Introduction

Background

Aggressive Behavior

Aggressive behavior connotes using actual physical violence toward self, others, or property or making specific imminent verbal threats.[1] In health care setting, approaches for actively aggressive patients 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 restraints (involuntary administration of mechanical, pharmacologic, or physical interventions, which is seen as more restrictive than seclusion); these practices continue today.[2,3] Since the late 1990s, the Centers for Medicaid & Medicare Services (CMS, formerly the Health Care Financing Administration [HCFA][3]) and the Joint Commission[4] (an accrediting body that evaluates health care organizations with performance standards) have required that seclusion and restraints must 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 when less restrictive measures have failed. Despite practice guidelines advocating limitations of seclusion or restraints as much as possible,[6] data in the United States and Europe show that 10 percent to 30 percent of patients (adolescents, adults and to elderly) admitted to acute psychiatric units receive these interventions.[7-9]

Deciding to use seclusion or restraints raises several significant clinical or policy issues. First is how to best balance the benefits and risks of seclusion or restraints with those of various alternatives to those practices.[7] Benefits of seclusion and restraints can include reduced physical risk to the patient, other patients, and staff; quick reduction of aggressive behaviors; and increased likelihood of receiving effective treatment for the psychiatric disorder (if the aggression is preventing proper treatment). Potential harms to patients include increased physical harm to the patient, such as severe and even fatal side effects,[10] with estimates of 50 to 150 seclusion- or restraint-related deaths annually.[11] Others may face the risk of various harms as well: e.g., other patients or even staff may experience assault. Yet other possible harms may involve punishment (perceived or real) of patients; loss of dignity; re-traumatization of patients; new traumatic effects of such coercion; and future aversion to returning to the hospital even if a patient is in great need (e.g., is suicidal).

Second, whether an evidence base even exists to support using seclusion or restraints is debatable.[7,12-15] Third, usual care (often represented in comparative studies as whatever was done before a new intervention was tried) varies substantially. Given the considerable potential harms and the availability of alternative strategies (briefly described below), most guidelines and standards from regulatory agencies and accrediting bodies now recommend using seclusion and restraints only as a last resort.[16-24]

Finally, using seclusion and restraints is closely followed as a quality-of-care measure, particularly for psychiatric patients in hospital settings.[25] Various organizations have defined quality care as the lowest possible use of seclusion and restraint, making it important to understand what evidence base exists in support of this definition.[26] The Joint Commission collects publically available, comparative data on patient hours of seclusion and restraints for acute care hospitals that offer hospital-based inpatient psychiatric services (HBIPS-2, HBIPS-3); it also includes time in seclusion or in restraints as part of its inpatient psychiatric services core

measure for accreditation.[27] In 2010, the organization reported more than 200 deaths related to seclusion or restraints over a prior 5-year period.[28]

In addition, some state psychiatric hospital systems have undertaken comprehensive efforts to reduce use of seclusion and restraints and collected data on their progress. For example, in Pennsylvania from 1990 to 2000, rates of seclusion decreased from 4.2 to 0.3 episodes per 1,000 patient days, and rates of restraints decreased from 3.5 to 1.2.[29] The authors cited many factors contributing to the change, including advocacy, policy change, staffing ratios, response teams, and second-generation antipsychotics. The federal government also gives this issue high priority—the Substance Abuse and Mental Health Services Administration, for one, makes consistent and active efforts to reduce and ultimately abolish the use of seclusion and restraints.[30,31]

Treatment Strategies

Much interest now focuses on using alternatives to seclusion and restraints. These strategies can address preventing aggressive behavior or reducing aggressive behavior once it has already developed (or both). Most of these alternatives are strongly influenced by the National Association of State Mental Health Program Directors' Six Core Strategies.[32] These principles are (1) leadership toward organization change, (2) use of data to inform change, (3) workforce development (strongly influenced by the principles of trauma-informed care),[33] (4) use of seclusion and restraint prevention tools, (5) consumer roles in inpatient settings, and (6) debriefing techniques. Such approaches appear to be comprehensive, noninvasive, and low risk; they offer promising results.[34]

These Six Core Strategies ultimately aim to forestall or at least decrease aggressive behavior. Strategies to prevent aggressive behavior can involve general, multicomponent strategies (applied to a whole group, usually via policy) or specific strategies (applied to specific individuals who are at especially high risk of becoming aggressive). Use of these two preventive approaches can overlap; specific strategies may also be applied as a general approach on a unit-wide basis. Other approaches aim to de-escalate or manage aggressive behavior once it has already developed.

Preventing aggressive behavior (general strategies): The vast majority of patients who are admitted to an acute care health setting because of a psychiatric illness or are being treated in an emergency department because of severe psychiatric symptomatology are at some increased risk of aggression relative to the general population. Preventive strategies to reduce the likelihood that such patients might become acutely aggressive focus on providing a calm environment in which aggression is less likely to develop.

Such approaches tend to focus on entire care units. They include the following: risk assessment, milieu-based changes such as sensory rooms, which provide a calm and supportive environment for patients;[35] staffing changes, such as increased staff-to-patient ratios;[19] specific staff training programs;[36] and peer-based interventions.[37] For example, one program introduced a 12-hour staff training program focused on previously identified barriers to reducing the use of seclusion or restraints.[36] These barriers for the staff included fear, prejudices, hopelessness, and negative attitudes. The focus of the peer-based intervention was to build trust and confidence in the patient and engage the patient on a mutual level.[37] The strengths of such approaches are that they are collaborative and pose only a low risk to patients and staff.[38] They also can help address the risk in groups that are harder to identify as being at risk of acute aggression—those who isolate themselves and withdraw from the unit environment (milieu).[39]

Preventing aggressive behavior (specific strategies): Agitation, commonly although not always, precedes aggression. Thus, specific strategies to prevent aggression often try to intercede at the point of agitation. If a patient becomes agitated (reflected in behaviors such as pacing, yelling, or making verbal threats or threatening gestures toward others), the patient is generally thought to be at increased risk of aggressive behavior, including physical violence. For agitated patients, the goal of an intervention is to decrease that agitation to prevent aggressive behavior.

Early agitation often resolves with supportive (often referred to as nonconfrontational) language and other verbal de-escalation techniques to help diffuse the interpersonal interaction. The use of restrictive interventions, such as restraints, at this early stage may only further escalate the situation.[19] More serious agitation may require cognitive behavioral techniques aimed at helping the patient manage his or her emotions and distress, so as to regain control of behavior. Such aggression prevention approaches[40] form the basis of guidelines for managing agitated patients in different settings.[41-45]

Pharmacologic intervention treating the underlying psychiatric illness is also a common specific strategy for preventing aggressive behavior. A case in point might be increasing the dose or adding an as-needed dose of an antipsychotic medication for a patient with a history of aggression and schizophrenia; the aim is to decrease current reactivity and impulsivity and, thereby, reduce the risk for current aggression. When successful, such medication-based steps can help prevent aggression.[45]

Furthermore, recognition of triggers for aggressive behavior can inform prevention strategies by identifying individualized patterns that can be addressed. For example, certain sensory stimuli, such as excessive noise, can trigger aggression in some patients. This problem could theoretically be addressed by offering ear plugs or headphones to those individuals. Similarly, paranoid patients may benefit from having only prepackaged foods on their meal tray to decrease agitation related to concerns about poisoning.

