Preventing and De-escalating Aggressive Behavior Among Adult Psychiatric Patients: A Systematic Review of the Evidence

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Objective: The project goal was to compare the effectiveness of strategies to prevent and de-escalate aggressive behaviors among psychiatric patients in acute care settings, including interventions for reducing use of seclusion and restraint.

Methods: Relevant databases were systematically reviewed for comparative studies of violence prevention and de-escalation strategies involving adult psychiatric patients in acute care settings. Studies (trials and cohort studies) were required to report on aggression or seclusion or restraint outcomes. Both risk of bias, an indicator of quality of individual studies, and strength of evidence (SOE) for each outcome were independently assessed by two study personnel.

Results: Seventeen primary studies met inclusion criteria. Evidence was limited for benefits and harms; information about characteristics that might modify the interventions' effectiveness, such as race or ethnicity, was especially limited. All but one study had a medium or high risk of bias and thus presented worrisome limitations. For prevention, risk assessment reduced both aggression and use of seclusion and restraint (low SOE), and multimodal interventions reduced the use of seclusion and restraint (low SOE). SOE for all other interventions, whether aimed at preventing or de-escalating aggression, and for modifying characteristics was insufficient.

Conclusions: Available evidence about strategies for preventing and de-escalating aggressive behavior among psychiatric patients is very limited. Two preventive strategies, risk assessment and multimodal interventions consistent with the Six Core Strategies principles, may effectively lower aggressive behavior and use of seclusion and restraint, but more research is needed on how best to prevent and de-escalate aggressive behavior in acute care settings.

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Aggressive behavior connotes using actual physical violence toward oneself, others, or property or making specific imminent verbal threats (1). In health care settings, approaches for de-escalating actively aggressive behavior have historically involved using either seclusion (involuntary placement of a patient in a locked room or area from which the patient is not allowed to leave) or restraint (involuntary administration of mechanical, pharmacologic, or physical interventions) (2,3). However, practice standards have moved toward less restrictive and more patient-centered approaches. Since the late 1990s, the Centers for Medicare and Medicaid Services (3) and the Joint Commission (4) have required that seclusion and restraint be used only for a behavior that "jeopardizes the immediate physical safety of the patient, a staff member, or others" (5) (including other patients) and only when less restrictive measures have failed.

Despite practice guidelines and quality-of-care measures that support reducing use of seclusion and restraint

(6,7), data in the United States and Europe show that 10% to 30% of patients (adolescents, adults, and elderly persons) admitted to acute psychiatric units receive these procedures (8–10). Thus much interest now focuses on using alternatives to seclusion and restraint. These strategies can address preventing aggressive behavior, reducing aggressive behavior once it has already developed, or both. Most alternatives are strongly influenced by the National Association of State Mental Health Program Directors' Six Core Strategies to prevent aggressive behavior, which include leadership toward organizational change, use of data to inform practice, workforce development, use of seclusion and restraint prevention tools, consumer roles in inpatient settings, and debriefing techniques (11).

Preventive strategies can be either multicomponent interventions that apply to all individuals (whether or not they are aggressive) or specific procedures aimed at persons who are at especially high risk of becoming aggressive. General

preventive strategies emphasize providing a calm environment in which aggression is less likely to develop; they usually focus on entire care units. They can include risk assessment (12); milieu-based changes, such as the use of sensory rooms (13); staffing changes, such as increased staff-to-patient ratios (14); specific staff training programs (15); and peer-based interventions (16).

Specific preventive strategies often try to intercede before the development of agitation, which is seen as a risk factor for becoming aggressive. These techniques can involve use of supportive (often referred to as nonconfrontational) language and other verbal de-escalation techniques, cognitive-behavioral techniques, pharmacologic intervention for treating the underlying psychiatric illness, and recognition of triggers for aggressive behavior. These preventive approaches can overlap; specific strategies may also be applied on a unitwide basis.

If patients become actively aggressive, clinicians can use seclusion with or without restraint, restraint by itself, or alternative strategies. In such cases, alternatives can include the use of emergency response teams (17,18). In addition, clinicians can employ pharmacologic interventions to reduce agitation quickly (rather than more gradually by treating the underlying illness).

The Evidence-Based Practice Center (EPC), under a contract with the Agency for Healthcare Research and Quality (AHRQ), conducted a systematic review of the effectiveness of strategies for preventing aggressive behavior, comparing the effectiveness of alternative strategies with each other or with the use of seclusion and restraint. As authors of the study, we conceptualized "de-escalate" in terms of both preventing aggressive behaviors and reducing use of seclusion and restraint. The focus of the review was on studies involving psychiatric patients who were hospitalized in acute health care settings with lengths of stay of fewer than 35 days. For this article, we included all acute care settings regardless of length of stay to make our findings applicable to settings that may have a longer length of study, such as state hospitals.

This article addressed four main issues for adult psychiatric patients in acute care settings. First, for those without aggressive behavior, what are the comparative benefits and harms of strategies to prevent aggressive behavior? Second, for those with active aggression, what are the comparative benefits and harms of strategies to de-escalate aggressive behavior? Third, for those with active aggression, what are the comparative benefits and harms of strategies to reduce the use of seclusion and restraint? Fourth, what characteristics, such as race and ethnicity, modify either benefits or harms of the strategies above to prevent or de-escalate aggressive behavior?

