

Appendix A. Literature Search Strategies and Yields

Published Literature

Table A1. PubMed Original Search, 7/23/15. Limited to date range of 1/1/1990 – present.

Search Query	Items found
#1 Search ("Substance-Related Disorders"[Mesh] OR ("Mental Disorders"[MeSH] OR "Mood Disorders"[Mesh] OR "Schizophrenia and Disorders with Psychotic Features"[Mesh] OR Depression[Mesh] OR ("Depressive Disorder, Major"[Mesh]) OR "Anxiety Disorders"[Mesh]) OR "Eating Disorders"[Mesh] OR "Personality Disorders"[Mesh] OR ((severe OR serious OR persistent) mental illness[Text Word]))	1050558
#2 Search ("Aggression"[Mesh] OR "Violence"[Mesh] OR ("Psychomotor Agitation"[Mesh]) OR "Hostility"[Mesh] OR "Crisis Intervention"[Mesh] OR "Restraint, Physical"[Mesh] OR "Patient Isolation"[Mesh])	122256
#3 Search ("Antipsychotic Agents"[MeSH Terms] OR "Antipsychotic Agents"[nm]) OR "Valproic Acid"[Mesh] OR "Droperidol"[Mesh] OR "Promethazine"[Mesh] OR "Trazodone"[Mesh] OR "Amitriptyline"[Mesh] OR "Chlormethiazole"[Mesh] OR "Citalopram"[Mesh] OR "Chlorpromazine"[Mesh] OR "topiramate" [Supplementary Concept] OR "Diphenhydramine"[Mesh] OR "Carbamazepine"[Mesh] OR "Pindolol"[Mesh] OR "Lithium Carbonate"[Mesh] OR "Hydroxyzine"[Mesh] OR "Nadolol"[Mesh] OR "Sertraline"[Mesh] OR "Diazepam"[Mesh] OR "lurasidone" [Supplementary Concept] OR "Metoprolol"[Mesh] OR "Lorazepam"[Mesh] OR "iloperidone" [Supplementary Concept])	127794
#4 Search (#2 OR #3)	246849
#5 Search #1 AND #4	84055
#6 Search (((("Hospitals, General"[Mesh]) OR "Emergency Service, Hospital"[Mesh] OR ("Hospitals, Psychiatric"[Mesh] OR "Psychiatric Department, Hospital"[Mesh]) OR "Inpatients"[Mesh] OR hospitalization [mesh]))	250345
#7 Search #5 AND #6	5805
#8 Search (((("Comparative Effectiveness Research"[Mesh] OR "Comparative Study" [Publication Type] OR "Pragmatic Clinical Trials as Topic"[Mesh]) OR comparison OR comparator OR comparative))	2352489
#9 Search (#7 AND #8)	1121
#12 Search (#7 AND #8) Filters: Publication date from 1990/01/01; Humans; English	844
#13 Search ("Crisis Intervention"[Majr] OR "Restraint, Physical"[Majr] OR "Patient Isolation"[Majr])	8503
#14 Search (#1 AND #6 AND #13)	605
#17 Search (#1 AND #6 AND #13) Filters: Publication date from 1990/01/01; Humans; English	363
#19 Search #5 AND #6 Filters: Clinical Trial; Randomized Controlled Trial	714
#24 Search (#12 OR #17 OR #19) Filters: Publication date from 1990/01/01; Humans; English	1452
#25 Search ("Restraint, Physical"[Mesh] OR "Patient Isolation"[Mesh]) Filters:Publication date from 1990/01/01; Humans; English	4669
#27 Search (#3 AND #25) Filters: Publication date from 1990/01/01; Humans; English	134
#29 Search (#1 AND #6 AND #27) Filters: Publication date from 1990/01/01; Humans; English	40
#32 Search ("Tranquilizing Agents/administration and dosage"[MAJR])	3614
#37 Search (#1 AND #2 AND #6 AND #32) Filters: Publication date from 1990/01/01; Humans; English	17
#41 Search (#12 OR #17 OR #19 OR #29 OR #37)) Filters: Publication date from 1990/01/01; Humans; English	1471

Table A2. Cochrane Original Library Search for Reviews, 7/23/15. No limits based on publication date.

ID	Search	Hits
#1	[(serious OR severe OR persistent) mental illness] AND ["crisis intervention" OR violence OR aggression OR agitation OR hostility OR "physical restraint" OR "isolation" OR "antipsychotic"] AND [comparative OR comparison] AND [hospitalization OR hospital OR "emergency department"]	18

Table A3. Cochrane Original Library Search for Clinical Trials, 7/23/15. No limits based on publication date.

ID	Search	Hits
#1	[(serious OR severe OR persistent) mental illness] AND ["crisis intervention" OR violence OR aggression OR agitation OR hostility OR "physical restraint" OR "isolation" OR "antipsychotic"] AND [comparative OR comparison] AND [hospitalization OR hospital OR "emergency department"]	8

Table A4. CINAHL Original Search, 7/23/15. No limits based on publication date.

ID	Search	Hits
#1	[(serious OR severe OR persistent) mental illness] AND ["crisis intervention" OR violence OR aggression OR agitation OR hostility OR "physical restraint" OR "isolation" OR "antipsychotic"] AND [comparative OR comparison] AND [hospitalization OR hospital OR "emergency department"]	5

Table A5. PsycINFO Original Search, 7/23/15. No limits based on publication date.

ID	Search	Hits
#1	[(serious OR severe OR persistent) mental illness] AND ["crisis intervention" OR violence OR aggression OR agitation OR hostility OR "physical restraint" OR "isolation" OR "antipsychotic"] AND [comparative OR comparison] AND [hospitalization OR hospital OR "emergency department"]	21

Table A6. EMBASE Original Search, 7/23/15. No limits based on publication date.

ID	Search	Hits
#1	[(serious OR severe OR persistent) mental illness] AND ["crisis intervention" OR violence OR aggression OR agitation OR hostility OR "physical restraint" OR "isolation" OR "antipsychotic"] AND [comparative OR comparison] AND [hospitalization OR hospital OR "emergency department"]	88

Gray Literature

Table A7. Academic Search Premier, Original Search, 7/23/15. No limits based on publication date.

ID	Search	Hits
#1	[(serious OR severe OR persistent) mental illness] AND ["crisis intervention" OR violence OR aggression OR agitation OR hostility OR "physical restraint" OR "isolation" OR "antipsychotic"] AND [comparative OR comparison] AND [hospitalization OR hospital OR "emergency department"]	30

Table A8. ClinicalTrials.gov, Original Search, 7/23/15. No limits based on publication date.

ID	Search	Hits
#1	[(serious OR severe OR persistent) mental illness] AND ["crisis intervention" OR violence OR aggression OR agitation OR hostility OR "physical restraint" OR "isolation" OR "antipsychotic"] AND [comparative OR comparison] AND [hospitalization OR hospital OR "emergency department"]	1

Table A9. NIH RePORTer, Original Search, 7/23/15. No limits based on publication date.

ID	Search	Hits
#1	[(serious OR severe OR persistent) mental illness] AND ["crisis intervention" OR violence OR aggression OR agitation OR hostility OR "physical restraint" OR "isolation" OR "antipsychotic"] AND [comparative OR comparison] AND [hospitalization OR hospital OR "emergency department"]	1

Table A10. WHOLIS, Original Search, 7/23/15. No limits based on publication date.