Managing acute aggression: If patients do become actively aggressive (i.e., exhibiting actual physical violence toward property, self, or others, or making specific imminent verbal threats), clinicians can use either seclusion or restraints or alternative strategies. In such cases, alternatives can include Emergency Response Teams; these encompass Behavioral Emergency Response Teams,[46] Rapid Response Teams,[46] and Psychiatric Emergency Response Teams.[47]

In addition, clinicians can employ pharmacologic interventions to reduce agitation quickly, rather than more gradually treating the underlying illness. These include, for example, the medication protocols described in the emergency department-focused Project BETA (Best Practices in Evaluation and Treatment of Agitation).[48] These involve medications approved by the U.S. Food and Drug Administration (FDA) whose indications specifically include use for agitation in adults (olanzapine, ziprasidone, aripiprazole, and inhaled loxapine).[49-52] Pharmacologic agents can also include those that do not have formal FDA approval for these specific purposes (e.g., haloperidol, risperidone, and lorazepam).

Scope and Key Questions

Scope of the Review

This small systematic review addresses interventions to prevent or de-escalate aggressive behavior and to reduce the use of seclusion and restraint for aggressive behaviors. Behaviors indicating the potential need for these types of interventions occur in both acute care settings (such as public and private mental hospitals, state mental hospitals, emergency departments,

Veterans Affairs hospitals, and medical or surgical units in general hospitals) and chronic care settings (such as nursing homes and psychiatric residential treatment facilities).[24] Although psychotic disorders account for 44 percent of individuals requiring seclusion or restraint (or both), multiple psychiatric diagnoses, including substance misuse and delirium, are associated with aggression in health care settings.[24,47,53] In addition, in some acute care settings (e.g., the emergency department) the psychiatric diagnosis may not yet be clear or patients may not have been formally diagnosed; treatment decisions are then often based on the presence of psychiatric symptoms including aggressive behaviors.

Although dementia is frequently associated with aggression and the use of seclusion and restraints,[54] individuals with dementia are often managed in chronic care settings; a separate report is covering this evidence.[55] Thus, our review focuses on adults in acute care settings. We include in the review studies of inpatients with any psychiatric diagnosis, including delirium and substance misuse (but not dementia), and patients in emergency departments with severe psychiatric symptomatology.

To our knowledge, no systematic review focusing on acute care settings has directly compared either (1) the effectiveness of different available alternative strategies to *prevent aggressive behavior* or (2) the effectiveness of alternative strategies compared with each other or with seclusion and restraints to *de-escalate aggressive behaviors or improve health outcomes for those who are acutely aggressive*. Existing systematic reviews of pharmacological de-escalation strategies often include placebo-controlled studies, focus only on a small subset of our eligible population, and are rarely limited to the acute care setting.

This review focuses on the comparative effectiveness of strategies to de-escalate aggressive behavior in psychiatric patients in acute care settings. In this case, we conceptualize "de-escalate" in terms of both preventing aggressive behaviors *and* reducing use of seclusion and restraints. We do not assess the accuracy of available risk assessment tools (a crucial step in the process of reducing aggressive behavior) or consider chronic care settings; although these are important considerations, they are beyond the scope of this review.

Based on our preliminary literature search and input from key informants, we appreciate that risk assessment is a crucial step in the process of reducing aggressive behavior and the potential use of seclusion and restraints for psychiatric patients. We understand that a practical need exists to assess the accuracy of available risk assessment tools. Similarly, we appreciate that seclusion and restraints are applied across a span of settings, including chronic care settings such as skilled nursing facilities and psychiatric residential treatment facilities. Nevertheless, risk assessment and consideration of chronic care settings are beyond the immediate scope of this comparative effectiveness review (CER); thus, we do not specifically address such topics or settings in this report.

Key Questions (KQ)

KQ 1: Regarding benefits for adult psychiatric patients in acute care settings:

a. For those without active aggression, what are the comparative benefits of strategies to prevent aggressive behavior?
b. For those with active aggression, what are the comparative benefits of strategies, including seclusion and restraints, to de-escalate aggressive behavior?
c. For those with active aggression, what are the comparative benefits of strategies to reduce the use of seclusion and restraints?

KQ 2: Regarding harms for adult psychiatric patients in acute care settings:

a. For those without active aggression, what are the comparative harms of strategies to prevent aggressive behavior?
b. For those with active aggression, what are the comparative harms of strategies, including seclusion and restraints, to de-escalate aggressive behavior?
c. For those with active aggression, what are the comparative harms of strategies to reduce the use of seclusion and restraints?

KQ 3: What characteristics of patients (including age, sex or gender, diagnosis, motivation to receive treatment), of intervention components, or of acute care settings modify the benefits or harms of interventions for psychiatric patients at risk of, or presenting with, active aggression?

For the three KQs in this review, we define aggressive behavior as making specific imminent verbal threats or using actual physical violence toward self, others, or property. As discussed above, we focus on patients with any psychiatric diagnosis per the Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised, Fourth Edition, or Fifth Edition (DSM-III-R, DSM-IV, or DSM-5).[56-58] Diagnostic categories include delirium and substance misuse (but not dementia); additionally, for patients in emergency departments, we include displaying severe psychiatric symptomatology. We view effectiveness in terms of both benefits and harms, so we frame our questions to address each class of outcomes.

We envision a continuum of risk and behavior, so the KQs cover a range of patients. This spectrum can include patients with these disorders who may be at risk of aggressive behavior (i.e., are not actively aggressive), in which case interventions are preventive. It can also include those who are exhibiting aggressive behaviors (i.e., are actively aggressive), in which case interventions are directly active. Interventions can occur at any point along this continuum, and they can involve a wide variety of strategies that can have educational, behavioral, emotional, organizational, environmental, and/or pharmacologic components. The interventions must target a reduction either in aggressive behavior or in use of seclusion and restraints.

For these KQs, we define and classify interventions to reflect either prevention or direct intercession. A preventive intervention is one applied to a group of individuals not wholly identified as being actively aggressive; i.e., some patients may not be actively aggressive but others may be. It can involve unit- or hospital-wide policies that address all patients on a unit, not just those who are actively aggressive. It can also involve patients identified as being at an increased risk of becoming aggressive (e.g., were assessed as being agitated) but who were not yet actively aggressive.

KQ 1 (benefits) and KQ 2 (harms) address such preventive interventions in these groups in their subquestion (a). KQs 1 and 2, in their subquestions (b) and (c), examine interventions targeted specifically to de-escalate aggressive behavior among actively aggressive patients. KQ 3 addresses specific patient, intervention, or setting factors that may modify benefits or harms of various strategies.