METHODS

We searched MEDLINE (via PubMed), Embase, the Cochrane Library, Academic Search Premier, PsycINFO, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) for studies from January 1, 1991, to February 3, 2016 (19). We also manually searched reference lists of pertinent reviews, trials

included in those reviews, and background articles to identify relevant citations that our searches might have missed. To find relevant gray literature, we followed guidance from the AHRQ's "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (20).

Our searches focused on comparative studies of de-escalation strategies (seclusion, restraint, or alternatives to seclusion or restraint) for adult patients with psychiatric disorders or severe psychiatric symptomatology who are at risk of, or present with, aggressive behavior across various acute care settings. Studies that limited populations to patients with dementia were ineligible. Studies that did not differentiate between results for patients with aggression and for those who were not currently aggressive were included in the prevention analyses.

For studies to be included, we required that interventions target reducing aggressive behavior or decreasing use of seclusion and restraint (or both). Eligible studies were required to have reported on at least one of our two primary outcomes: decreased aggression in terms of frequency, severity, or duration (measured by either direct counts or validated aggression scales) and reduced use of seclusion or restraint (decreased rate, amount, or duration). Investigators must have tested interventions in acute care settings (general hospitals, psychiatric hospitals, and emergency departments in these hospitals) with no limitations by length of stay. Studies were required to have had a control group, potentially allowing for causal inferences to be made. Randomized controlled trials (RCTs), cluster randomized controlled trials (CRTs), non-randomized controlled trials (NRCTs), and cohort studies were eligible, but pre-post designs were not. [The full eligibility criteria are available as an online supplement to this article.]

Two research team members independently reviewed all titles and abstracts against our inclusion and exclusion criteria. For potentially eligible abstracts, two investigators independently reviewed the full text to determine final inclusion or exclusion. To assess the risk of bias of included studies, we followed EPC methods guidance (21) and each investigator individually rated the risk of bias for each relevant outcome as low, medium, or high. Specifically, we used the Cochrane Risk of Bias tool to appraise RCTs and CRTs (where the cluster, or group, that was randomized was the unit in the facilities where the studies took place). To appraise the risk of bias in NRCTs and cohort studies, we employed criteria from the Research Triangle Institute Risk of Bias Tool for Observational Studies (22). To minimize risk of bias for addressing adverse outcomes, or harms—a key focus of the study—we required a minimum total sample of 100 patients for NRCTs and cohort studies, consistent with our work in prior reviews (23).

Two investigators independently graded the strength of evidence (SOE) for primary outcomes on the basis of guidance established by the EPC (24) for incorporating five key domains: study limitations (study design and aggregate risk of bias), consistency, directness (whether evidence links an intervention directly to a relevant health outcome), precision (including whether a study included the number of patients

required for an adequately powered individual trial [optimal information size, or OIS]) (25), and reporting bias.

RESULTS

Evidence Base

Searches of all sources identified a total of 1,983 potentially relevant citations [see online supplement]. Twenty-two studies that otherwise met selection criteria were deemed ineligible because of a pre-post design. We identified 17 eligible controlled studies (described in 22 articles) that provided data for this review; the studies included more than 3,628 participants, and the samples ranged in size from 20 to 973 participants (not all studies reported sample size) (26–47). Thirteen studies were randomized trials (eight RCTs and five CRTs), two were NRCTs, and two were retrospective cohort studies (Table 1). Nearly half took place in the United States; most interventions took place in public psychiatric hospitals or inpatient psychiatric treatment units or facilities. For studies reporting demographic characteristics for their patient populations, the mean age ranged primarily between 38 and 40 years, the distribution of men and women varied widely across studies, and race or ethnicity was sparsely reported.

There are no agreed-upon categories for stratifying violence prevention and de-escalation interventions, so we sorted the interventions described in the eligible studies into the following five broad categories on the basis of the intervention's main focus: staff training, risk assessment, multimodal programs, environmental or group psychotherapeutic interventions, and medication protocols. Table 2 describes the design of the eligible studies in each of the intervention categories.

Staff training interventions for clinical staff who provide acute care to patients with psychiatric symptomatology aim to equip staff with new skills or to promote staff attitudes that can help prevent or de-escalate aggression. Risk assessment interventions involve clinical staff's use of structured assessment of individual patients' risk of becoming actively aggressive. Multimodal programs involve a combination of various intervention types, such as enhanced administrative review of patients with high restraint use and staff training in strategies to better manage patients' difficult behavior; the goal of the programs is to decrease the occurrence of active aggression or use of seclusion or restraint for managing active aggression.

Environmental or group psychotherapeutic interventions involve changes to the physical environment of the acute care setting or the introduction of group psychotherapeutic interventions meant to diminish precursors of active aggression. Finally, medication protocols encompass any medication-focused intervention to de-escalate active aggression, ranging from hospital- or unitwide policies specifically affecting how or which medications can be used to manage active aggression to the use of one or more emergency medications. Key characteristics of the eligible studies are listed in Table 3 [see the online supplement for more details about the studies and their risk of bias assessments].