ID	Search	Hits
#1	[(serious OR severe OR persistent) mental illness] AND ["crisis intervention" OR violence OR aggression OR agitation OR hostility OR "physical restraint" OR "isolation" OR "antipsychotic"] AND [comparative OR comparison] AND [hospitalization OR hospital OR "emergency department"]	0

Appendix B: Exclusions

- X1: Non-English
- X2: Ineligible publication type
- X3: Ineligible study design
- X4: Ineligible population
- X5: Ineligible or no intervention
- X6: Ineligible or no comparator(s)
- X7: Ineligible or no outcome(s)
- X8: Ineligible timing
- X9: Ineligible clinical setting(s)
- X10: Ineligible geographic setting
- X11: No KQs addressed
- X12: Sample size <100 (nonrandomized studies only)

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| <p>1. Rapid tranquillisation for agitated patients in emergency psychiatric rooms: a randomised trial of midazolam versus haloperidol plus promethazine. <i>BMJ</i>. 2003 Sep 27;327(7417):708-13. PMID: 14512476. Exclusion Code: X4</p> <p>2. Taking the first step. <i>Schizophr Bull</i>. 2010 Sep;36(5):895-9. PMID: 20554784. Exclusion Code: X2</p> <p>3. Agid O, Kapur S, Warrington L, et al. Early onset of antipsychotic response in the treatment of acutely agitated patients with psychotic disorders. <i>Schizophr Res</i>. 2008 Jul;102(1-3):241-8. PMID: 18495436. Exclusion Code: X7</p> <p>4. Alexander J, Tharyan P, Adams C, et al. Rapid tranquillisation of violent or agitated patients in a psychiatric emergency setting. Pragmatic randomised trial of intramuscular lorazepam v. haloperidol plus promethazine. <i>Br J Psychiatry</i>. 2004 Jul;185:63-9. PMID: 15231557. Exclusion Code: X7</p> <p>5. Alexander M. Violence in the emergency department: a firsthand account. <i>J Emerg Nurs</i>. 2001 Jun;27(3):279-85. PMID: 11387566. Exclusion Code: X3</p> <p>6. Ali A, Hassiotis A. Managing the violent patient. <i>Br J Hosp Med (Lond)</i>. 2006 Aug;67(8):M142-4. PMID: 16918097. Exclusion Code: X2</p> <p>7. Allan ER, Alpert M, Sison CE, et al. Adjunctive nadolol in the treatment of acutely aggressive schizophrenic patients. <i>J Clin Psychiatry</i>. 1996 Oct;57(10):455-9. PMID: 8909331. Exclusion Code: X3</p> | <p>8. Allen MH. The organization of psychiatric emergency services and related differences in restraint practices. <i>Gen Hosp Psychiatry</i>. 2007 Nov-Dec;29(6):467-9. PMID: 18022037. Exclusion Code: X2</p> <p>9. Altenor A. Seclusion and restraints. <i>Psychiatr Serv</i>. 2000 Oct;51(10):1318. PMID: 11013340. Exclusion Code: X2</p> <p>10. Ashcraft L, Anthony W. Eliminating seclusion and restraint in recovery-oriented crisis services. <i>Psychiatr Serv</i>. 2008 Oct;59(10):1198-202. PMID: 18832507. Exclusion Code: X4</p> <p>11. Battaglia J, Moss S, Rush J, et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. <i>Am J Emerg Med</i>. 1997 Jul;15(4):335-40. PMID: 9217519. Exclusion Code: X7</p> <p>12. Belgamwar RB, Fenton M. Olanzapine IM or velotab for acutely disturbed/agitated people with suspected serious mental illnesses. <i>Cochrane Database of Syst Rev</i>. 2009(4). Exclusion Code: X6</p> <p>13. Bellus SB, Vergo JG, Kost PP, et al. Behavioral rehabilitation and the reduction of aggressive and self-injurious behaviors with cognitively impaired, chronic psychiatric inpatients. <i>Psychiatr Q</i>. 1999 Spring;70(1):27-37. PMID: 9924730. Exclusion Code: X8</p> |
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Appendix C. Risk of Bias Ratings

We provide our detailed risk of bias (ROB) ratings and the questions used to assign ratings below. ROB rating information for randomized controlled trials is presented in Tables C1 through C4, while ROB rating information for our one eligible cohort study is shown in Tables C6 through 7, which has three parts.

Table C1. Risk of bias assessments for RCTs, part 1

Author, Year Trial Name (if applicable)	Type of randomization	Eligibility criteria clearly described?	Method of randomization method appropriate?	Allocation concealment adequate?	Patients blind to treatment assignment	Outcome assessors blind to txmt assignment?	Care providers blind to txmt assignment?	Any variation from study protocol?	Groups recruited over same time period?
Isbister et al., 2010 ¹	Parallel	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Abderhalden et al., 2008 ²	Cluster	Yes	Yes	Yes	Unclear	No	No	No	Yes
Dorevitch et al., 2008 ³	Parallel	Yes	No	Unclear	Yes	Yes	Unclear	No	Yes
Putkonen et al., 2013 ⁴	Cluster	Yes	Unclear	No Data	No	Unclear	No	No Data	Yes
Georgieva et al., 2013 ⁵	Parallel	Yes	Unclear	Unclear	Unclear	Yes	No	No	Yes
van de Sande et al., 2011 ⁶	Cluster	Yes	Yes	Yes	Unclear	No	No	No	Yes
Currier et al., 2004 ⁷	Parallel	Yes	Unclear	Yes	Unclear	Yes	Unclear	No	Yes

txmt = treatment

Table C2. Risk of bias assessments for RCTs, part 2

Author, Year	Baseline chx similar? If not similar, did design or analyses account for this?	Intervention s adequately described?	Intervention fidelity adequate?	Cross-overs or contamination raising concern for bias?	KQ 1 Primary Outcomes: Valid and reliable measures consistently used for all participants?	KQ 1 Secondary Outcomes: Valid and reliable measures consistently used for all participants?	KQ 1: Benefits outcome data clearly reported without discrepancies?
Isbister et al., 2010 ¹	No, and design/analyses did not account for differences	Yes	Unclear	No	Yes	Yes	Yes
Abderhalden et al., 2008 ²	No, and design/analyses did not account for differences	Yes	No	Unclear	Yes	Yes	Yes
Dorevitch et al., 2008 ³	Unclear	Yes	Yes	No	Yes	NA	Yes
Putkonen et al., 2013 ⁴	No data	Yes	No Data	No Data	Yes	NA	Yes
Georgjeva et al., 2013 ⁵	Yes, similar characteristics	Yes	Unclear	Unclear	Yes	Yes	Yes
van de Sande et al., 2011 ⁶	No, but design/analyses accounted for differences	Yes	Unclear	Yes	Yes	Yes	Yes
Currier et al., 2004 ⁷	Yes, similar characteristics	Yes	NA	No	Yes	Yes	Yes

Chx = characteristics; KQ = Key Question; NA = not applicable.

Table C3. Risk of bias assessments for RCTs, part 3

Author, Year	KQ 2 Harms: Valid and reliable measures consistently used for all participants?	KQ 2: Harms outcome data clearly reported without discrepancies?	Important outcomes pre-specified? If yes, reported?	Overall attrition?	Differential attrition?	Differential ($\geq 15\%$) or overall high attrition (generally $\geq 20\%$) raising concern for bias?
Putkonen et al., 2013 ⁴	Yes	Unclear	Yes	No Data	No Data	No Data
Abderhalden et al., 2008 ²	NA	NA	Yes	0%	0%	No
Dorevitch et al., 2008 ³	NA	NA	Yes	0%	0%	No
Georgieva et al., 2013 ⁵	NA	NA	Yes	0%	0%	No
Isbister et al., 2010 ¹	Yes	Yes	Yes	13%	11.3% (droperidol vs. droperidol plus midazolam); 6.9% (droperidol vs. midazolam); 4.4% (droperidol vs. midazolam)	No
van de Sande et al., 2011 ⁶	NA	NA	Yes	0%	0%	No
Currier et al., 2004 ⁷	Unclear	Yes	Yes	20.4%	5.2%	Yes

KQ = Key Question; NA = not applicable; vs. = versus

Table C4. Risk of bias assessments for RCTs, part 4

Author, Year	Appropriate statistical method for missing data?	If multicenter study, accounted for in analysis?	Potential confounders and modifying variables taken into account in design and/or analysis?	Other potential sources of bias?	ROB	Rationale for ROB Rating
Putkonen et al., 2013 ⁴	No Data	NA	Yes	No	Medium	To avoid unbalanced comparisons, intervention and control wards were stratified by use of seclusion and restraint. One senior psychiatrist, not associated with the study, made all pharmacological decisions in both wards. The unit of randomization was the hospital ward; as such, there was no blinding of treatment allocation. It was unclear, though probable, that the outcome examiners knew which ward the patient came from (or if the ward had been randomized to 6 Core Strategies) based on health records. There was minimal control of confounding.
Abderhalden et al., 2008 ²	Unclear	NA	No	No	Medium	At baseline, rates of aggression were higher in intervention wards; unclear if interventions were implemented because of risk assessment. Because the unit of randomization was the hospital ward, raters were not blinded to treatment allocation across multiple psychiatric hospitals. There were fewer patients with schizophrenia in the preference group but all other characteristics were similar between groups. There was no reporting of attrition or intervention fidelity. Authors did not describe how wards from multiple hospitals were handled in analyses. No control for confounding.
Dorevitch et al., 2008 ³	NA	NA	No	No	Medium	The study was very small (N=28). Unclear whether important sociodemographic variables differed between the two arms (no demographic or other clinical parameters were described); no control of potential confounders between two arms. The authors don't report on treatment fidelity or contamination, but it is unlikely to be a large concern given the study's small size. Authors don't provide info on attrition, but it seems unlikely to be a problem given the population and setting.

