.61 (0.44 to 0.86)	161 fewer per 1000 (from 58 fewer to 231 fewer)	LOW	
Tranquil or asleep: 5. Never tranquil or asleep during first 4 hours											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1/150 (0.67%)	4/150 (2.7%)	RR 0.25 (0.03 to 2.21)	20 fewer per 1000 (from 26 fewer to 32 more)	LOW	

Adverse effects: 1. Serious adverse effect – by 4 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1/150 (0.67%)	3/150 (2%)	RR 0.33 (0.04 to 3.17)	13 fewer per 1000 (from 19 fewer to 43 more)	LOW	
Adverse effects: 1. Serious adverse effect – at 2 weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/150 (0%)	1/150 (0.67%)	RR 0.33 (0.01 to 8.12)	4 fewer per 1000 (from 7 fewer to 47 more)	LOW	
Adverse effects: 2. Extrapyramidal problems – 0-4 hours – any change in scale-rated extrapyramidal problems (Simpson-Angus Scale)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/150 (0%)	0/150 (0%)	See comment	-	LOW	
Global effect: 1. Requiring additional drugs during initial phase – by 4 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	31/150 (20.7%)	65/150 (43.3%)	RR 0.48 (0.33 to 0.69)	225 fewer per 1000 (from 134 fewer to 290 fewer)	LOW	
Global effect: 2. Not clinically improved – by 15 minutes												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	41/150 (27.3%)	52/150 (34.7%)	RR 0.79 (0.56 to 1.11)	73 fewer per 1000 (from 153 fewer to 38 more)	LOW	
Global effect: 2. Not clinically improved – by 30 minutes												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	23/150 (15.3%)	40/150 (26.7%)	RR 0.57 (0.36 to 0.91)	115 fewer per 1000 (from 24 fewer to 171 fewer)	LOW	
Global effect: 2. Not clinically improved – by 1 hour												
1	randomised	serious[1]	no serious	no serious	serious[3]	none	12/150	30/150	RR 0.4 (0.21	120 fewer per 1000 (from 50 fewer to		

	trials		inconsistency	indirectness			(8%)	(20%)	to 0.75)	158 fewer)	LOW	
Global effect: 2. Not clinically improved – by 2 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	14/150 (9.3%)	32/150 (21.3%)	RR 0.44 (0.24 to 0.79)	119 fewer per 1000 (from 45 fewer to 162 fewer)	LOW	
Global effect: 2. Not clinically improved – by 4 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	9/150 (6%)	19/150 (12.7%)	RR 0.47 (0.22 to 1.01)	67 fewer per 1000 (from 99 fewer to 1 more)	LOW	
Global effect: 5. Further observation after 4 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	42/150 (28%)	36/150 (24%)	RR 1.17 (0.8 to 1.71)	41 more per 1000 (from 48 fewer to 170 more)	LOW	

[1] Risk of bias generally high or unclear and funding not reported.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) met but CIs cross line of no effect.
[3] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

1.2.1.13 IM olanzapine versus IM placebo

Quality assessment							**Number of patients**		**Effect**		**Quality**	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IM olanzapine**	**IM placebo**	**Relative (95% CI)**	**Absolute**		
Global effect: 1. Did not respond – by 2 hours												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	242/607 (39.9%)	157/241 (65.1%)	RR 0.65 (0.47 to 0.9)	228 fewer per 1000 (from 65 fewer to 345 fewer)	MODERATE	

Behaviour: 2. Requiring further IM injection – by 24 hours												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	139/460 (30.2%)	113/199 (56.8%)	RR 0.54 (0.45 to 0.65)	261 fewer per 1000 (from 199 fewer to 312 fewer)	LOW	
Behaviour: 3. Requiring additional benzodiazepines – within 24 hours												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33/316 (10.4%)	37/104 (35.6%)	RR 0.3 (0.15 to 0.6)	249 fewer per 1000 (from 142 fewer to 302 fewer)	LOW	
Adverse event: 1. Any adverse event – in 24 hours												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	51/161 (31.7%)	21/112 (18.8%)	RR 1.56 (1 to 2.43)	105 more per 1000 (from 0 more to 268 more)	LOW	
Adverse event: 2. Anxiety – by 24 hours												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	0/185 (0%)	3/50 (6%)	RR 0.04 (0 to 0.75)	58 fewer per 1000 (from 15 fewer to 60 fewer)	LOW	
Adverse event: 3. EPS – requiring anticholinergic medication – by 24 hours												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15/415 (3.6%)	5/155 (3.2%)	RR 1.26 (0.49 to 3.26)	8 more per 1000 (from 16 fewer to 73 more)	LOW	
Adverse event: 4. Serious adverse event – by 24 hours												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/378 (0.53%)	0/160 (0%)	RR 0.96 (0.1 to 9.15)	-	LOW	

[1] Risk of bias generally unclear and funded by manufacturer.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Risk of bias generally unclear and funding not reported.