TABLE 1. Characteristics of 17 studies included in this literature review

Characteristic	N	%
Design		
Randomized controlled trial	8	47
Cluster randomized trial	5	29
Nonrandomized controlled trial	2	12
Retrospective cohort study	2	12
Comparison arm		
Active treatment	9	53
Usual care	8	47
Country		
United States	8	47
Other	9	53
Funding		
Government	5	29
Foundation or nonprofit	1	6
Pharmaceutical company	1	6
Multiple sources (pharmaceutical and government)	1	6
Multiple sources (foundation or nonprofit, treating hospital, and government)	1	6
No financial support	1	6
Not reported	7	41
Setting		
Public psychiatric hospital	6	35
Inpatient psychiatric treatment unit or facility[a]	5	29
Multiple settings (inpatient psychiatric or forensic hospitals)	1	6
General medical hospital	1	6
General emergency department	2	12
Psychiatric emergency department	2	12
Primary outcome[b]		
Aggression	13	77
Seclusion	5	29
Restraint	4	24
Seclusion and restraint	5	29
Harm	9	53
Risk of bias		
Low	1	6
Medium	9	53
High	7	41

[a] Further information about the studies' public, private, or academic status was not available.
[b] The number of studies listed exceeds 17 because multiple studies measured more than one primary outcome.

Overall SOE for Findings

The highest SOE grade for any outcome was low. The outcomes with low SOE involved two types of preventive interventions; two studies compared the benefits of risk assessment and one study compared the benefits of a multimodal intervention with usual care (Table 4). The SOE was insufficient for all other preventive interventions, for de-escalating interventions, and for modifying characteristics. For all ratings, the supporting evidence had medium risk of bias, had unknown consistency (because each finding was supported by a single study), was direct, and had precision. Of note, the CRTs in this

TABLE 2. Available evidence from 17 studies of interventions for preventing or de-escalating aggressive behavior, decreasing use of seclusion and restraint, and identifying variables that modify use of interventions, by type of intervention[a]

Intervention	Type of study	Prevention	De-escalation	De-escalation and reduction in seclusion or restraint	Modifying variables
Staff training					
Kontio et al., 2014 (29)	CRT			Benefits	
Smoot and Gonzales, 1995 (46)	CRT	Benefits and harms			
Risk assessment					
Abderhalden et al., 2008 (27)	CRT	Benefits			
Van de Sande, et al., 2011 (34)	CRT	Benefits			
Multimodal program					
Putkonen et al., 2013 (32)	CRT	Benefits			
Environmental or group psychotherapeutic intervention					
Carlson and Holm, 1993 (43)	Retrospective cohort			Benefits	
Nurenberg et al., 2015 (44)	RCT	Benefits			
Medication protocol					
Isbister et al., 2010 (26)	RCT		Benefits and harms		
Dorevitch et al., 1999 (28)	RCT		Benefits and harms		
Michaud et al., 2014 (31)	Retrospective cohort			Benefits	
Georgieva et al., 2013 (33)	RCT			Benefits	
Volavka et al., 2004 (35)	RCT		Benefits and harms		
Bieniek et al., 1998 (38)	RCT		Benefits and harms		
Krakowski et al., 2006 (39)	RCT		Benefits and harms		Harms
Villari et al., 2008 (42)	NRCT		Benefits and harms		
Richards et al., 1998 (45)	RCT		Benefits and harms		
Wilhelm et al., 2008 (47)	NRCT		Benefits and harms		

[a] Abbreviations: CRT, cluster randomized trial; NRCT, nonrandomized controlled trial; RCT, randomized controlled trial

review did not control for clustering in their statistical analyses, which weakened the SOE grade for those interventions.

Preventing Aggressive Behavior

Benefits. Two CRTs of risk assessment protocols provided evidence supporting benefits of this preventive approach compared with usual care; such protocols decreased subsequent aggressive incidents (27,34) (Table 4). One CRT reported a lower risk of severe aggressive incidents and a lower number of physical attacks (27); the other reported a decrease in the risk of any aggressive incident (34). Both outcomes had low SOE.

These studies also yielded evidence that risk assessment reduced subsequent use of seclusion and restraint. Compared with usual care units, units administering risk assessment reported use of significantly fewer coercive measures (involving a range of measures from forced injection of psychotropic medication to seclusion and restraint) (27) and reported that patients spent significantly fewer hours in seclusion (34). Both outcomes had low SOE.

A multimodal intervention based on the Six Core Strategies also had evidence supporting effectiveness in reducing subsequent use of seclusion and restraint (Table 4). In one CRT, units employing such interventions reported greater reductions compared with usual care units in the percentage of patient-days involving seclusion, restraint, or room

observation and shorter duration of seclusion and restraint use (32). Both outcomes had low SOE.

Two studies provided insufficient evidence of benefit for other interventions. One CRT of staff training in interpersonal communication found fewer incidents of seclusion and restraint and a larger decrease in incidents of seclusion and restraint compared with usual care on a control unit (46). One RCT of an environmental or group psychotherapeutic intervention (equine-assisted therapy) provided insufficient evidence of pre-post reductions in the rate of violent incidents and mean monthly episodes of seclusion or restraint (44). No studies assessed medication protocols in patients without active aggression.