Table C4. Risk of bias assessments for RCTs, part 4 (continued)

Author, Year	Appropriate statistical method for missing data?	If multicenter study, accounted for in analysis?	Potential confounders and modifying variables taken into account in design and/or analysis?	Other potential sources of bias?	ROB	Rationale for ROB Rating
Georgieva et al., 2013 ⁵	NA	NA	No	No	High	The authors did not provide any details about randomization procedures, and clinicians on unit were not clearly blinded from patient assignments to the intervention arm. Data on the use of restrictive measures were extracted from the hospital database, but it is unclear who did the extracting and if s/he was blind to the randomization. Could not collect reliable data on the number of aggressive incidents in each arm. Authors didn't appear to take into account repeated measures, nor did they report results for only first admission, even though 21% of patients were repeat patients. Unclear whether confounders were controlled for; all presented results are unadjusted. Nearly three-quarters of the patients in Group 1 (first-choice involuntary medication) were also secluded, suggesting contamination.
Isbister et al., 2010 ¹	Unclear	NA	Yes		Medium	There were potential confounding variables not addressed in the analysis (e.g., gender). The effect of additional sedation (when needed) in the ITT sample vs. the completers sample receiving only their randomized medication was not described. Unclear how the physical restraints required with medication administration affected outcomes of interest. Unclear how missing data were handled.
van de Sande et al., 2011 ⁶	Unclear	NA	Yes	No	Medium	There was a risk of rater bias because same nurses who used Crisis Monitor scale as part of intervention also evaluated aggression and seclusion outcomes. The authors state potential risk of contamination, but they make a case that notification of control ward nurses by intervention ward nurses likely did not impact outcome. Analysis controlled for potentially confounding measures.

Table C4. Risk of bias assessments for RCTs, part 4 (continued)

Author, Year	Appropriate statistical method for missing data?	If multicenter study, accounted for in analysis?	Potential confounders and modifying variables taken into account in design and/or analysis?	Other potential sources of bias?	ROB	Rationale for ROB Rating
Currier et al., 2004 ⁷	Yes	Unclear	Yes	Yes	Medium	Potential residual confounding from occurrence of aggressive incident within week preceding enrollment (56% of sample), although lack of baseline differences in OAS scores may be sufficient as a proxy for this. No indication if completers analysis results differed from those of ITT analyses. Unclear if clinicians delivering medications were blind to randomization. No description of randomization or information on fidelity. There was no multi-site approach to analyses.

ITT = intent-to-treat; N = number of patients; NA = not applicable; OAS = Overt Aggression Scale; ROB, risk of bias; vs. = versus

Table C5. Risk of bias assessments for observational studies and nonrandomized controlled trials, part 1

Author, Year Trial Name (if applicable)	Study Design	Eligibility criteria clearly described?	Eligibility criteria measured with valid and reliable measures, consistently across all participants?	Strategy for recruiting participant s different across groups?	Sample size sufficient to detect meaningfully significant differences?	Intervention s adequately described?	Important outcomes pre- specified? If yes, reported?	Comparison group selection appropriate? ^a	Any attempt to balance patient allocation between groups?	Impacts from concurrent interventions or unintended exposures that might bias results ruled out?
Michaud et al., 2014 ⁸	Cohort (retrospec tive)	Yes	Unclear	No	Yes	No	Yes	Yes	No	No

^a After taking into account feasibility and ethical considerations.

Table C6. Risk of bias assessments for observational studies and nonrandomized controlled trials, part 2

Author, Year Trial Name (if applicable)	Study Design	Outcome assessors blind to txmt or exposure status?	Interventions/exposures assessed using valid and reliable measures, consistently across all participants?	Follow-up length sufficient to support benefits/harms evaluation?	Overall attrition?	Differential attrition?	Differential (≥15%) or overall high attrition (generally ≥20%) raising concern for bias?
Michaud et al., 2014 ⁸	Cohort (retrospecti ve)	No	Unclear	Yes	0%	0%	No

txmt = treatment

Table C7. Risk of bias assessments for observational studies and nonrandomized controlled trials, part 3

Author, Year Trial Name (if applicable)	Study Design	Confounding and/or effect modifying variables assessed using valid and reliable measures, consistently across all participants?	KQ 1: Appropriate statistical methods used for assessing primary benefit outcomes?	KQ 2: Appropriate statistical methods used for assessing harms outcomes?	Any impt information about primary outcomes missing?	ROB	Rationale for ROB Rating
Michaud et al., 2014 ⁸	Cohort (retrospective)	Unclear	Yes	Yes	No	High	Unclear how many patients did not receive screen. Medication dosing is unknown. There was no control for differences in concomitant medication use between arms; no control for confounding in primary analyses. Unclear if/how restraint assessment was consistently applied. Study was powered to detect a 20% difference in primary outcome. There were no major differences between groups except a much higher percentage of hypervigilance documented in the treatment group. More than half of patients with at least 1 positive delirium score were not enrolled (mostly due to lack of mechanical ventilation, some due to missing data), which has the potential to bias the results.

impt = important; KQ = Key Question; ROB = risk of bias

References

Appendix D. Strength of Evidence Grade Tables

Evidence Table D1. KQ 1a – Risk assessment intervention studies: Primary outcomes

Outcome Category	Outcome	N of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence ^c
Aggressive behavior	N of aggressive patients	1 RCT ⁶ (n = 170 during baseline period, 458 during intervention period)	Medium	Unknown, single study	Direct	Imprecise	Insufficient
	N or aggressive incidents	1 RCT ⁶ (n = 170 during baseline period, 458 during intervention period)	Medium	Unknown, single study	Direct	Precise	Low
	Mean rate of aggressive incidents per 100 treatment days (SOAS score ≥9)	1 RCT ² (n = 973 post-intervention)	Medium	Unknown, single study	Direct	Precise	Low
	Change in physical attacks ^a	1 RCT ² (n = 973 post-intervention)	Medium	Unknown, single study	Direct	Precise	Low
Use of seclusion or restraints	N of seclusion patients	1 RCT ⁶ (n = 170 during baseline period, 458 during intervention period)	Medium	Unknown, single study	Direct	Imprecise	Insufficient
	N of secluded incidents	1 RCT ⁶ (n = 170 during baseline period, 458 during intervention period)	Medium	Unknown, single study	Direct	Imprecise	Insufficient
	Hours in seclusion in hours	1 RCT ⁶ (n = 170 during baseline period, 458 during intervention period)	Medium	Unknown, single study	Direct	Precise	Low
	Change in coercion incidents ^b	1 RCT ² (n = 973 post-intervention)	Medium	Unknown, single study	Indirect	Precise	Low

^a Physical attacks were defined as aggressive incidents in which the SOAS-R description met both of the following criteria: (1) means of aggression involved objects, dangerous objects, or parts of the body, and (2) the target of aggression was a person other than the patient him or herself.

^b Coercive measures covered a wide range of measures, from forced injection of psychotropic medication to seclusion and mechanical restraint.

^c Based on the comparisons, we graded the SOE as low for both the aggression and restraint and seclusion outcomes due to differential operationalization across studies; this precluded a direct comparison.

^c Imprecise due to failure to control for clustering related to statistical analyses

Abbreviations: n, or N. = number; RCT = randomized controlled trial; SOAS = Staff Observation Aggression Scale; SOAS-R = Staff Observation Aggression Scale-Revised; SOE = strength of evidence

Evidence Table D2. KQ 1a – Multi-modal intervention studies: Primary outcomes

Outcome Category	Outcome	N of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence
Aggressive behavior	Number of violent incidents	1 RCT ⁴ (n = NR)	Medium	N/A	Indirect	Imprecise	Insufficient
Use of Seclusion and Restraints	Percentage change in patient-days with seclusion, restraints, or room observation (per 1000 patient-days) ^a	1 RCT ⁴ (n = NR)	Medium	N/A	Direct	Precise	Low
	Duration of seclusion or restraint use (per 1000 patient-days) in hours	1 RCT ⁴ (n = NR)	Medium	N/A	Direct	Precise	Low

^a For "stabilized" intervention period July to December 2009; first six months of intervention not recorded.