Our two primary comparative outcome benefits, which are intermediate outcomes, are a decrease in (1) aggressive behaviors and (2) use of seclusion and restraints. For patients who are not acutely aggressive (i.e., not threatening the immediate physical safety of themselves, the staff, or others), use of seclusion and restraints is not allowed under current regulatory statutes.[59] Here, the potential outcomes include a reduction in aggressive behaviors or in the eventual use of seclusion and restraints (or both). However, for those who are actively aggressive, use of

seclusion and restraints may be an option; in comparative studies where seclusion and restraints are used, reduction in aggressive behaviors is the primary benefit outcome.

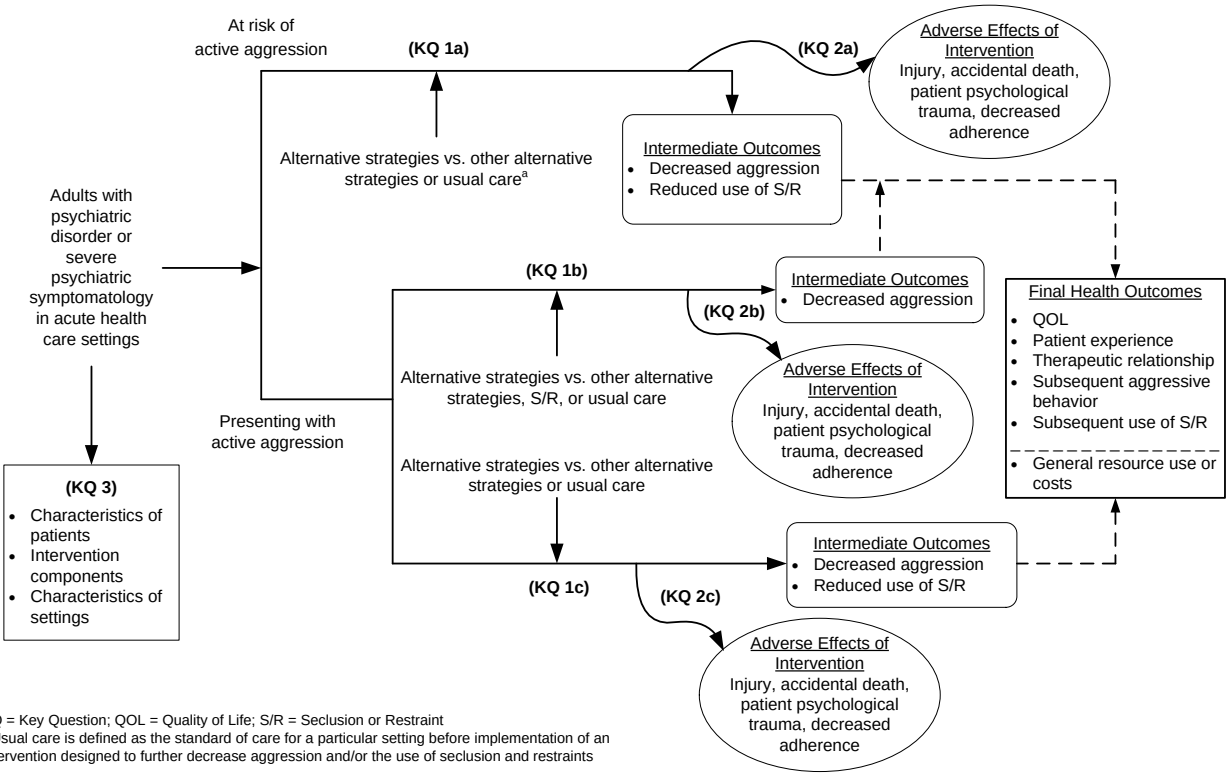
We also look at longer term or final health outcomes. These include improved quality of life, functioning, or patient experience; improved therapeutic relationship; and decreased subsequent aggressive behavior. In addition, we consider general resource use or costs. Although measures such as staff turnover or the sustainability of interventions are also important, our scope did not allow us to address these issues in this report.

Because of safety concerns in relation to aggressive behavior, our harms outcomes, addressed in KQ2, are more inclusive. Also, we note that harms to staff members or to patients can come from the use of seclusion or restraints as well as the failure to use seclusion or restraints. Any comparison study we examine must account for this complexity.

Acute health care settings are defined as public and private mental hospitals, acute care units at state mental hospitals, acute care components of Veterans Health Administration (VA) hospitals, medical or surgical units in general hospitals, and emergency departments. In all cases, patient discharges occur within 35 days of beginning treatment.[60] Stays longer than 35 days would indicate a chronic care setting.

We present our analytic framework that guided this review (Figure 1); it identifies specific KQs.

Figure 1. Analytic framework for comparative effectiveness of strategies to de-escalate aggressive behavior in psychiatric patients



KQ = Key Question; QOL = Quality of Life; S/R = Seclusion or Restraint
[a] Usual care is defined as the standard of care for a particular setting before implementation of an intervention designed to further decrease aggression and/or the use of seclusion and restraints

Methods

The methods for this comparative effectiveness review (CER) follow the guidance provided in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (www.effectivehealthcare.ahrq.gov/methodsguide.cfm) for the Evidence-based Practice Center (EPC) program.[61] Certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[62] All methods and analyses were determined a priori.

The AHRQ Effective Health Care (EHC) program's Topic Triage group developed and reviewed the topic; because this group deemed the topic sufficiently relevant, they moved it forward for the Topic Refinement phase. All topics are reviewed and assessed for appropriateness for systematic review (see EHC Web site for information on the process for selecting topics: http://www.effectivehealthcare.ahrq.gov/index.cfm/submit-a-suggestion-for-research/how-are-research-topics-chosen/). Once a topic is assessed and determined to be appropriate for further product development in the EHC program, AHRQ assigns it to a research team. Further development of the topic occurs with the input of Key Informants and Technical Experts (see the EHC Web site for information on the research process: http://www.effectivehealthcare.ahrq.gov/index.cfm/submit-a-suggestion-for-research/what-is-the-research-process/).

Topic Refinement and Review Protocol

During topic refinement for this topic, we engaged in a public process to develop Key Questions (KQs) for the review. We also developed a draft and then final review protocol. Specifically, we generated an analytic framework, preliminary KQs, and preliminary inclusion/exclusion criteria; these reflect PICOTS constructs (patients or populations, interventions, comparators, outcomes, timing, and settings) and other details about eligible studies. Information from the topic nominator helped guide our processes. A panel of 10 Key Informants (KIs) gave input on the scope and details of initial KQs; they supported the KQs as described, but suggested adding gender and staff training and competence as important potential effect modifiers for KQ 3. These KQs were posted on AHRQ's Web site for public comment (www.effectivehealthcare.ahrq.gov) from June 8, 2015, through June 29, 2015. We then revised the KQs as needed.

In addition, we consulted with seven experts (members of a Technical Expert Panel), who provided feedback as we developed our review protocol. Their inputs addressed points such as sample size thresholds for eligible studies and whether and how to limit assessments of risk of bias of individual studies.

Literature Search Strategy

Search Strategy

To identify relevant KQ-specific articles, we searched MEDLINE® (via PubMed), Embase®, the Cochrane Library, Academic Search Premier, PsycINFO, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) from January 1, 1991, through February 3, 2016. Appendix A presents the full search strategy (limiting searches to English and human-only studies). We selected this opening date because this year marks the time that the Health Care Financing Administration (now the Centers for Medicare & Medicaid Services) first released

rules to minimize the use of seclusion and restraints in health care facilities, with this first rule addressing nursing homes.[63] An experienced information scientist—our EPC librarian—ran all searches.