Harms. One CRT addressed harms of staff training to prevent aggressive behavior, but the outcomes had insufficient SOE (46). No eligible studies examined harms of any of the other strategies to prevent aggressive behavior.

De-Escalating Aggressive Behavior

Benefits. Eight studies (five RCTs [26,28,33,38,45], two NRCTs [42,47], and one retrospective cohort study [31]) assessed various medication protocols for de-escalating aggressive behavior but provided insufficient evidence to assess their benefits. Two trials (each reported in two separate articles) both conducted on inpatient psychiatric units, had significant findings but small sample sizes that did not meet

the minimum criteria for OIS (35,36,39,40). Most of the remaining studies of medication protocols found no differences between active interventions, but they had been underpowered to test noninferiority.

No relevant studies of the effects of staff training, risk assessment, multimodal, or environmental or group psychotherapeutic interventions on de-escalating aggressive behavior were identified.

Harms. Six RCTs (26,28,35,38,42,45) and two NRCTs (42,47) provided harms data for medication protocols, but the outcomes had insufficient SOE. Two RCTs found significantly higher weight gain among patients treated with olanzapine or clozapine compared with patients receiving haloperidol, but their combined sample size did not reach the minimum OIS (37,41). Another RCT found greater extrapyramidal symptom severity (indexed by the percentage of patients prescribed benztropine) in the risperidone-treated group versus the clozapine or haloperidol groups (36), but similarly it did not meet the OIS threshold, and the outcomes had insufficient SOE. The other five studies reported small numbers of events and performed no statistical testing; SOE was insufficient for all outcomes.

No eligible studies tested harms of staff training, risk assessment, multimodal, or environmental protocols for de-escalating aggressive behavior.

Reducing Seclusion and Restraint Use

Benefits. Four studies measured the benefits of strategies to reduce use of seclusion and restraint among patients with active aggression, but there was insufficient SOE for all reported outcomes (29,31,33,43). No eligible studies tested the benefits of risk assessment or multimodal interventions for reducing seclusion and restraint.

Harms. No studies provided information on the comparative harms of any intervention for reducing seclusion and restraint use among patients with active aggression.

Modifying Comparative Benefits or Harms of Strategies

Information about variables that might modify the effectiveness of interventions was limited. One RCT found significantly greater increases in weight, triglycerides, and cholesterol levels among black patients treated with clozapine compared with white or Hispanic patients treated with haloperidol, but the sample size did not reach the minimum OIS (insufficient SOE) (41).

DISCUSSION

Key Findings

Our review aimed to fill gaps in available literature about the comparative effectiveness of various strategies to prevent aggressive behavior, de-escalate aggressive behaviors, or decrease reliance on seclusion or restraint in acute care settings. An overarching objective of these strategies, of course, is to improve health outcomes for patients who are actively aggressive or at risk of acute aggressive behavior.

Overall, the evidence base was extremely limited. We identified 17 studies (mainly RCTs and CRTs) for which we could grade the SOE of one or more outcomes. Most evidence addressed preventive, unitwide programs rather than interventions specifically targeting actively aggressive patients; this focus represented the core difference between the CRTs (which randomize groups) and the RCTs (which randomize individuals). Moreover, some of these analyses included patients who were not actively aggressive These factors prevented us from attributing reduction of aggressive behavior among actively aggressive patients to any particular intervention. Furthermore, inexact descriptions of many interventions made it difficult to attribute a change to particular components. For example, the multimodal intervention had components of risk assessment and staff training, and distinguishing between their components was challenging.

None of the comparative data from the studies supported an SOE grade of higher than low, and all findings with low SOE were from studies of preventive interventions. The two studies of risk assessment protocols identified fewer aggressive incidents (34) and lower rates of severe aggressive incidents and physical attacks (27) compared with the usual care conditions. The protocols overlapped somewhat but differed in important ways. Both trials used the Brøset Violence Checklist as part of the protocol, but the trial from the Netherlands used a more comprehensive protocol that included completing a crisis monitor form and the Kennedy Axis V (short version) on a daily basis and the full version of the Kennedy Axis V, the Brief Psychiatric Rating Scale, the Dangerousness Scale, and the Social Dysfunction and Aggression Scale on a weekly basis (34). The trials also differed in the length of time during which they evaluated their risk assessment protocols. For example, one study (27) implemented the risk assessment protocol for the first three days of the patient's hospital stay, whereas the other study (34) used the risk assessment protocol throughout each patient's hospital stay.

The CRT of a multimodal intervention examined the safety and effectiveness of seclusion or restraint reduction strategies (modeled after the Six Core Strategies [11]) in the setting of high-security psychiatric units of a Finnish state hospital (32). Unlike prior examination of the Six Core Strategies in the United States (48), this CRT included data from a control group; thus, it provided the first outcome data eligible for an SOE assessment. Specifically, it reported decreases in the proportion of patient-days in seclusion, restraint, or room observation and in the duration of seclusion or restraint use. Importantly, both reductions were achieved without a concomitant increase in violent incidents, and these results were demonstrated in a patient population inherently at high risk of aggression (males with schizophrenia and history of violent behavior).