Abbreviations: n or N = number; NR = not reported; RCT = randomized controlled trial

Evidence Table D3. KQ 1b – Medication protocols: Primary outcomes

Outcome Category	Outcome	N of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence
Aggressive behavior	Rate of reduction in total OAS severity scores	1 RCT ³ (n = 28)	Medium	Single study	Direct	Imprecise	Insufficient
	Mean change from baseline in OAS Aggression severity scores ^a	1 RCT ⁷ (n = 162)	Medium	Single study	Direct	Imprecise	Insufficient
	Mean change from baseline in OAS Total Aggression severity scores ^b	1 RCT ⁷ (n = 162)	Medium	Single study	Direct	Imprecise	Insufficient
	Violent and acute behavioral disturbance, mean duration	1 RCT ¹ (n = 91)	Medium	Single study	Direct	Imprecise	Insufficient

^a OAS Aggression: sum of the weighted scores for the most severe behavior in each of the OAS' 4 categories.⁷

^b OAS Total Aggression: sum of the weighted scores for the most severe behavior in each of the OAS' 4 categories plus the score for the most restrictive intervention required.⁷

Abbreviations: n or N = number of patients; No. = number; NR = not reported; OAS = Overt Aggression Scale; RCT = randomized controlled trial

Evidence Table D4. KQ 1c – Medication protocols: Primary outcomes

Outcome Category	Outcome	N of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence
Use of seclusion or restraints	Seclusion incidents (per 1000 admission days)	1 RCT ⁵ (n = 659)	High	Single study	Direct	Precise	Insufficient
	Seclusion hours, total number	1 RCT ⁵ (n = 659)	High	Single study	Direct	Imprecise	Insufficient
	Seclusion, mean duration of incidents in hours	1 RCT ⁵ (n = 659)	High	Single study	Direct	Imprecise	Insufficient
	Mechanical restraint incidents (per 1000 admission days)	1 RCT ⁵ (n = 659)	High	Single study	Direct	Imprecise	Insufficient
	Mechanical restraint duration	1 RCT ⁸ (n = 200)	High	Single study	Direct	Precise	Insufficient
	Coercion incidents (individual or combined) (per 1000 admission days) ^a	1 RCT ⁵ (n = 659)	High	Single study	Direct	Imprecise	Insufficient

^a “Coercion” refers to a sequence of coercive episodes (seclusion, mechanical restraint, or involuntary medication) for less than 24 hours.⁵

^b Details about the involuntary medications used were NR.

Abbreviations: n or N = number of patients; NR = not reported; RCT = randomized controlled trial

Evidence Table D5. KQ 2b – Medication protocols: Adverse events or harms

Outcome Category	Outcome	N of Studies (Subjects)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence
Staff injuries	Staff injuries	1 RCT ¹ (n=91)	Medium	Single study	Direct	Imprecise	Insufficient
Medication side effects	Overall, medication-related side effects (droperidol vs. midazolam vs. combination)	1 RCT ¹ (n=91)	Medium	Single study	Direct	Imprecise	Insufficient
	Abnormal QT interval	1 RCT ¹ (n=91)	Medium	Single study	Direct	Imprecise	Insufficient
	Acute extrapyramidal effects	1 RCT ³ (n=28)	Medium	Single study	Direct	Imprecise	Insufficient
	Marked sedation	1 RCT ³ (n=28)	Medium	Single study	Direct	Imprecise	Insufficient
	Treatment-related adverse events	1 RCT ⁷ (n=162)	Medium	Single study	Direct	Imprecise	Insufficient

^a Measured with mean heart rate and blood pressure

^b Measured with BAS and SAS scores

Abbreviations: n or N = number of patients; QT = Q and T wave; RCT = randomized controlled trial

References for Appendix D

Appendix E. Detailed Study Characteristics Tables

Table E1. Detailed study characteristics: Staff training interventions

Author, Year	N of patients ^a			Funding Source	Brief summary of population (summarize relevant inclusion criteria)	Age: mean (SD)	Psychiatric diagnoses (%)	Mean (SD) severity of psychiatric symptomatology
Study Design	Duration of nonpharmacologic interventions for patients	Duration of entire study from baseline through follow-up	Intervention(s) and Comparator(s)			Percent female		
Clinical Setting, Country								
Trial (if named)								
Bowers et al., 2006 ⁹ Single-group pre-post study Acute admission psychiatric wards (n=14) (private or public status NR), U.K.	NR	NR One year	G1: Nurse intervention G2: Before intervention	Foundation/non-profit	Multiethnic, highly deprived, acute admission patients to psychiatric wards	NR	NR	NR
Chang et al., 2014 ¹⁰ Single-group pre-post study Locked acute care unit in a psychiatric hospital (private or public status NR), U.S.	NR (provided over course of patients' inpatient stays)	NR 32 weeks	G1: Recovery-oriented cognitive therapy (CT-R) staff training program (16 weeks) G2: Before intervention (16 weeks)	NR	Adult inpatients with a psychotic disorder	NR	Presumably 100% with psychosis ^b	NR

^a Describes the entire study from baseline through post-intervention or longer-term follow-up.

^b Study's inpatient unit was for individuals with psychotic disorders.¹⁰CT-R = Recovery-oriented cognitive therapy training; G = group or condition; N = number of patients; NR = not reported; SD = standard deviation; U.K. = United Kingdom.

Table E2. Detailed study characteristics: Risk assessment interventions

Author, Year	N of patients ^a		Intervention(s) and Comparator(s)	Funding Source	Brief summary of population of population (summarize relevant inclusion criteria)	Age: mean (SD)		Psychiatric diagnoses (%)	Mean (SD) severity of psychiatric symptomatology
Study Design	Duration of nonpharmacologic interventions for patients	Duration of entire study from baseline through follow-up				Percent female	Percent non-white		
Clinical Setting, Country									
Trial (if named)									
Abderhalden et al., 2008 ²	12 weeks	879 (baseline) and 973 (intervention) ^b	G1: Structured Risk Assessment: Structured short-term risk assessment for every new patient twice a day during the first 3 days of hospitalization	Government	Adult patients between 18 and 65 years of age, most of which had an acute psychiatric disorder	Age Overall: 39.5 (14.2) ^c G1: 39.0 (13.1) G2: 38.0 (14.3)	Organic, including symptomatic, mental disorders: Overall: 3.3 ^c G1: 3.8 G2: 4.3	NR	
RCT (cluster)	Total days in treatment Baseline (3 months) G1: 6,074 G2: 8,449 Intervention (3 months) G1: 7,727 G2: 10,485	92 weeks	G2: No intervention			Percent female Overall: 46.6 ^c G1: 45.6 G2: 44.8	Disorders due to psychoactive substance use Overall: 24.3 ^c G1: 26.2 G2: 24.2		
Psychiatric inpatient treatment facilities (private or public status NR), Switzerland						Percent non-white: NR	Schizophrenia, schizotypal and delusional disorders Overall: 31.0 ^c G1: 33.4 G2: 35.7 Mood (affective) disorders Overall: 16.2 ^c G1: 15.5 G3: 15.3 Neurotic, stress-related and somatoform disorders, behavioral syndromes associated with physiological disturbances and physical factors Overall: 14.3 ^c G1: 14.3 G3: 11.5		

Table E2. Detailed study characteristics: Risk assessment interventions (continued)

Author, Year	N of patients ^a	Duration of nonpharmacologic interventions for patients	Intervention(s) and Comparator(s)	Funding Source	Brief summary of population of population (summarize relevant inclusion criteria)	Age: mean (SD)	Percent female	Percent non-white	Psychiatric diagnoses (%)	Mean (SD) severity of psychiatric symptomatology
Study Design	Duration of entire study from baseline through follow-up									
Clinical Setting, Country										
Trial (if named)										
									Personality disorders of adult personality and behavior Overall: 3.2 ^c G1: 4.0 G3: 5.0 Others ^d Overall: 2.8 ^c G1: 2.7 G3: 4.1 Missing Overall: 4.9 ^c G1: NR G2: NR	

Table E2. Detailed study characteristics: Risk assessment interventions (continued)

Author, Year	N of patients ^a		Intervention(s) and Comparator(s)	Funding Source	Brief summary of population of population relevant inclusion criteria)	Age: mean (SD)		Psychiatric diagnoses (%)	Mean (SD) severity of psychiatric symptomatology
Study Design	Duration of nonpharmacologic interventions for patients	Duration of entire study from baseline through follow-up				Percent female	Percent non-white		
Clinical Setting, Country									
Trial (if named)									
van de Sande et al., 2011 ⁶	30 weeks	170 (baseline period over 10 weeks);	G1: Structured Risk Assessment (30 weeks):	Government	Patients admitted to acute psychiatric wards	Mean age (SD) Overall: NR G1: 38 (13) G2: 40 (11)	Psychotic disorder Overall: NR G1: 59 G2: 51	NR	
RCT (cluster)		458 (intervention period over 30 weeks)	1) Daily risk assessments (5 minutes)			Percent female Overall: NR G1: 47 G2: 46	Personality disorders Overall: NR G1: 20 G2: 5		
Acute psychiatric wards, Netherlands		40 weeks	2) Weekly risk assessments (15 minutes)			Percent non-white Overall: NR G1: 31 G2: 16	Drug misuse first diagnosis Overall: NR G1: 3 G2: 3		
			G2: Usual care / Treatment as usual (30 weeks)						

^a Describes the entire study from baseline through post-intervention or longer-term follow-up.