1.2.1.14 IM olanzapine versus IM AP

Quality assessment							Number of patients		Effect		Quality	
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IM olanzapine	IM AP	Relative (95% CI)	Absolute		
Global effect: Did not respond – by 2 hours (≥40% change on PANSS-EC)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	97/316 (30.7%)	49/166 (29.5%)	RR 1.02 (0.67 to 1.55)	6 more per 1000 (from 97 fewer to 162 more)	LOW	
Behaviour: 1. Leaving the study – by 24 hours												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/131 (6.9%)	10/126 (7.9%)	RR 0.87 (0.36 to 2.06)	10 fewer per 1000 (from 51 fewer to 84 more)	LOW	
Behaviour: 2. Requiring additional IM injection – by 24 hours												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	93/316 (29.4%)	46/166 (27.7%)	RR 1.01 (0.63 to 1.61)	3 more per 1000 (from 103 fewer to 169 more)	LOW	
Behaviour: 3. Requiring additional benzodiazepines – by 24 hours												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33/316 (10.4%)	25/166 (15.1%)	RR 1.31 (0.24 to 7.21)	47 more per 1000 (from 114 fewer to 935 more)	LOW	
Adverse event: 1b. EPS – requiring anticholinergic medication – by 24 hours												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/316 (2.2%)	29/166 (17.5%)	RR 0.19 (0.09 to 0.43)	142 fewer per 1000 (from 100 fewer to 159 fewer)	LOW	
Adverse event: 1c. EPS – dystonia – by 24 hours												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/316 (0%)	11/166 (6.6%)	RR 0.05 (0.01 to 0.37)	63 fewer per 1000 (from 42 fewer to 66 fewer)	LOW	

Adverse event: 1d. EPS – general EPS – extrapyramidal syndrome												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/131 (0.76%)	7/126 (5.6%)	RR 0.14 (0.02 to 1.1)	48 fewer per 1000 (from 54 fewer to 6 more)	LOW	
Adverse event: 2. Serious adverse event												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/340 (0.59%)	2/191 (1%)	RR 0.54 (0.08 to 3.64)	5 fewer per 1000 (from 10 fewer to 28 more)	LOW	

[1] Risk of bias generally unclear and funded by manufacturer.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.

1.2.1.15 Inhaled loxapine versus placebo

Quality assessment							Number of patients		Effect		Quality	
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Inhaled loxapine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Global impression: 1. Mild to marked agitation at 2 hours post dose (ACES) – 5 mg												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	39/104 (37.5%)	75/105 (71.4%)	RR 0.52 (0.4 to 0.69)	343 fewer per 1000 (from 221 fewer to 429 fewer)	LOW	
Global impression: 1. Mild to marked agitation at 2 hours post dose (ACES) – 10 mg												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28/105 (26.7%)	75/105 (71.4%)	RR 0.37 (0.27 to 0.52)	450 fewer per 1000 (from 343 fewer to 521 fewer)	LOW	
Global impression: 2. Non-response (Clinical Global Impressions – Improvement) – 5 mg												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	108/265 (40.8%)	184/263 (70%)	RR 0.59 (0.47 to 0.74)	287 fewer per 1000 (from 182 fewer to 371	LOW	