Our work is consistent with prior findings. Earlier reviews emphasized the lack of high-quality intervention

TABLE 3. Key characteristics of 17 studies of interventions to de-escalate aggressive behaviors in acute care settings, by intervention type[a]

Intervention	Study design	Risk of bias	Clinical setting	Country	N	Duration of intervention	Intervention and comparison groups	Patient population
Staff training								
Kontio et al., 2014 (29); Kontio et al., 2011 (30)	CRT	High	Psychiatric hospitals (8 units)	Finland	nr	2 years	Online eLearning course for unit nurses on managing aggression or violence and preventing coercion; education as usual	Inpatients on acute, closed units that practice seclusion or restraint
Smoot and Gonzales, 1995 (46)	CRT	High	Inpatient psychiatric recidivist units	United States	nr[b]	6 months	Empathic interpersonal communication training program for hospital staff; usual care	Primary diagnosis of mental illness for patients who had returned to the hospital within 1 year of a previous discharge
Risk assessment								
Abderhalden et al., 2008 (27)	CRT	Medium	Psychiatric inpatient treatment facilities	Switzerland	973[c]	3 months	Structured risk assessment by using BVC for every new patient twice a day during the first 3 days of hospitalization (N=390); usual care (N=583)	Inpatients, most with an acute psychiatric disorder
Van de Sande et al., 2011 (34)	CRT	Medium	Acute psychiatric units	The Netherlands	458	30 weeks	Structured risk assessment for 5 minutes daily by using BVC and short version of Kennedy Axis V and for 15 minutes weekly by using full version of Kennedy Axis V, BPRS, Dangerousness Scale, and SDAS (N=207); usual care or treatment as usual (N=251)	Patients admitted to acute psychiatric units, 74% with psychotic disorders and 25% with personality disorders
Multimodal intervention								
Putkonen et al., 2013 (32)	CRT	Medium	Public psychiatric hospital	Finland	nr[d]	6 months	Implementation of Six Core Strategies for Reducing Seclusion and Restraint Use; usual care or treatment as usual	Male inpatients in high-security units who had psychotic illness and a history of violence
Environmental or group psychotherapeutic intervention								
Carlson and Holm, 1993 (43)	Retrospective cohort	High	State psychiatric hospital	United States	120	90 days	Occupational therapy at least 1 time every 30 days (N=60); no occupational therapy in at least 1 of the 3 30-day periods (N=60)	Patients with at least a 90-day inpatient stay on psychiatric unit; only data from first 90 days of stay were included
Nurenberg et al., 2015 (44)	RCT	Medium	State psychiatric hospital	United States	90	3 months	Equine-assisted psychotherapy (N=24); canine-assisted psychotherapy (N=25); environmentally enhanced social skills group psychotherapy (N=23); usual care (N=18)	Inpatients with "aggressive or regressed behavior" or "persistent social isolation" and difficulty engaging in discharge-related programs
Medication protocol								
Isbister et al., 2010 (26)	RCT	Medium	Public psychiatric hospital	Australia	91	6 hours	Droperidol, 10 mg im (N=33); midazolam, 10 mg im (N=29); droperidol, 5 mg im, plus midazolam, 5 mg im (N=29)	Patients presenting to the emergency department with violence and acute behavioral disturbance and requiring both physical restraint and parenteral sedation

continued

TABLE 3, continued

Intervention	Study design	Risk of bias	Clinical setting	Country	N	Duration of intervention	Intervention and comparison groups	Patient population
Dorevitch et al., 1999 (28)	RCT	Medium	Psychiatric hospital	Israel	28	90 minutes, during aggressive event	Haloperidol, 5 mg im (N=13); flunitrazepam, 1 mg im (N=15)	Acute-unit patients with active psychosis, disruptive or aggressive behavior, pronounced psychomotor agitation, or violent outbursts
Michaud et al., 2014 (31)	Retrospective cohort	High	Public psychiatric hospital	United States	200	24 hours	Delirium treatment within 24 hours (N=102); no delirium treatment within 24 hours or treatment after 24 hours (N=98)	Adults in an intensive care unit with a documented positive delirium screen at time of mechanical ventilation
Georgieva et al., 2013 (33)	RCT	High	Psychiatric hospital	The Netherlands	520	144 weeks	Intervention of first choice for agitation and risk of violence: involuntary medication (N=236); seclusion (N=284)	Patients admitted to acute units, most with either addiction or a psychotic, mood, personality, or posttraumatic stress disorder
Volavka et al., 2004 (35); Volavka et al., 2002 (36); Czobor et al., 2002 (37)	RCT	Medium	State psychiatric hospitals	United States	157	14 weeks	Clozapine, oral 500 mg/day (N=40); olanzapine, oral 20 mg/day (N=39); risperidone, oral 8 mg/day (N=41); haloperidol, oral 20 mg/day (N=37)	Treatment-resistant inpatients diagnosed with chronic schizophrenia or schizoaffective disorder
Bieniek et al., 1998 (38)	RCT	Low	Psychiatric emergency service (in hospital)	United States	20	3 hours	Haloperidol, 5 mg im plus lorazepam 2 mg im (N=9); lorazepam, 2 mg im (N=11)	Patients with serious, acutely agitated or aggressive behavior who met clinical criteria for use of chemical restraint
Krakowski et al., 2006 (39) ; Krakowski et al., 2008 (40); Krakowski et al., 2009 (41)	RCT	Medium	State psychiatric in-hospital facilities	United States	110	12 weeks	Clozapine, oral 500 mg/day (N=37); olanzapine, oral 20 mg/day (N=37); haloperidol, oral 20 mg/day (N=36)	Patients with confirmed episode of physical assault directed at another person during their current hospitalization and some persistence of aggression
Villari et al., 2008 (42)	NRCT	Medium	Psychiatric in-hospital emergency service	Italy	101	72 hours	Risperidone, oral 2–6 mg/day (N=27); olanzapine, oral 10–20 mg/day (N=24); quetiapine, oral 300–800 mg/day (N=22); haloperidol, oral 5–15 mg/day (N=28)	Inpatients with psychosis who require emergency medication for control of agitation
Richards et al., 1998 (45)	RCT	High	Large urban university emergency department	United States	202	60 minutes	Droperidol, 2.5–5.0 mg iv (N=102); lorazepam, 2–4 mg iv (N=100)[e]	Acutely agitated patients with violent, controlled, or uncontrolled muscular movement placing themselves and staff at danger and requiring constant supervision