^b Neither the baseline nor intervention period count includes patients admitted to the five wards that preferred to introduce the study protocol of structured risk assessment without randomization.²

^c In addition to arms presented in this table, overall mean based on information from five wards that preferred to introduce the study protocol of structured risk assessment without randomization.²

^d Other diagnoses included mental retardation, disorders of psychological development, behavioural and emotional disorders with onset occurring in childhood and adolescence.²

G = group; N = number; NR = not reported; NS = not significant; RCT = randomized controlled trial; SD = standard deviation.

Table E3. Detailed study characteristics: Multi-modal interventions

Author, Year	Duration of non-pharmacologic interventions for patients	N of patients ^a	Intervention(s) and Comparator(s)	Funding Source	Brief summary of population (summarize relevant inclusion criteria)	Age: mean (SD)	Psychiatric diagnoses (%)	Mean (SD) severity of psychiatric symptomatology
Study Design		Duration of entire study from baseline through follow-up				Percent female		
Clinical Setting, Country						Percent non-white		
Trial (if named)								
Currier et al., 2002 ¹¹	NR	NR	G1: HCFA One-hour rule: Assessment within one hour of initiation of S/R G2: Pre-intervention	NR	Three eligible psychiatric units in a University hospital, one unit medically ill chemical-abusing, second unit general adult, third is neurogeriatric	NR	NR	NR
Single-group pre-post study		6 months (3 months pre and 3 months post)						
Academic psychiatric hospital, U.S.								
D'Orio et al., 2004 ¹²	9 months	484	G1: Comprehensive Plan focusing on the early identification and management of problematic behaviors G2: Pre-intervention	NR	Walk-ins, brought by law enforcement, city jail, mobile crisis team – no other information provided	NR	Substance use disorders: 35 ^b Psychotic disorders: 25 ^b Unipolar mood disorders: 13 ^b Bipolar disorders: 11 ^b Adjustment disorders: 6 ^b Anxiety disorders: 2 ^b Other: 8 ^b	NR
Single-group pre-post study		18 months (9 months pre and 9 months post)						
Psychiatric emergency service, U.S.								

Table E3. Detailed study characteristics: Multi-modal interventions (continued)

Author, Year	Duration of non-pharmacologic interventions for patients	N of patients ^a Duration of entire study from baseline through follow-up	Intervention(s) and Comparator(s)	Funding Source	Brief summary of population (summarize relevant inclusion criteria)	Age: mean (SD) Percent female Percent non-white	Psychiatric diagnoses (%)	Mean (SD) severity of psychiatric symptomatology
Emmerson et al., 2007 ¹³	29 months	NR 29 months	G1: 4T Aggression Management Strategy G2: Pre-intervention	NR	NR, but of those with aggression, they were usually adult, male, manic, of no fixed abode, abusing amphetamines and had no previous psychiatric history; and admitted on weekend	NR	NR	NR
Single-group pre-post study Mental Health Services - part of Royal Brisbane and Women's Hospital, refers to wards, Australia								
Hellerstein et al., 2007 ¹⁴	268 weeks; 67 months which is closer to 290 weeks because more than 4 weeks in a month	NR 348 weeks (pre-intervention); 87 months or about 377 weeks (post-intervention)	G1: Hospital-wide, multicomponent intervention G2: Pre-intervention	NR	Adult patients admitted to the Washington Heights Community Service clinical unit and schizophrenia research unit for acute inpatient care, most with diagnoses of schizophrenia, schizoaffective disorders, and mood disorders, such as depression and bipolar disorder	Age: NR Percent female: G1: NR G2: 46 for WHCS unit, 33 for SRU unit Percent non-white: G1: NR G2: 88 for WHCS unit; 42 for SRU	NR, but "schizophrenia, schizoaffective, and mood disorders listed as most common"	NR
Single-group pre-post study (N ≥100) Public psychiatric hospital(s), U.S								

Table E3. Detailed study characteristics: Multi-modal interventions (continued)

Author, Year	N of patients ^a		Intervention(s) and Comparator(s)	Funding Source	Brief summary of population (summarize relevant inclusion criteria)	Age: mean (SD)	Psychiatric diagnoses (%)	Mean (SD) severity of psychiatric symptomatology
Study Design	Duration of non-pharmacologic interventions for patients	Duration of entire study from baseline through follow-up				Percent female		
Clinical Setting, Country								
Trial (if named)								
Jonikas et al., 2004 ¹⁵	18 months	NR	G1: Program to Reduce Restraints (15 months) G2: Before intervention (15 months)	Government	Majority had schizophrenia, other psychotic disorders or mood disorders, about half were white, about half were female, age NR	Age: NR	Schizophrenia or other psychotic disorders: 21% on general ward; 52% on research unit	NR
Single-group pre-post study		30 months				Percent female 57% on general ward; 46% on research unit		
Public university hospital, U.S.							Mood disorders: 79% on general ward; 43% on research unit	
Khadivi et al., 2004 ¹⁶	12 months	NR	G1: JCAHO standards (date NR) G2: Pre-intervention	NR	NR, patients in the hospital tend to be poor, are insured primarily through Medicaid or Medicare, tend to have severe and persistent mental illness, most often in the context of dual diagnosis, and are frequently admitted involuntarily	NR	NR	NR
Single-group pre-post study		12 months						
Private/academic psychiatric hospital(s), U.S.								

Table E3. Detailed study characteristics: Multi-modal interventions (continued)

Author, Year		N of patients ^a				Age: mean (SD)		
Study Design	Duration of non-pharmacologic interventions for patients	Duration of entire study from baseline through follow-up	Intervention(s) and Comparator(s)	Funding Source	Brief summary of population (summarize relevant inclusion criteria)	Percent female	Psychiatric diagnoses (%)	Mean (SD) severity of psychiatric symptomatology
Clinical Setting, Country						Percent non-white		
Trial (if named)								
Melson et al., 2014 ¹⁷	NA	462	G1: Alcohol Withdrawal Symptom Management Care Management Guideline G2: Pre-implementation of guideline	Internal funding only	Adult medical inpatients with alcohol withdrawal syndrome	NR	NR	NR
Single-group pre-post study		54 months (228 weeks)						
General medical hospital, U.S.								
Pollard et al., 2007 ¹⁸	18 months	NR	G1: JCAHO 2000 standards G2: Pre-intervention	Government	NR, but voluntary and involuntary patients in a secured, acute mental health unit	NR	NR	NR
Single-group pre-post study		18 months						
Public psychiatric hospital(s), U.S.								
Putkonen et al., 2013 ⁴	26 weeks	NR	G1: Six Core Strategies implementation G2: Usual care / Treatment as usual	Government	Adult male inpatients in high-security wards with psychotic illness and a history of violence	Age G1: 40.2 (10.6) G2: 38.4 (10.6)	Schizophrenia: NR 100	
RCT (cluster)		26 weeks						
Public psychiatric hospital(s), Finland						Percent female: 0 Percent non-white: NR		

Table E3. Detailed study characteristics: Multi-modal interventions (continued)

Author, Year	N of patients ^a				Brief summary of population of population (summarize relevant inclusion criteria)	Age: mean (SD)	Psychiatric diagnoses (%)	Mean (SD) severity of psychiatric symptomatology
Study Design	Duration of non-pharmacologic interventions for patients	Duration of entire study from baseline through follow-up	Intervention(s) and Comparator(s)	Funding Source		Percent female		
Clinical Setting, Country						Percent non-white		
Trial (if named)								
Taxis et al., 2002 ¹⁹	NR	NR	G1: Education, programmatic alterations to implement alternative strategies to S/R G2: Pre-intervention	NR	Adult patients in a psychiatric hospital— no other details	NR	NR	NR
Single-group pre-post study		45 months (3 months pre and 42 months post)						
Public (state) psychiatric facility, U.S.								

^a Total number of randomized or enrolled participants at baseline in relevant arms of trial.

^b Only overall sample means provided.

G = group; JCAHO = Joint Commission on Accreditation of Healthcare Organizations; N = overall number of patients; NR = not reported; SD = standard deviation; SRU = Schizophrenia Research Unit; U.S. = United States; WHCS = Washington Heights Community Service.