Our searches focused on comparative studies of de-escalation strategies (seclusion, restraints, or alternatives to seclusion or restraints) for patients with psychiatric disorders or severe psychiatric symptomatology who are at risk of, or presenting with, aggressive behavior across various acute health care settings. Search strings included various Medical Subject Heading (MeSH) terms for psychiatric disorders, acute health care settings, and aggressive behavior. Our inclusion criteria limited populations to patients 18 years of age and older.

Also, they included any psychiatric or substance use disorder, as well as delirium. If the study population was limited to patients with dementia, we deemed that article ineligible. Acute health care settings could include general hospitals, psychiatric hospitals, and emergency departments in these hospitals. To capture aggressive behavior, we used MeSH terms for aggression, violence, psychomotor agitation, hostility, crisis intervention, physical restraint, patient isolation, and psychotropic medications.

We also manually searched reference lists of pertinent reviews, included trials, and background articles to identify relevant citations that our searches might have missed. We imported all citations into an EndNote® X7 electronic database.

To find relevant gray literature we followed guidance from the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* for these steps.[64] Sources of gray literature included ClinicalTrials.gov, the World Health Organization's Library Database, the National Institutes of Health Research Portfolio Online Reporting Tools (RePORTer) database, the National Institute of Mental Health Web site, the American Psychological Association Web site, the American Psychiatric Association Web site, and the Substance Abuse and Mental Health Services Administration Web site. We opted not to search all of the gray literature sources described in our published protocol, specifically, Drugs@FDA, the European Medicines Agency, Scopus, and the Conference Proceedings Citation Index, because we felt confident that our other searches would have already captured any literature relevant to our Key Questions that these sources might have yielded.

The AHRQ Scientific Resource Center requested scientific information packets or information on unpublished studies or data relevant for this systematic review from relevant pharmaceutical manufacturing companies and other stakeholders and organizations related to the use of pharmacologic and nonpharmacologic alternatives to seclusion or restraints. No responses were received.

Inclusion and Exclusion Criteria

For the above KQs, the following PICOTS criteria for populations, interventions, comparators, outcomes, time frames, and settings apply (see also Table 1):

Table 1. Eligibility criteria for review of strategies to de-escalate aggressive behavior

PICOTS	Inclusion	Exclusion
Populations	KQs 1 through 3: • Adult individuals (ages 18 or older) with an identified psychiatric disorder (if in an inpatient setting), including substance use disorders and delirium (but not dementia), or with severe psychiatric symptomatology (if in an emergency department setting where a formal psychiatric diagnosis often is not made), who are at risk of or actively exhibiting aggressive behavior toward self, others, or property.	All other populations
Interventions	KQs 1a and 2a: • Strategies (early intervention techniques) targeted to reduce the likelihood of aggressive behavior (examples provided in the PICOTS criteria) KQs 1b/1c and 2b/2c: • Strategies targeted to decrease aggression for those who are actively aggressive (examples provided in the PICOTS criteria) KQ 3: Same as KQs 1 and 2	All other interventions • For medication-based interventions, those that are not FDA-approved for any indication
Comparators	KQs 1a and 2a: • Other strategies (early intervention techniques), but not seclusion and restraints, targeted to reduce the likelihood of aggressive behavior, as described above for KQs 1a and 2a • Usual care, defined as the standard of care for a particular setting before implementation of an intervention designed to decrease the likelihood of aggression and/or the use of seclusion and restraint KQs 1b/1c and 2b/2c: • Other strategies targeted to decrease aggression for those who are actively aggressive, as described above for KQs 1b/1c and 2b/2c • Seclusion or restraint (for 1b and 2b only) (as defined in the PICOTS criteria) • Usual care, defined as the standard of care for a particular setting before implementation of an intervention designed to decrease aggression and/or the use of seclusion and restraint KQ 3: Same as KQs 1 and 2	All KQs: • A study with no comparison group • For medication-based strategies, placebo-only comparisons and those comparing different doses or routes of administration
Outcomes	KQs 1a, 1b, and 1c: • Intermediate outcomes: – Primary outcomes: o Decreased aggression in terms of frequency, severity, or duration (as measured by direct counts or by validated aggression scales) o <u>KQs 1a and 1c only</u>: Reduced use of seclusion or restraints (decreased rate, amount, or duration) o To be eligible, each study must have reported on at least one of the outcomes above – Secondary outcomes: ~~o~~ As defined in the PICOTS criteria • Final health outcomes: – As defined in the PICOTS criteria KQs 2a, 2b, and 2c: As defined in the PICOTS criteria KQ 3: Same as KQs 1 and 2	None

Table 1. Eligibility criteria for review of strategies to de-escalate aggressive behavior (continued)

PICOTS	Inclusion	Exclusion
Timing	All KQs: Imminently or within current episode of care (e.g., inpatient hospitalization, emergency department stay)	All KQs: Outside current episode of care
Settings	All KQs: Acute care settings, including emergency department or hospital (e.g., private or public psychiatric hospitals, general medical hospitals at which discharge occurs within 35 days of beginning treatment)[a]	All KQs: Outpatient, community-based, jails, prisons, schools, chronic care, forensic-only,[b] or long-term care settings
Study designs	All KQs: • Systematic reviews, with or without meta-analyses • Randomized controlled trials • Nonrandomized controlled trials • Cohorts (prospective and retrospective) • Case-control studies • Single group pre/post studies (including pre/post studies with <3 pre- and <3 post-intervention time points)[c, d] • Interrupted time-series designs (i.e., time-series studies with ≥3 pre-intervention and ≥3 post-intervention measurements with one or more groups)[c]	All KQs: • Case studies or series • Cross-sectional studies • Studies without a comparison group • Nonsystematic review
Publications	All KQs: Original research	All KQs: Not original research (e.g., editorials without original data, newspaper articles)
Geographic locations	Developed countries ("very high" human development index per the United Nations Development Programme[65])	All other countries
Language	English	All other languages

[a] Studies of settings that treated patients receiving both acute and chronic care were excluded. To be clear, a single unit or wing of a hospital could be eligible if inpatient stays were 35 days or less, even if other sections of the larger hospital provided longer-term care. We assumed that studies describing their sample's inpatient clinical services as "acute care" referred to discharge within 35 days of admission, when no specific information about lengths of stay was available. We attempted to locate information about the types of care provided in study-specific settings if there was concern that study analyses may have included a mixture of acute-care and chronic-care patients. When no information was available to confirm that a study's inpatient clinical services were acute care or that lengths of inpatient stays were 35 days or less, we excluded it.

[b] We excluded studies focusing only on forensic units or hospitals, but studies conducted in acute care settings were eligible if their samples included both forensic and nonforensic patients.

[c] A "group" could indicate a group of patients, acute care unit, or hospital evaluated before and after implementation of an intervention.

[d] We considered time-series studies with 2 pre-intervention and/or 2 post-intervention measurements as pre/post studies.