continued

TABLE 3, *continued*

Intervention	Study design	Risk of bias	Clinical setting	Country	N	Duration of intervention	Intervention and comparison groups	Patient population
Wilhelm et al., 2008 (47)	NRCT	High	Psychiatric or forensic hospitals	Germany	558	6 days[f]	Olanzapine, oral dose (N=390); non-olanzapine medication, oral dose (N=168); risperidone, oral dose (N=72); non-risperidone medication, oral dose (N=486); haloperidol, oral dose (N=132); non-haloperidol medication, oral dose (N=426)[g]	Inpatients with psychiatric disorders who presented with agitation with or without aggression and required antipsychotic treatment and who were newly admitted to a psychiatric hospital (98%) or a forensic hospital (2%)

[a] Abbreviations: BPRS, Brief Psychiatric Rating Scale; BVC, Brøset Violence Checklist; CRT, cluster randomized trial; nr, not reported; NRCT, nonrandomized controlled trial; RCT, randomized controlled trial; SDAS, Social Dysfunction and Aggression Scale

[b] An average of 92 patients were discharged per month in each unit, meaning about 184 patients were included in the study each month.

[c] Does not include patients admitted to the five units that preferred to introduce the study protocol of structured risk assessment without randomization

[d] Each arm accounted for approximately 1,000 patient-days per month.

[e] Dosages of study drugs were selected on the basis of patients' weight, which was visually estimated by the treating clinician.

[f] The study followed enrolled patients over the first 6 days of their hospitalizations. Baseline was day 1, and the following 5 days (days 2–6) represented the follow-up period.

[g] Patients' antipsychotic treatment was categorized as including any olanzapine or not, including any risperidone or not, and including any haloperidol or not. The three cohorts thus overlapped, because each cohort included all patients who received the respective drug in any amount and at any time throughout the 5-day study period.

studies of strategies to prevent the development of aggressive behavior in acute care settings (49–52). An absence of relevant literature on interventions for actively aggressive behavior has been similarly reported, regardless of whether alternative strategies to seclusion and restraint were being compared with each other (49–51,53) or with seclusion and restraint (49,51). A lack of literature about comparative harms of these interventions has also been identified (54). Our review updates and confirms these findings. Of particular relevance for clinical and administrative audiences, the review expands considerations of potentially relevant interventions to include staff training, environmental or group psychotherapeutic, multimodal, and pharmacologic interventions not previously reported.

Our review adds to existing reviews by including findings highlighting the potential benefits of two preventive interventions. First, a general application of a strategy that involves a risk assessment component for all individuals on inpatient psychiatric units—not just actively aggressive patients—may produce less aggressive behavior and less use of seclusion and restraint compared with usual care. The former finding extends what is known about the relationship between risk assessment and subsequent behavior. Earlier reviews of risk assessment found that using such a service was associated with decreased agitation (12), often considered an intermediate precursor of more dangerous aggressive behavior. Lowering agitation may or may not lead to decreased aggression, but our review found that risk assessment may lead to reduced subsequent aggression (as indicated by fewer aggressive incidents).

Second, both risk assessment and multimodal interventions may lower use of seclusion and restraint (as indicated by duration of seclusion or restraint and by use of forced treatment, including seclusion and restraint). These findings highlight a key potential benefit relevant to practice guidelines and quality-of-care measures advocating decreasing use of seclusion and restraint. Nevertheless, the SOE for these findings (all from CRTs) was limited by data analyses that did not account appropriately for the clustering of these data; this drawback likely affected each trial's results, for example, by increasing the risk of a type I error. Further, the three studies forming the basis for the low SOE findings (risk assessment [27,34] and multimodal interventions [32]) were conducted outside the United States. How substantially clinical practice outside the United States differs from current U.S. practice is unclear, which may bring into question the applicability of findings from non-U.S. studies.