Table E4. Detailed study characteristics: Environmental interventions

Author, Year	N of patients ^a		Intervention(s) and Comparator(s)	Funding Source	Brief summary of population (summarize relevant inclusion criteria)	Age: mean (SD)		Psychiatric diagnoses (%)	Mean (SD) severity of psychiatric symptomatology	
Study Design	Duration of nonpharmacologic interventions for patients	Duration of entire study from baseline through follow-up				Percent female	Percent non-white			
Clinical Setting, Country										
Trial (if named)										
Vaaler et al., 2006 ^{20, 21}	At least 3 days (both closed-door and open-door PICU conditions)	118	G1: Segregation nursing in closed-door PICU (post-intervention) G2: Segregation nursing in open-door PICU (pre-intervention)	Academic (treating hospital)	Adult inpatients 18 years of age or older determined to be in need of PICU stay by physician on duty except those with dementia, mental retardation, severe autism, or not able to speak Norwegian or English	Age Overall: 37.0 (14.8) G1: 37.1 (15.9) G2: 36.8 (13.7)	Percent female Overall: 44.1 G1: 50 G2: 38.7	Organic mental disorders: Overall: 5.9 G1: 5.4 G2: 6.5 Substance-related disorders Overall: 19.5 G1: 19.6 G2: 19.4 Schizophrenia Overall: 38.1 G1: 39.3 G2: 37.1 Mood disorders Overall: 18.6 G1: 21.4 G2: 16.1 Other mental and behavioral disorders Overall: 17.8 G1: 14.3 G2: 21.0	PANSS Total: G1: 75.6 (21.2) G2: 72.4 (23.1) PANSS Positive: G1: 18.1 (8.1) G2: 17.3 (8.2) PANSS Negative G1: 18.7 (7.9) G2: 17.1 (8.5) PANSS General G1: 38.8 (9.3) G2: 38.0 (10.4) GAF-F G1: 32.2 (12.5) G2: 33.1 (12.7) GAF-S G1: 31.8 (13.9) G2: 31.8 (12.0) BVC G1: 0.95 (1.24) G2: 0.69 (1.15)	

^a Describes the entire study from baseline through post-intervention or longer-term follow-up.

BVC = Broset Violence Checklist; G = group; GAF-F = Global Assessment of Functioning, function score; GAF-S = Global Assessment of Functioning, symptom score; N = number; NR = not reported; PANSS = Positive and Negative Symptom Score; SD = standard deviation.

Table E5. Detailed study characteristics: Medication protocols

Author, Year							
Study Design	N of patients ^a	Intervention and Comparator Details (e.g., Medication Dose)	Funding Source	Age: mean (SD)		Total Sample Mean Baseline Severity of Psychiatric Symptomatology	Brief summary of population (summarize relevant inclusion criteria)
Clinical Setting, Country	Duration of study ^b			Percent female	Psychiatric diagnoses (%)		
Trial (if named)				Percent non-white			
Currier et al., 2004 ⁷	162	G1: Risperidone plus lorazepam: Oral, 2 mg risperidone + 2 mg lorazepam	Pharmaceutical company	Age G1: 39.7 (10.1) G2: 38.7 (12.3)	Paranoid schizophrenia G1: 31 G2: 35	Mean (SD) OAS Aggression Scores ^e G1: 2.5 (3.4) G2: 2.8 (3.5)	Adult emergency department patients and inpatients between 18 and 65 years of age
Emergency department, U.S.	28 weeks	G2: Haloperidol plus lorazepam: IM, 5 mg haloperidol + 2 mg lorazepam		Female G1: 33 G2: 38	Schizoaffective disorder G1: 22 G2: 23	OAS Aggression Scores, ^e Least-squares mean (SE) G1: 2.8 (3.5) G2: 2.5 (3.4) P = 0.346	exhibiting both psychosis and agitation (schizophrenia or schizoaffective disorder, mania with psychotic features, acute paranoid reaction, or delusional disorders; PANSS 5-item acute-agitation cluster score ≥ 14; CGI-S score ≥ 3)
RCT (parallel)				African American G1: 40 G2: 42	Bipolar I disorder, manic severe with psychotic features G1: 8 G2: 8	Mean (SD) OAS Total Aggression Scores ^f G1: 3.6 (4.2) G2: 3.4 (4.2) P = 0.443	
				Hispanic: G1: 12 G2: 15			
				Other G1: 1 G2: 5	Psychotic disorder, not otherwise specified G1: 17 G2: 22	Mean (SD) PANSS Total G1: 95.7 (17.5) G2: 97.0 (18.5) P = 0.63	
						Mean (SD) CGI-S Severity of Illness Score: % of patients with marked-to-severe disease (scores of 5-7) G1: 53 G2: 54 P = NR	

Table E5. Detailed study characteristics: Medication protocols (continued)

Author, Year							
Study Design	N of patients^a	Intervention and Comparator Details (e.g., Medication Dose)	Funding Source	Age: mean (SD)	Psychiatric diagnoses (%)	Total Sample Mean Baseline Severity of Psychiatric Symptomatology	Brief summary of population (summarize relevant inclusion criteria)
Clinical Setting, Country	Duration of study^b			Percent female Percent non-white			
Trial (if named)							
Dorevitch et al., 1999 ³	28	During aggressive event:	NR	Age G1: 36.8 (15.1) G2: 34.9 (8.1)	Schizophrenic & schizoaffective disorder G1: 92.3 G2: 93.3	BPRS G1: 49.0 (6.6) G2: 45.4 (6.7)	Adult inpatients between 20 and 60 years of age with active psychosis, disruptive or aggressive behavior, pronounced psychomotor agitation or violent outbursts, and hospitalization in an acute ward
Private/academic psychiatric hospital, Israel	90 mins	G1: Haloperidol (5 mg IM) G2: Flunitrazepam (1 mg IM)		Female G1: 61.5 G2: 46.7	Bipolar I disorder G1: 7.7 G2: 6.7	CGI G1: 4.5 (0.5) G2: 4.5 (0.7)	
RCT (parallel)				Non-white: NR			

Table E5. Detailed study characteristics: Medication protocols (continued)

Author, Year								
Study Design	N of patients^a	Intervention and Comparator Details (e.g., Medication Dose)	Funding Source	Age: mean (SD)	Percent female	Psychiatric diagnoses (%)	Total Sample Mean Baseline Severity of Psychiatric Symptomatology	Brief summary of population (summarize relevant inclusion criteria)
Clinical Setting, Country	Duration of study^b			Percent non-white				
Trial (if named)								
Georgieva et al., 2013 ⁵	659	Intervention of first choice for agitation and risk of violence	Government	Age G1: 40 (13) G2: 40 (12)		Psychotic disorder G1: 20 G2: 20	GAF Kennedy: G1: 58 (12) G2: 59 (13)	Adult patients admitted to acute wards in a psychiatric hospital, most with either addiction or a psychotic, mood, personality, or post-traumatic stress disorder
Psychiatric hospital (no other details reported), Netherlands	144 weeks	G1: Involuntary medication G2: Seclusion		Female G1: 52 G2: 47		Mood disorder G1: 31 G2: 32	PANSS (Uncooperativeness) G1: 2.6 (2.6) G2: 2.7 (1.6)	
RCT (parallel)				Non-Dutch ethnicity G1: 17 G2: 18		Personality disorder G1: 24 G2: 23 Addiction G1: 31 G2: 32 PTSD G1: 5 G2: 8	PANSS (Lack of judgment and insight): G1: 3.0 (1.4) G2: 3.0 (1.6)	

Table E5. Detailed study characteristics: Medication protocols (continued)

Author, Year								
Study Design	N of patients^a	Intervention and Comparator Details (e.g., Medication Dose)	Funding Source	Age: mean (SD)	Percent female	Psychiatric diagnoses (%)	Total Sample Mean Baseline Severity of Psychiatric Symptomatology	Brief summary of population (summarize relevant inclusion criteria)
Clinical Setting, Country	Duration of study^b			Percent non-white				
Trial (if named)								
Isbister et al., 2010 ¹	91	G1: Droperidol: 10 mg IM	Government	Age, mean (range) G1: 37 (25 to 45) G2: 35 (27 to 43) G3: 30 (22 to 40)		Alcohol intoxication G1: 70 G2: 76 G3: 66	NR	Adult patients presenting to the ED with violence and acute behavioral disturbance and requiring both physical restraint and parenteral sedation according to ED nursing or medical staff assessment
Public psychiatric hospital, Australia	6 hours	G2: Midazolam: 10 mg IM		Female G1: 64 G2: 38 G3: 48	Deliberate self-harm G1: 48 G2: 41 G3: 45			
RCT (parallel)		G3: Droperidol (5 mg IM) plus Midazolam (5 mg IM)		Non-white: NR	Drug-induced delirium G1: 6 G2: 10 G3: 10			
DORM					Acute psychosis G1: 6 G2: 3 G3: 6			
					Other G1: 3 G2: 0 G3: 3			