FDA = U.S. Food and Drug Administration; KQ = Key Question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings.

Population(s)

- KQs 1 through 3
  - Adult individuals (ages 18 or older) with an identified psychiatric disorder, including substance use disorders and delirium (but not dementia), *or* with severe psychiatric symptomatology, who are at risk of or actively exhibiting active aggression toward self, others, or property.
    - We excluded mixed-age samples if data for adults were not reported separately.

- We included studies that did not specify the age distributions of their samples when their measures of central tendency (e.g., mean or median ages) strongly suggested that only adults were included.

Interventions

- KQs 1a and 2a: Strategies (early intervention techniques) targeted to reduce the likelihood of active aggression, such as:
  - Supportive language and verbal de-escalation;
  - Milieu-based changes, such as sensory rooms or staffing changes (including increased staff-to-patient ratios), specific staff training programs (including psychoeducation about collaborating with patients to reduce risk of aggression), or peer-based interventions;
  - Adjustments to the primary psychotropic regimen for the purpose of decreasing agitation or preventing aggression; these approaches (adjustments) may include an increase in an antipsychotic or mood stabilizer that treats the underlying psychiatric disorder);
  - Any intervention, or combination of interventions, different from seclusion and restraints that is aimed at preventing aggressive behavior (e.g., implementation of a procedure informed by the Six Core Strategies of the National Association of State Mental Health Program Directors (NASMHPD).
- KQs 1b, 1c, 2b, and 2c: Strategies targeted to decrease aggression for those who are actively aggressive, such as:
  - Psychiatric Emergency Response Teams
  - Medication protocols to treat aggressive behavior that use on- or off-label medications approved by the US Food and Drug Administration (FDA),[32] such as those described in project *BETA (Best practices in Evaluation and Treatment of Agitation)*
  - Any intervention, or combination of interventions, different from seclusion and restraints that is aimed at decreasing aggressive behavior (e.g., implementation of a procedure informed by NASMHPD's Six Core Strategies).
- KQ 3: Same as KQs 1 and 2.

Comparators

- KQs 1a and 2a:
  - Other strategies (early intervention techniques), but not seclusion and restraints, targeted to reduce the likelihood of active aggression, as described above for KQs 1a and 2a
  - Usual care, defined as the standard of care for a particular setting before implementation of an intervention designed to decrease the likelihood of active aggression and/or the use of seclusion and restraints
- KQs 1b, 1c, 2b, and 2c:
  - Other strategies targeted to decrease aggression for those who are actively aggressive, as described above for KQs 1b and 1c and for KQs 2b and 2c

- Seclusion or restraints (for 1b and 2b only):
  - Seclusion (involuntary confinement where individual is physically prevented from leaving)
  - Restraints, whether physical (e.g., any manual method, physical or mechanical device, material, or equipment that immobilizes or reduces the ability of a patient to move freely) or chemical (e.g., a psychotropic drug or medication when it is used as a restriction to manage the patient's behavior)
- Usual care, defined as the standard of care for a particular setting before implementation of an intervention designed to decrease aggression and/or the use of seclusion and restraints

- KQ 3: Same as KQs 1 and 2

Outcomes

- KQs 1a, 1b, and 1c (benefits):
  - Intermediate outcomes:
    - Primary outcomes:
      - Decreased aggression in terms of frequency, severity, or duration (as measured by direct counts or by validated aggression scales)
      - KQs 1a and 1c only: Reduced use of seclusion or restraints (decreased rate, amount, or duration)
      - To be eligible, each study must have reported on at least one of these two primary outcomes
    - Secondary outcomes:
      - For studies eligible for inclusion for primary outcomes, we also considered secondary outcomes, including: need for (and time to) additional sedation for patients presenting with violent and acute behavioral disturbances; need for additional security in response to violent and acute behavioral disturbances; number of patients sedated by emergency medication; psychiatric symptom severity scores (i.e., the Positive and Negative Symptom Scale, Total; the Clinical Global Impressions – Severity scale; the 5-item Acute-Agitation Cluster Score; and the Global Assessment of Functioning scale – Symptom score (GAF-S); medication-specific adverse events; incidence of delirium tremens in patients with alcohol withdrawal syndrome; and number of patients with alcohol withdrawal syndrome requiring transfer to an intensive care unit.
  - Final health outcomes:
    - improved quality of life, functioning, or patient experience
    - improved therapeutic relationship
    - decreased subsequent aggressive behavior
      - decreased subsequent use of seclusion or restraints
      - general resource use or costs

- KQs 2a, 2b, and 2c (harms): Patient injury or accidental death, staff injury, staff distress, patient distress (per self-report or clinical assessment); decreased adherence or engagement with treatment by patient; other side effects of interventions (e.g., medication side effects, such as excessive sedation, acute dystonia, and akathisia)
- KQ 3: Same as KQs 1 and 2

Timing

- KQs 1 through 3:
  - Imminently or within current episode of care (e.g., inpatient hospitalization, emergency department stay)

Setting

- KQs 1 through 3:
  - Acute care settings: emergency department or hospital (e.g., private or public psychiatric hospitals, general medical hospitals at which discharge occurs within 35 days of beginning treatment)
    - Studies of settings that treated patients receiving both acute and chronic care were excluded.
    - To be clear, a single unit or wing of a hospital could be eligible if inpatient stays were 35 days or less, even if other sections of the larger hospital provided longer-term care. We assumed that studies describing their sample's inpatient clinical services as "acute care" referred to discharge within 35 days of admission, when no specific information about lengths of stay was available. We attempted to locate information about the types of care provided in study-specific settings if there was concern that study analyses may have included a mixture of acute-care and chronic-care patients. When no information was available to confirm that a study's inpatient clinical services were acute care or that lengths of inpatient stays were 35 days or less, we excluded it.

In addition to the foregoing PICOTS, we considered the following other inclusion or exclusion criteria. Given concerns about risk of bias in observational and noncontrolled trials, and drawing from the experience of prior systematic reviews, we required a total sample size (or N) of 100 or more patients for any nonrandomized study after discussions with our Technical Expert Panel.

Study Design

- Systematic reviews, with or without meta-analyses
- Randomized controlled trials (RCTs), including cluster randomized trials
- Nonrandomized controlled trials ($N \geq 100$)
- Cohort studies (prospective and retrospective, $N \geq 100$)
- Case-control studies ($N \geq 100$)
- Pre/post studies ($N \geq 100$)
  - Note: A "group" could indicate a group of patients, acute care unit, or hospital evaluated before and after implementation of an intervention.
  - Note: We considered studies with 2 pre-intervention and/or 2 post-intervention measurements as pre/post studies.
  - Note: When the number of patients was not reported in a study we calculated it based on the number of beds, average length of stay and occupancy rate of the unit (if available).

    - Interrupted time-series designs (i.e., time-series studies with ≥3 pre-intervention and ≥3 post-intervention measurements with one or more groups and that reported an interrupted time series analysis)[66] (N ≥ 100)
  - Note: A "group" could indicate a group of patients, acute care unit, or hospital evaluated before and after implementation of an intervention.