Potential Clinical and Policy Implications

The handful of findings that we graded as low SOE may provide some clinical or policy implications. In particular, a limited number of risk assessment interventions subsequently led to less aggressive behavior and reduced the use of seclusion and restraint. These findings suggest that clinicians must consider carefully the role of these strategies on psychiatric inpatient units. Specifically, acute care practitioners and

TABLE 4. Primary outcomes with low strength of evidence among studies of interventions for preventing aggressive behavior among adult psychiatric patients[a]

Outcome	Study	Intervention	Comparison group	N	Findings and direction of effect
Change in aggressive behavior					
N of aggressive incidents	Van de Sande et al., 2011 (34)	Risk assessment	Usual care	N=170 (baseline), N=458 (intervention period)	Significant 68% relative risk (RR) reduction with risk assessment (p≤.001); failure to control for intraclass correlations weakened the finding.
Rate of severe aggressive incidents	Abderhalden et al., 2008 (27)	Risk assessment	Usual care	N=973 (postintervention)	Significantly lower risk with structured risk assessment (RR=.59; 95% confidence interval (CI)=.41−.83, p<.001); failure to control for intraclass correlations weakened the finding. Decrease since baseline of 41% with risk assessment vs. 15% with usual care; no statistical testing reported
N of physical attacks	Abderhalden et al., 2008 (27)	Risk assessment	Usual care	N=973 (postintervention)	Significantly greater decrease with risk assessment vs. usual care (41% vs. 7%, p<.001); failure to control for intraclass correlations weakened the finding.
Change in seclusion or restraint					
Hours in seclusion	Van de Sande et al., 2011 (34)	Risk assessment	Usual care	N=170 (baseline), N=458 (intervention period)	Significant 45% RR with risk assessment (p≤.001); failure to control for intraclass correlations weakened the finding.
N of coercive incidents[b]	Abderhalden et al., 2008 (27)	Risk assessment	Usual care	N=973 (postintervention)	Significant decrease of 27% from baseline with risk assessment compared with increase of 10% with usual care (p<.001); failure to control for intraclass correlations weakened the finding
Proportion of patient-days with seclusion, restraint, or room observation	Putkonen et al., 2013 (32)	Multimodal[c]	Usual care	Not reported, but each arm accounted for approximately 1,000 patients	Significant difference in calculated change with intervention vs. usual care (−15% vs. −6%, p=.001). No between-group CI reported. Failure to control for intraclass correlations weakened the finding.
Hours in seclusion or restraint	Putkonen et al., 2013 (32)	Multimodal[c]	Usual care	Not reported, but each arm accounted for approximately 1,000 patients	Significant difference in calculated change with intervention vs. usual care (decrease of 54 hours vs. increase of 17 hours, p=.001). No between-group CI reported. Failure to control for intraclass correlations weakened the finding.

[a] All of the studies were cluster randomized trials. Due to differential operationalization of the two risk assessment studies, it was not possible to conduct a direct comparison of the two studies.
[b] Coercive measures covered a wide range of measures from forced injection of psychotropic medication to seclusion and mechanical restraint.
[c] Based on the Six Core Strategies for Reducing Seclusion and Restraint Use (11)

administrative staff must balance the low SOE with the reality that violence is a pressing—indeed, growing—concern and poses significant disruptions to quality of care in such settings. Broad implementation of a well-validated, structured risk assessment instrument in acute care settings illustrates a recommendation that could facilitate the prevention of aggression. Similarly, some evidence supports using multimodal interventions consistent with the Six Core Strategies to reduce

seclusion and restraint, even in populations with psychiatric diagnoses or symptomatology that may be difficult to treat.

Several questions may arise, however. Is currently available limited evidence sufficient for evaluating effectiveness? Should implementation decisions be delayed until more evidence becomes available? How should the substantial barriers to conducting RCTs in these populations, involving both the challenges of obtaining informed consent as well as limited

funds supporting such research, be considered in weighing and acting on the available evidence? What is the role of quality measures, designed to create incentives for improving quality of care, if the evidence base for those measures is unclear?

Regarding the last question, we are unaware of any ongoing trials that will add to the current sparse body of evidence addressing the benefits of risk assessment protocols and multimodal interventions. Furthermore, we cannot comment on potential harms or costs associated with implementing risk assessment protocols. Therefore, determining how to apply interventions from other countries to settings in the United States—and determining the modifications that might be necessary to do so—are key next steps, given the absence of SOE findings from inpatient psychiatric settings in the United States.

Research Recommendations
The paucity of evidence means that most implications of our review pertain to future research rather than to clinical or policy judgments. Major evidence gaps exist in this increasingly worrisome clinical arena; they point to important next steps for research in preventing and de-escalating aggressive behavior in acute care settings. The SOE grades informing decision making in this area were minimal. A major void is the lack of well-designed, adequately powered, properly analyzed comparative trials that address questions of preventing and de-escalating aggressive behavior. The validity of findings from the three reasonably well-designed CRTs was constrained by analyses that did not properly control for the clustered nature of the data. We applaud the efforts to conduct comparative trials, but this evidence base does not convincingly show the efficacy of most of these strategies; that fact complicates the design of strong comparative studies and reflects a gap in efficacy data that may need to be addressed first.