Table E5. Detailed study characteristics: Medication protocols (continued)

Author, Year							
Study Design	N of patients^a	Intervention and Comparator Details (e.g., Medication Dose)	Funding Source	Age: mean (SD)		Total Sample Mean Baseline Severity of Psychiatric Symptomatology	Brief summary of population (summarize relevant inclusion criteria)
Clinical Setting, Country	Duration of study^b			Percent female	Psychiatric diagnoses (%)		
Trial (if named)				Percent non-white			
Michaud et al., 2014 ⁸	200	G1: Delirium treatment within 24 hrs (n=102)	No funding	Age G1: 58 (17) G2: 62 (15)	NR	NR	Adults in an ICU with a documented positive delirium screen at time of mechanical ventilation
Public psychiatric hospital, U.S.	24 hrs	G2: No delirium treatment, or treatment after 24 hrs (n=98)		Female G1: 53 G2: 53			
Retrospective cohort study (N ≥100)				Non-white: NR			
Thapa et al., 2003 ²²	437	G1: After hospital-wide policy banning PRN medications	Foundation/non-profit, government	Age G1: 38 (11.5) G2: 35.5 (11)	<u>Axis I diagnoses</u> Psychosis G1: 40 G2: 46	NR	Newly admitted adults to psychiatric units
Public psychiatric hospital, U.S.	6 months	G2: Before hospital-wide policy banning PRN medication		Female G1: 55 G2: 53	Bipolar disorder G1: 9 ⁹ G2:		
Single-group pre-post study (N ≥100)				Non-white: G1: 31 G2: 30	Depressive disorder G1: 23 G2: 22 Substance abuse or dependence G1: 9 G2: 5 Other G1: 10 G2: 6		
					<u>Axis II diagnoses</u> Antisocial personality disorder G1: 8 G2: 9		

Author, Year		Study Design		Age: mean (SD)		Total Sample Mean Baseline Severity of Psychiatric Symptomatology	Brief summary of population (summarize relevant inclusion criteria)
Clinical Setting, Country	N of patients ^a Duration of study ^b	Intervention and Comparator Details (e.g., Medication Dose)	Funding Source	Percent female	Percent non-white		
Trial (if named)							
						Borderline personality disorder G1: 10 G2: 11 Cluster B traits G1: 6 G2: 8 Other Axis II diagnosis G1: 4 G2: 2 Mental retardation G1: 7 G2: 6 Overall G1: 69 G2: 70	

^a Total number of randomized or enrolled participants at baseline in relevant arms of trial.

^b Describes the entire study from baseline through post-intervention or longer-term follow-up.

^c OAS Aggression: sum of the weighted scores for the most severe behavior in each of the OAS' 4 categories.

^f OAS Total Aggression: sum of the weighted scores for the most severe behavior in each of the OAS' 4 categories plus the score for the most restrictive intervention required.

^g The percentage of patients with a diagnosis of bipolar disorder was not reported in the study article, the result of an unintentional omission. Also, the percentages of patients with different Axis I diagnoses do not add up to 100%, and the N of patients do not add up to the total N of included admissions (224), reflecting error(s) in reporting.²²

CGI-S = Clinical Global Impression-Severity scale; CI = confidence interval; G = group; GAF = General Assessment of Functioning scale; ICU = intensive care unit; IM = intramuscular; IV = intravenous; mg = milligram; mins = minutes; N = number; NR = not reported; OAS = Overt Aggression Scale; PANSS = Positive and Negative Symptom Score; PRN = pro re nata (as-needed); SD = standard deviation; SE = standard error.

References for Appendix E

Appendix F. Summary of Findings for Pre-Post Studies, Not rated for Risk of Bias

Intervention, Citation, Sample Size, Length of Followup	Population: Diagnosis Type, Country, Setting	Intervention: Components, Duration, Number of patients	Comparator: Duration, Number of patients	Outcomes: Benefits, Harms	Results
Staff training Bowers et al., 2006 ⁹ NR 12 months	Multiethnic, highly deprived, acute admission patients to psychiatric wards U.K., two psychiatric wards in a hospital (private or public NR)	Nurse-led intervention, months (n=NR) Components: Experienced psychiatric acute inpatient nurse delivered intervention; worked directly with unit staff 3 days per week to move toward low-conflict low-containment, high therapy nursing	Usual care, months (n=NR)	Conflict scores (overall, containment, verbal aggression physical aggression against self, physical aggression against others) Suicide attempts	All statistically significant decreases in benefit outcomes: overall conflict mean scores from 10.1 to 8.8 (p<0.001); verbal aggression (from 0.64 to 0.36 mean incidents per shift, p<0.001); physical aggression against self (0.03 to 0.01 mean incidents per shift, p=0.004); and physical aggression towards others (0.10 to 0.08 mean incidents per shift, p=0.002) No statistical change in suicide attempt rates following implementation of the intervention (0.004 to 0.003 mean incidents per shift, p=0.9)
Staff training Chang et al., 2014 ¹⁰ NR 8 months	Adult inpatients with a psychotic disorder U.S., psychiatric hospital	Recovery-oriented cognitive therapy staff training program, 4 months (n=NR)	Usual care, 4 months (n=NR)	Seclusion and restraint incidents	S/R incidents declined from 19 in the 4 months prior to the intervention to 7 in the 4 months after, no statistical analyses due to limited number of cases

Intervention, Citation, Sample Size, Length of Followup	Population: Diagnosis Type, Country, Setting	Intervention: Components, Duration, Number of patients	Comparator: Duration, Number of patients	Outcomes: Benefits, Harms	Results
Multimodal Currier et al., 2002 ¹¹ NR 6 months	Adult psychiatric inpatients U.S., three units (General Adult Unit, Chemical Abuse Unit, Neurogeriatric Unit) in an academic psychiatric hospital	HCFA One-hour rule, 3 months (n=NR) Components: Face-to-face assessment within one hour of initiation of S/R Shortened interval between mandatory renewal orders Required specific staff training More stringent requirements for documentation	Usual care, 3 months prior to intervention (n=NR)	Restraint use (episodes, duration) Injury to staff; Falls (on neurogeriatric unit)	General Adult Unit: Episodes of restraint decreased from 20 to 3, mean duration decreased from 8.6 to 8.3 hours Chemical Abuse Unit: Episodes of restraint increased from 15 to 22, Mean duration decreased from 11 to 8.3 hours Neurogeriatric Unit: Episodes of restraint decreased from 37 to 7, Mean duration decreased from 4.7 to 3.6 hours No increase in rate of injuries to staff by patients; Significant increase in number of patient falls without injury on neurogeriatric unit
Multimodal D'Orio et al., 2004 ¹² NR 18 months	Adult emergency service patients (35% substance use disorders, 25% psychotic disorders) U.S., psychiatric emergency service	Comprehensive Plan, 9 months (n=NR) Components: Implementation of a response team for behavioral emergencies (code team) Staff training in the preventive management of aggressive behavior with an emphasis on development of verbal de-escalation Implementation of modified versions of the Overt Agitation Severity and the Overt Aggression Scales to assist in patient risk assessment.	Usual care, 9 months prior to intervention (n=NR)	Seclusion and restraint use (episode and duration) NR	Mean episodes of seclusion and restraint per month decreased from 65 to 38, p<0.001

Intervention, Citation, Sample Size, Length of Followup	Population: Diagnosis Type, Country, Setting	Intervention: Components, Duration, Number of patients	Comparator: Duration, Number of patients	Outcomes: Benefits, Harms	Results
Multimodal Emmerson et al., 2007 ¹³ NR 43 months	Adult psychiatric inpatients Australia, public mental health hospital	4T Aggression Management Strategy, 24 months (n=NR) Team work: Human Error and Patient Safety Program (HEAPS) implemented; MD and unit manager identified patients at risk for aggression Training: Full-time aggression management trainer appointed; One day aggression management training for staff (83% completion) Treatment: New protocols instituted for prn medication and "rapid tranquilization" Tools: New risk screening tool employed; personal duress alarm system installed for staff; full-time occupational therapy assistant hired for each ward (HEAPS)	Usual care, 19 months prior to intervention (n=NR)	Aggressive behavior incidents Staff injuries, medication adverse effects	Average aggressive incidents per month decreased from 17 to 13. p<0.01); Total number of monthly staff injuries decreased from 4 to 2.33, p<0.01); No significant increase in sedation related adverse effects