Geographic location

- Developed countries ("very high" human development index as defined by the United Nations Development Programme[65])

Language

- English language only

Study Selection

Two members of the research team independently reviewed all titles and abstracts (generated by searches) against our inclusion/exclusion criteria (Table 1). We retrieved any publications marked for inclusion by either reviewer for evaluation of the full text. For titles and abstracts that lacked adequate information to determine inclusion or exclusion, we retrieved the full text for review. Then, two investigators independently reviewed the full texts to determine final inclusion or exclusion. The reviewers resolved any disagreements by discussion and consensus or by consulting a third member of the review team.

We considered systematic reviews for eligibility by determining whether their inclusion/exclusion criteria for population, comparisons, outcomes, and settings met our own criteria. However, we did not identify any eligible systematic reviews.

All results in both review stages were tracked in an EndNote® database. We recorded the principal reason that each excluded full-text publication did not satisfy the eligibility criteria (Appendix B).

Data Extraction

We designed, pilot-tested, and used a structured data abstraction form generated in AHRQ's Systematic Review Data Repository (http://srdr.ahrq.gov/) to ensure consistency of data abstraction. Trained reviewers initially abstracted data from each study. The data were then exported from Systematic Review Data Repository into a Microsoft® Excel spreadsheet, a senior reviewer then read each abstracted record and evaluated the completeness and accuracy of the data abstraction. We resolved discrepancies by consensus or by involving a third, senior reviewer.

We abstracted the following data from included trials and studies: study designs, eligibility criteria, population characteristics (such as age, sex, race, ethnicity), interventions, comparators, additional medications or interventions allowed, outcomes of interest and methods of outcome assessment, sample sizes, attrition, settings, geographic locations, and study funders. We recorded intention-to-treat results (i.e., all patients were analyzed as randomized with missing values imputed) if available. When eligible studies reported other data that were incomplete or missing, we contacted authors.

Quality (Risk of Bias) Assessment of Individual Studies

To assess the risk of bias of trials and studies, we followed EPC methods guidance[67] and rated the risk of bias for each relevant outcome as low, medium, or high. In general terms, results of a study with low risk of bias are considered to be valid. Medium risk of bias implies some confidence that the results represent true treatment effect. The study is susceptible to some bias, but the problems are not sufficient to invalidate the results (i.e., no flaw is likely to cause major bias). A study with high risk of bias has significant methodological flaws (e.g., stemming from serious errors in design or analysis) that may invalidate its results.

Ratings of risk of bias are not comparable across study designs. That is, a low-risk-of-bias nonrandomized study does not necessarily equal a low-risk-of-bias RCT. We considered the limitations of certain study designs when grading the strength of the evidence (explained below).

To determine risk of bias in a standardized way, we used the Cochrane Risk of Bias tool to appraise RCTs. We also used it to appraise the few cluster randomized trials (hereafter CRTs, where clusters were based on specific units in the facilities where the studies took place). Guidance for assessing risk of bias is similar for RCTs and CRTs[68] but the latter may need special attention to issues such as recruitment bias, baseline imbalance, loss of clusters, and inadequate or incorrect analytic techniques, and we made an effort to consider these matters in reviewing eligible CRTs.

For nonrandomized trials and observational studies, we employed criteria from the RTI Risk of Bias Tool for Observational Studies.[69] To minimize risk of bias in observational and noncontrolled studies addressing adverse outcomes (i.e., harms, a key focus of our report), we required a minimum total sample of 100 patients in nonrandomized studies (consistent with our work in prior reviews[70]). We did not assess risk of bias in noncontrolled or pre/post studies. The main reason is that the ability of these study designs to support causal inferences is very limited because of potential confounding from multiple sources that generally do not affect controlled studies as much (e.g., secular, time-based changes in outcomes of interest, selection bias, the influence of concurrent interventions, and attrition-related bias). We made an exception for single-group studies using an interrupted time-series design (i.e., using ≥3 pre-intervention measurements and ≥3 post-intervention measurements). That is, we included them in our assessments of risk of bias because their longitudinal assessment of outcomes before and after an intervention provided for a more specific evaluation of the intervention apart from secular, time-related changes, thereby reducing any related risk of bias. We reviewed each of these considerations with our Technical Expert Panel, who agreed with our approach.

Although no systematic review met our inclusion/exclusion criteria, we had intended to review eligible SRs that addressed any parts of our KQs and dually assess them for quality using a modified AMSTAR (Assessment of Multiple Systematic Reviews) instrument.[71]

Two independent reviewers assigned risk of bias ratings. Disagreements were resolved by discussion and consensus or by consulting a third, senior reviewer. Appendix C presents the risk of bias assessments of individual studies included in this review.

Data Synthesis

We synthesized all literature qualitatively and included all eligible studies regardless of risk of bias. We stratified study data by whether they came from controlled studies (e.g., RCT, cohort studies) or noncontrolled studies (e.g., pre/post, interrupted time-series).

A study might report data relevant to both preventive measures (subquestion [a]) and actively aggressive measures (subquestion [b] or [c]). Data for study groups not restricted to highly aggressive patients (i.e., the denominator involved both aggressive and non-aggressive patients) were considered relevant for subquestion (a). Data for groups restricted to highly aggressive patients were considered relevant to subquestion (b) and/or (c).

To determine whether quantitative analyses (i.e., meta-analysis) were appropriate, we assessed the clinical and methodological heterogeneity of the studies under consideration following established guidance.[72] After qualitatively assessing the PICOTS of included studies, looking for similarities and differences, we determined that our body of evidence was too heterogeneous to justify quantitative analyses.

We followed EPC guidance to assess publication bias for the final report.[61] However, we did not find enough comparative evidence to warrant quantitative tests of publication bias, such as funnel plot asymmetry, the trim and fill method, or selection modeling.[73]

Strength of the Body of Evidence

We graded the strength of evidence (SOE) for primary outcomes based on the guidance established by the EPC Program.[69] Developed to grade the overall strength of a body of evidence, this approach incorporates five key domains: study limitations (study design and aggregate risk of bias), consistency, directness, precision, and reporting bias. For some scenarios, this approach also considers other optional domains that may be relevant: a dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect). SOE receives one of four grades: high, moderate, low, or insufficient.

Grades reflect the strength of the body of evidence to answer KQs on the comparative benefits and harms of the interventions in this review. Table 2 defines the four SOE grades.[69]

Table 2. Definition of strength of evidence grades

Grade	Definition
High	We are very confident that the estimate of effect lies close to the *true effect* for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We are moderately confident that the estimate of effect lies close to the *true effect* for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the *true effect* for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the *true effect*.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Source: Berkman et al., 2014[74]

In grading evidence from single trials or studies (typically regarded as insufficient evidence), we gave more weight to those in which the reported findings were precise and graded some as low SOE. Mirroring our decision not to assess the risk of bias of pre/post studies, we did not grade the SOE from such studies, as they cannot be used to draw causal inferences about comparative benefits and harms.

Two trained reviewers assessed each domain for each primary outcome; differences were resolved by consensus. One of the two reviewers was always a senior researcher with experience

in grading SOE. Appendix D presents tables showing our assessments for each domain and the resulting SOE grades for KQ 1's primary outcomes (i.e., measures of aggressive behavior and use of seclusion and/or restraints) and for KQ 2's harms outcomes, organized by outcome category.