Nonetheless, head-to-head trials that compare various interventions with each other rather than with usual care are needed to guide decision making. Most critical is identifying the "right" interventions to compare, which would allow the most efficient use of research time and funding for this topic. More evidence about the differential effectiveness of interventions would allow clinicians and administrators to balance evidence of effectiveness with implementation and resource costs.

Investigators who lead future trials must clearly describe their interventions. Only in this way can other research teams sensibly try to reproduce or replicate such studies and help confirm which components of the interventions are the most (or least) effective. Risk assessment strategies and multimodal interventions, which have some evidence for preventing aggressive behavior, must be described in more detail to allow comparisons with each other and to allow variations within these approaches to be compared as well.

Currently, clinicians and investigators do not know the accuracy of risk assessment tools. Because these tools are necessary to identify patients at high risk of aggressive behavior and, hence, to develop an effective plan to manage aggressive behavior, more work on documenting the measurement capabilities of these tools is needed.

In the future, all trials must report on consistently defined and clinically meaningful outcomes, both short term and long term. Crucial short-term outcomes include reliable and valid measures of aggressive behavior and of seclusion and restraint actions. Using well-established, reliable, and valid assessments of aggression that can be harmonized across studies (and ideally countries) is crucial, as well, for future systematic reviews on these topics. In addition, research teams should increase adherence to the Consolidated Standards of Reporting Trials statement regarding the reporting of clinical trials, including CRTs (55).

Key long-term outcomes must involve more patient-centered outcomes, such as health-related quality of life. Patient perspectives of harms, including treatment preferences, in acute care settings are largely missing from the literature; this gap should be remedied. Measures of the use of health services are important, as are cost implications. Investigators should incorporate factors involving implementation of interventions, such as acceptability, feasibility, and sustainability, into their designs for intervention research in acute care settings.

Available acute care data are almost entirely from inpatient psychiatric settings and settings outside the United States. In the latter case, standard practices, patient populations, insurance coverage, costs, and various other variables may differ in the United States, perhaps considerably. Future well-designed studies of inpatient psychiatric settings must be conducted in U.S. settings. In addition, informative data must be collected from acute care medical and surgical units and from emergency department settings.

Finally, we had no informative data on modifiers of treatment effectiveness. Future studies, including comparative trials, must assess how variables may modify or mediate the effects of the interventions studied. These variables could include age and other sociodemographic or economic factors, specific primary diagnoses (and perhaps coexisting conditions), and explicit treatment components.

Our review had limitations. First, we bounded its scope to focus on data relevant to adults in acute care settings. This emphasis left out consideration of data from chronic care and psychiatric residential settings; it also omitted treatment of children and adolescents. In both these clinical areas, however, use of seclusion and restraint is common and potentially concerning (56). Second, to allow a meaningful synthesis of outcomes, we required that studies report at least one of our main outcomes—change in aggressive behavior or in seclusion and restraint use. This restriction may have reduced the number of eligible studies and the number of patient-centered outcomes we could examine, for example, by omitting outcomes such as improved quality of life and improved therapeutic relationship. However, synthesizing such data with the other collected outcomes would have been difficult and would likely have not affected our SOE findings.

Finally, we excluded reviews and primary studies that examined agitation as the primary outcome when evaluating the effectiveness of inpatient or acute care risk assessment protocols (12). This exclusion limited consideration of

interventions to reduce agitation, which may also lead to decreased aggression. An evidence base for reducing agitation exists (39,57), and it may inform aggression management. The decision to focus on aggression and not agitation, although narrowing the scope of our review, also reduced the heterogeneity of the outcomes under examination. Each exclusion decision was made with the intention of focusing the review and controlling for important sources of heterogeneity. By better delineating situations in which agitation leads to aggression, future research can better guide selection of a specific intervention, for example, a psychotherapeutic approach versus medication.

CONCLUSIONS

Given the ethical imperative to treat all patients with dignity, the clinical mandate of finding evidence-based solutions to these mental health challenges, and the legal liability associated with failure to assess and manage violence risk across the treatment continuum, the need for evidence to guide clinical and policy decision making about de-escalating aggressive behavior is critical. This point is particularly true of acute care settings for at least two reasons: comprehensive clinical and violence risk information may not always be readily available in such institutions, and patient management must be balanced against staffing and treatment limitations unique to each setting.

The current evidence base provides clinicians, administrators, policy makers, and patients with no definitive guidance on how to best prevent and de-escalate aggressive behaviors in acute care settings. It suggests, however, that risk assessment is a reasonable strategy for decreasing aggression and reducing the use of seclusion and restraint and that a multimodal intervention approach based on the Six Core Strategies also reduces the use of seclusion and restraint. Evidence for the comparative effectiveness of strategies to de-escalate aggressive behavior is currently inadequate to give definitive advice about treatment selection. More research is needed to guide clinicians, administrators, and policy makers on how to best prevent and de-escalate aggressive behavior in acute care settings.

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