Intervention, Citation, Sample Size, Length of Followup	Population: Diagnosis Type, Country, Setting	Intervention: Components, Duration, Number of patients	Comparator: Duration, Number of patients	Outcomes: Benefits, Harms	Results
Multimodal Hellerstein et al., 2007 ¹⁴ NR 87 months	Adult psychiatric inpatients U.S. Two units (Schizophrenia Research Unit, Community Service Unit) in public psychiatric hospital	Three-component intervention, 67 months, (n=NR) Policy change to limit S/R to 2 hours before a new order required Education of staff on identification of at risk patients and early intervention options Use of Coping Agreement questionnaire to assess patient preference for dealing with agitation	Usual care, 20 months prior to intervention (n=NR)	Restraint use (number of patients, duration, duration rate); seclusion use (number of patients, duration, duration rate) Patient related staff-injuries; patients involved in fights/month	Mean number of patients restrained per month decreased from 0.35 to 0.32, p NR Total hours of patients restrained/month decreased from 1.7 to 1.0, p NR Mean number of patients secluded per month decreased from 3.1 to 1.0, p<0.0001; Total hours patients secluded per month decreased from 41.6 to 2.7, p<0.003 Number of patient-related staff injuries/month decreased from 0.7 to 0.18, p=0.03; Number of patients involved in fights per month decreased from 0.5 to 0.3, p NR
Multimodal Jonikas, 2004 ¹⁵ NR 30 months	Adult psychiatric inpatients; majority with mood or psychotic disorder U.S. Two units (General Psychiatry, Clinical Research) of a university hospital	Two components to reduce restraints, 15 months (n=NR) Advance crisis management training to teach patients how to determine personal triggers and staff to collaboratively create individualized crisis management plans Nonviolent crisis intervention training (per Crisis Prevention Institute, Inc.) to teach staff to recognize factors precipitating crisis and management of aggressive behaviors	Usual care, 15 months prior to intervention (n=NR)	Restraint rate (patient hours per quarter) NR	General Psychiatry Unit: 85% decrease in restraint rate one quarter after both trainings; 99% decrease two quarters after both trainings Clinical Research Unit: 51% decrease in restraint rate in first quarter after crisis management training; 49% decrease in restraint rate in first quarter after crisis intervention training

Intervention, Citation, Sample Size, Length of Followup	Population: Diagnosis Type, Country, Setting	Intervention: Components, Duration, Number of patients	Comparator: Duration, Number of patients	Outcomes: Benefits, Harms	Results
Multimodal Khadivi et al., 2004 ¹⁶ NR 24 months	Adult psychiatric inpatients U.S. Large, inner city community hospital with academic affiliation	JCAHO standards, no date provided, 12 months (n=NR) Components: Staff education: focus on early recognition of agitation and early intervention Addition of history of inpatient violence to admission forms Continuous nursing monitoring to minimize duration of S/R episodes Post-episode debriefing of staff and patient, senior nurse and physician review of each episode	Usual care, 12 months prior to intervention (n=NR)	Seclusion and restraint (episodes) Assaults (staff, patients), self-destructive behavior	Episodes of seclusion and restraint decreased from 310 to 148, p<0.01 Assaults on staff increased from 31 to 83, p<0.01 Assaults on patients increased from 67 to 85, p<0.05 Self-destructive behavior decreased from 27 to 24, p=NR
Multimodal Melson, 2014 ¹⁷ 462 54 months	Adult inpatients U.S. General medical hospital	Alcohol withdrawal care management guideline, 12 months (n=NR)-AUDIT-PC added to all nursing assessments to screen for alcohol withdrawal risk If AUDIT-PC score 5 or higher, CIWA-Ar administered If CIWA-Ar score 8 or below patient monitored for symptoms If CIWA-Ar score 9 or greater treatment algorithm followed	Usual care, 9 months prior to intervention (n=NR)	Restraint use (in patients with DT) NR	Restraint use decreased from 60.4% to 44.4%, p=NS

Intervention, Citation, Sample Size, Length of Followup	Population: Diagnosis Type, Country, Setting	Intervention: Components, Duration, Number of patients	Comparator: Duration, Number of patients	Outcomes: Benefits, Harms	Results
Multimodal Pollard et al., 2007 ¹⁸	Adult psychiatric inpatients	JCAHO 2000 standards, 18 months (n=NR)	Usual care, 28 months prior to intervention (n=NR)	Seclusion and restraint hours (both per patient and overall hours), risk adjusted by acuity	Mean S/R hours decreased from 182 to 56, p<0.001
NR	U.S.	Facility policies and procedures updates to reflect expanded leadership involvement in S/R usage (including review of all episodes of restraint)		Critical incidents in 24 hours	Hours S/R per patient decreased from 8.6 to 2.7, p<0.001
46 months	Veteran's Administration Hospital (public psychiatric hospital)	Senior leadership commitment to a restraint free environment expressed through videotapes			Critical incidents in 24-hours decreased from a mean of 1.07 to 0.72, p=0.004
		Discussions with staff about alternatives to S/R, exploration of staff concerns			
		Positive feedback for use of alternative strategies			
		Committee to identify opportunities for improvement of care and patient safety			
		Review of performance data by clinical executive committee and leadership review of all episodes of behavioral restraints for appropriateness and documentation			

Intervention, Citation, Sample Size, Length of Followup	Population: Diagnosis Type, Country, Setting	Intervention: Components, Duration, Number of patients	Comparator: Duration, Number of patients	Outcomes: Benefits, Harms	Results
Multimodal Taxis et al., 2002 ¹⁹	Adult psychiatric inpatients	Comprehensive Change Program (7 components), 42 months (n=NR)	Usual care, 9 months prior to intervention (n=NR)	Seclusion and restraint incidents	94% decrease after implementation, p=NR; decreased rate sustained for one year
NR 45 months	U.S., public (state) psychiatric facility	Development of an assault program Expanded use of individual treatment planning Implementation of mandatory staff education on alternatives to S/R Patient empowerment education Environmental alterations Creation of a feedback loop around progress in reducing S/R Administrative and programmatic changes		NR	

Intervention, Citation, Sample Size, Length of Followup	Population: Diagnosis Type, Country, Setting	Intervention: Components, Duration, Number of patients	Comparator: Duration, Number of patients	Outcomes: Benefits, Harms	Results
Environmental Vaaler et al., 2006 ^{20, 21} 118 41 weeks (40 weeks 5 days, to be exact)	Adult psychiatric inpatients determined to be in need of PICU stay by physician on duty Norway, public psychiatric hospital	Segregation nursing in closed-door PICU, at least 3 days	Segregation nursing in open-door PICU, at least 3 days	Violent or threatening incidents (incidents, patients), change in aggression risk scores from baseline Mechanical restraint (incidents) Serious suicide attempts	Fewer patients with violent or threatening incidents in closed-door PICU than in open-door PICU (3 versus 10), but difference nonsignificant (unadjusted p=0.08) Significantly fewer violent or threatening incidents in closed-door PICU than in open-door PICU (3 versus 19) (adjusted p<0.05) ^a Change (reduction) in BVC aggression risk from baseline significantly greater in closed-door PICU than in open-door PICU (-0.61 versus -0.11) (adjusted p<0.05) No difference in incidents of mechanical restraint (2 in closed-door and open-door PICU) Single serious suicide attempt after implementation of closed-door PICU, but none in open-door PICU
Medication Protocol Thapa et al., 2003 ²² 437 6 months	Newly admitted adults to psychiatric units U.S., public psychiatric hospital	Hospital-wide policy banning PRN orders for psychotropic medications, 3 months (n=219)	Usual care, 3 months (n=218)	Restraint (incidents, duration), seclusion (incidents, duration) NR	Fewer incidents of restraint and seclusion after new policy, although the mean duration of seclusion was higher (13.1 versus 19.2 hours), but none of these observed differences were statistically significant.

^a P-value adjusted for BVC scores, physicians' prediction scores (0-4, with higher scores indicating increasing assumed probability of violent or threatening incidents), and diagnoses of schizophrenia or substance abuse disorder.^{20, 21}

AUDIT-PC = Alcohol Use Disorders Identification Test-Piccinelli Consumption; BVC = Broset Violence Checklist; CIWA-Ar = Clinical Institute Withdrawal Assessment of Alcohol Scale; JCAHO = Joint Commission on Accreditation of Healthcare Organizations; MD = physician; n = number of patients; NR = not reported; PICU = psychiatric intensive care unit; PRN = pro re nata (as-needed); S/R = seclusion/restraints; U.S. = United States

Appendix F References

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