										fewer)		
Global impression: 2. Non-response (Clinical Global Impressions – Improvement) – 10 mg												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	79/257 (30.7%)	184/263 (70%)	RR 0.44 (0.35 to 0.56)	392 fewer per 1000 (from 308 fewer to 455 fewer)	LOW	
Global impression: 3. Deep sleep (ACES) – 5 mg												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/104 (9.6%)	2/105 (1.9%)	RR 5.05 (1.13 to 22.48)	77 more per 1000 (from 2 more to 409 more)	LOW	
Global impression: 3. Deep sleep (ACES) – 10 mg												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/105 (12.4%)	2/105 (1.9%)	RR 6.5 (1.5 to 28.1)	105 more per 1000 (from 10 more to 516 more)	LOW	
Global impression: 4. Unarousable (ACES) – 5 mg												
2	randomised trials					none	0/220 (0%)	0/220 (0%)	not pooled	not pooled		
Global impression: 4. Unarousable (ACES) – 10 mg												
2	randomised trials					none	0/217 (0%)	0/220 (0%)	not pooled	not pooled		
Global impression: 5. Need for rescue medication at 4 hours – 5 mg												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	2/45 (4.4%)	3/43 (7%)	RR 0.64 (0.11 to 3.63)	25 fewer per 1000 (from 62 fewer to 183 more)	LOW	
Global impression: 5. Need for rescue medication at 4 hours – 10 mg												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	0/41 (0%)	3/43 (7%)	RR 0.15 (0.01 to 2.81)	59 fewer per 1000 (from 69 fewer to 126 more)	LOW	

Global impression: 5. Need for rescue medication at 24 hours – 5 mg											
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	5/45 (11.1%)	14/43 (32.6%)	RR 0.34 (0.13 to 0.87)	215 fewer per 1000 (from 42 fewer to 283 fewer)	LOW	
Global impression: 5. Need for rescue medication at 24 hours – 10 mg											
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	6/41 (14.6%)	14/43 (32.6%)	RR 0.45 (0.19 to 1.06)	179 fewer per 1000 (from 264 fewer to 20 more)	LOW	
Adverse event: 1. At least 1 antiepileptic – 5 mg											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	90/265 (34%)	82/263 (31.2%)	RR 1.09 (0.77 to 1.54)	28 more per 1000 (from 72 fewer to 168 more)	LOW	
Adverse event: 1. At least 1 antiepileptic – 10 mg											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	89/259 (34.4%)	82/263 (31.2%)	RR 1.1 (0.86 to 1.4)	31 more per 1000 (from 44 fewer to 125 more)	LOW	
Adverse event: 2. TEAE in ≥ 5% of patients – 5 mg versus placebo – dizziness											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/265 (6.4%)	23/263 (8.7%)	RR 0.74 (0.4 to 1.36)	23 fewer per 1000 (from 52 fewer to 31 more)	LOW	
Adverse event: 2. TEAE in ≥ 5% of patients – 5 mg versus placebo – dysgeusia (distortion or bad taste)											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30/265 (11.3%)	13/263 (4.9%)	RR 1.99 (0.71 to 5.57)	49 more per 1000 (from 14 fewer to 226 more)	LOW	
Adverse event: 2. TEAE in ≥ 5% of patients – 5 mg versus placebo – headache											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/265 (3.4%)	26/263 (9.9%)	RR 0.4 (0.14 to 1.14)	59 fewer per 1000 (from 85 fewer to 14 more)	LOW	

Adverse event: 2. TEAE in ≥ 5% of patients – 5 mg versus placebo – sedation											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28/265 (10.6%)	20/263 (7.6%)	RR 1.35 (0.78 to 2.34)	27 more per 1000 (from 17 fewer to 102 more)	LOW
Adverse event: 2. TEAE in ≥ 5% of patients – 10 mg versus placebo – dizziness											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/259 (7.3%)	23/263 (8.7%)	RR 0.85 (0.47 to 1.53)	13 fewer per 1000 (from 46 fewer to 46 more)	LOW
Adverse event: 2. TEAE in ≥ 5% of patients – 10 mg versus placebo – dysgeusia (distortion or bad taste)											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37/259 (14.3%)	13/263 (4.9%)	RR 2.81 (1.53 to 5.18)	89 more per 1000 (from 26 more to 207 more)	LOW
Adverse event: 2. TEAE in ≥ 5% of patients – 10 mg versus placebo – headache											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/259 (2.7%)	26/263 (9.9%)	RR 0.32 (0.1 to 1.04)	67 fewer per 1000 (from 89 fewer to 4 more)	LOW
Adverse event: 2. TEAE in ≥ 5% of patients – 10 mg versus placebo – sedation											
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27/259 (10.4%)	20/263 (7.6%)	RR 1.37 (0.8 to 2.38)	28 more per 1000 (from 15 fewer to 105 more)	LOW

[1] Risk of bias generally unclear and funding not reported.
[2] Optimal information size (for dichotomous outcomes, OIS = 300 events; for continuous outcomes, OIS = 400 participants) not met.
[3] Risk of bias generally unclear or high and funded by manufacturer.