Applicability

We assessed applicability of the evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[75] We used the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the following: age of enrolled populations, sex of enrolled populations (e.g., fewer men may be enrolled in some studies), race or ethnicity of enrolled populations, diagnoses of involved sample, and location of and staffing for specific interventions.

Peer Review and Public Commentary

This report was posted for public comment and peer review. We addressed all comments in the final report, making revisions as needed. A disposition of comments report will be publicly posted 3 months after release of the final report.

Results

Introduction

This chapter presents the results of our systematic review. We first present the results of our literature searches and identify studies that met our inclusion criteria (referred to as "included studies"). We then discuss the findings from our analyses for each Key Question (KQ), providing an overview of key points and summarizing the supporting judgment for our strength of evidence (SOE) grades[74] (Tables 5, 6, and 7).

Next, we present the detailed synthesis organized first by subquestion (e.g., 1a, 1b, 1c), second by intervention type, and third by the study design. The last factor involves two main classifications: (a) randomized controlled trials (RCTs), nonrandomized controlled trials (NRCTs), and cohort studies and (b) pre/post studies without an independent control group (referred to as "pre/post studies"). The former group represents all studies with at least one independent control group; we included them in SOE grades. The second pre/post group refers to studies that we did not use for SOE grading. As described in Methods, we did not assign risk of bias ratings to pre/post studies or grade the SOE for those studies because they are very limited in their ability to support causal inferences, largely as a result of potential confounding from multiple sources that generally do not affect controlled studies as much.

KQ 1 focuses on the effectiveness of strategies to prevent aggressive behavior in persons without active aggression (KQ 1a) and, in those exhibiting active aggression, to de-escalate aggressive behavior (KQ 1b) or reduce the use of seclusion and/or restraints (KQ 1c). A study could have data relevant to one or more subquestions. Some studies were challenging to classify into these subquestions. For example, some outcome measures combined prevention of aggression (1a) with response to aggressive behavior (relevant to 1b or 1c). Multimodal interventions were usually policies and considered preventive (1a), but sometimes they included components that were specifically in response to aggressive behavior (1b or 1c). Our decisions about classification were guided by the populations involved in the reported analyses. For example, if the denominator included all patients on a unit (which could involve both those actively aggressive and those not), we considered the data to be relevant to subquestion (a). If the denominator included only those patients who were actively aggressive, we regarded those data as relevant to subquestion (b) or (c). If the study provided an analysis for the general population (a) but also provided a subanalysis for the aggressive group (b or c), it could provide data relevant to multiple subquestions.

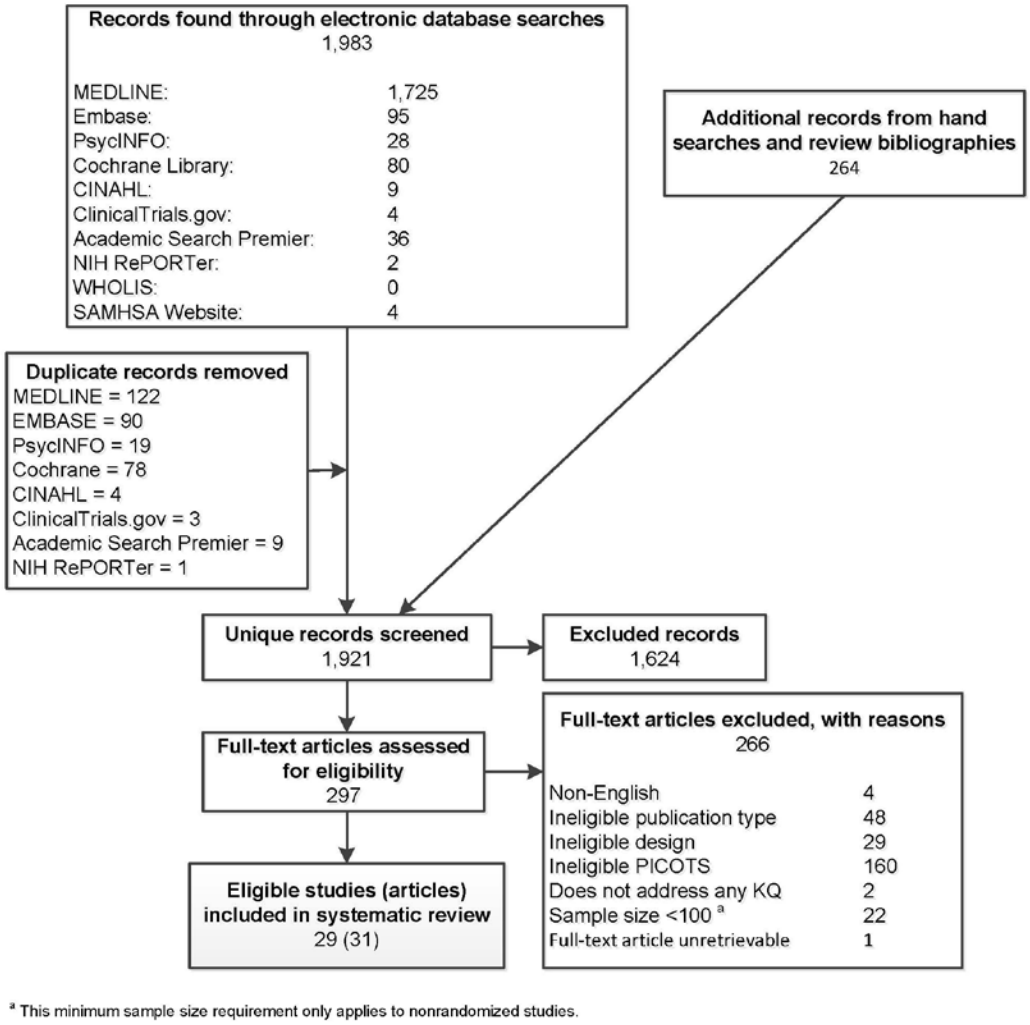
KQ 2 evaluates the harms resulting from the same strategies evaluated in KQ 1; its organization of findings and classification of studies mirrors that of KQ 1. KQ 3 evaluates potential moderators of the benefits or harms of strategies to prevent or de-escalate aggressive behavior or use of seclusion or restraints, and it also follows the same structure as KQs 1 and 2.

Results of Literature Searches

Searches of all sources identified a total of 1,921 potentially relevant citations. In all, we included 29 primary studies (described in 31 articles) that compared interventions to de-escalate aggressive behavior or reduce the use of seclusion or restraints with an alternative strategy or usual care and provided data for our KQs.[76-106] Figure 2 describes the flow of literature through the screening process according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) categories.[62] Appendix A presents our search strategy, and Appendix B

provides a complete list of articles excluded at the full-text screening stage with reasons for exclusion.

Figure 2. Disposition of articles for strategies to de-escalate aggressive behavior



KQ = Key Question; PICOTS = Populations-Interventions-Comparators-Outcomes-Time Frames-Settings.

Description of Included Studies

The included studies focused predominantly on benefits, reporting on aggressive behavior and seclusion or restraint use (or both); 15 studies also reported harms, such as adverse effects of medications or suicide attempts[76,77,80-82,88,90,91,94,98,99,101-103,106] (Table 3). Most interventions (n=19) took place in psychiatric hospitals or inpatient psychiatric treatment units or facilities;[76,79-81,88,89,92] five were in emergency department settings.[77,93,98,99,102] Half (n=15) took place in the United States.

Table 3. Characteristics of included studies

Study Characteristic	Number (%)
Country	
United States	15 (52)
Outside the United States	14 (48)
Funding[a]	
Government	7 (24)
Foundations/nonprofit	3 (10)
Academic (treating hospital)	1 (3)
Pharmaceutical company	1 (3)
Multiple (foundation and government)	2 (7)
Internal funding	1 (3)
No financial support	1 (3)
Not reported	13 (45)
Settings	
Public psychiatric hospital	5 (17)
Private or academic psychiatric hospital	2 (7)
Inpatient psychiatric treatment units or facilities[b]	10 (35)
Multiple (inpatient psychiatric or forensic hospitals)	1 (3)
Multiple (inpatient psychiatric wards and psychiatric emergency department)	1 (3)
General medical hospital	2 (7)
General emergency department	2 (7)
Psychiatric emergency department	3 (10)
Psychiatric intensive care unit	3 (10)
Study design	
Randomized controlled trial	5 (17)
Cluster randomized trial	3 (10)
Nonrandomized controlled trial	2 (7)
Retrospective cohort study	1 (3)
Pre/post study with no control group (not included in strength of evidence grading)	18 (62)
Used an active treatment comparison arm	6 (21)
Primary outcomes measured	
Aggression	21 (72)
Seclusion	7 (24)
Restraints	12 (41)
Seclusion and restraints	10 (35)
Harms	15 (52)
Risk of Bias	
Low	1 (9)
Medium	5 (45.5)[c]
High	5 (45.5)[c]

[a] Percentages of studies funded by different sources add up to a slightly smaller or greater value than 100%, but these numbers do reflect all included studies.

[b] No further information about their public, private, or academic status.

[c] Percentages based on a total of 11 studies that used controlled designs and therefore received risk of bias ratings.

Generally, for those studies reporting on demographics for their patient populations, the mean age ranged between 38 and 40 years, the distribution by males and females varied widely across studies, and race or ethnicity was sparsely reported. Of these 29 studies, 19 took place in acute inpatient psychiatric settings, and most involved serious mental illness diagnoses. The majority of articles did not, however, report the proportion of patients with agitated or aggressive behavior. Patient characteristics are further detailed in Appendix E.

Our interventions are presented in five broad categories of interventions: staff training, risk assessment, multimodal, environmental or group psychotherapeutic, or medication protocols. Staff training interventions aim to equip clinical staff providing acute care to patients with psychiatric symptomatology with new skills and/or 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 interventions involve a combination of different intervention types (e.g., enhanced administrative review of patients with high restraint use, staff training in strategies to better manage patients' difficult behavior) with the purpose of decreasing the occurrence of active aggression or use of seclusion and/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 to active aggression. Finally, medication protocols encompass any medication-focused intervention, ranging from hospital or unit-wide policies specifically affecting how or which medications can be used to manage active aggression to the use of emergency medication(s) to de-escalate active aggression.

Interventions could focus on preventing aggression (KQ 1a, KQ 2a), de-escalating aggression (KQ 1b, KQ 2b), and de-escalating aggression to reduce use of seclusion and restraints (KQ 1c, KQ 2c). Studies that did not differentiate their results between those patients with aggression and those who were not yet aggressive were included in the prevention of aggressive behavior results. Table 4 shows the assumed main focus of the studies, the two KQs (and subquestions) they address, and the nature of evidence report (benefits only or benefits and harms). The table has no information on KQ 3, because no studies reported on potential modifiers that would have been relevant to the other KQs.

Table 4. Five classes of interventions by focus and available evidence

Intervention Category	Prevention (KQ 1a, KQ 2a)	De-escalation (KQ 1b, KQ 2b)	De-escalation and Reduce Seclusion or Restraints (KQ 1c, KQ 2c)
Staff training	1 NRCT reporting benefits and harms; 3 pre/post studies reporting only on benefits	Data not reported by those presenting with aggression	No studies
Risk assessment	2 CRTs reporting on only benefits	Not applicable	Not applicable
Multimodal programs	11 pre/post studies, 5 reporting benefits and harms, 6 reporting only on benefits	Data not reported by those presenting with aggression	No studies
Environmental or group psychotherapeutic interventions	3 pre/post studies, 1 reporting both benefits and harms, 2 reporting only on benefits	No studies	No studies
Medication protocols	No studies	4 RCTs reporting benefits and harms 2 NRCTs reporting benefits and harms	1 RCT and 1 retrospective cohort reporting only on benefits 1 pre/post study reporting on benefits and harms

CRT = cluster randomized trial; KQ = Key Question; NRCT = nonrandomized controlled trial; RCT = randomized controlled trial.

Of the 29 primary studies, 11 were controlled trials that provided eligible data for SOE ratings; only 4 took place in the United States,[85,98,102,103] 1 in a psychiatric inpatient unit,[103] 2 in an emergency department,[98,102] and 1 in an intensive care unit with intubated patients.[85] All controlled trials occurred in inpatient psychiatric settings except for those involving medication protocols, which also involved emergency department[73,77,98,99,102] or intensive care unit (ICU) settings.[85] The remaining 18 studies were pre/post studies, for which we did not grade SOE; we identified no interrupted time-series studies. We report below in Key Points only on findings from trials or studies for which we could grade SOE.

We had data for KQs 1 (benefits) and 2 (harms) from the following types of trials or studies: KQ 1a (benefits of prevention), three CRTs; KQ 1b (benefits of de-escalating aggression), four RCTs and two NRCTs; KQ 1c (benefits of reducing seclusion/restraint use), one RCT and one retrospective cohort study; KQ 2a (harms of prevention), one CRT; and KQ 2b (harms of de-escalating aggression), four RCTs and two NRCTs. No eligible studies pertained to KQ 2c. We identified no eligible studies for KQ 3.

We found the SOE for most of the findings to be insufficient, with the justification for these assessments provided in the tables below (see Appendix D of the main report for detail about scores for each SOE domain). To help clarify this literature's range of different types of studies, and the heterogeneity of approaches, populations, settings, and outcomes, we report below the findings for all 11 eligible studies, whether the SOE was insufficient or low. We report the findings as the authors reported them; we then indicate the SOE for the finding.

Comparative Benefits of Strategies (Key Question 1)

Key Points

Key Question 1a: Benefits of Strategies To Prevent Aggressive Behavior

Staff Training Interventions Versus Usual Care

- One CRT reported staff training in interpersonal communication led to fewer incidents of seclusion and restraint, and a larger decrease in incidents of seclusion and restraint compared to usual care on a control unit[103] (one CRT, insufficient SOE).

Risk Assessment Interventions Versus Usual Care

- Units employing structured risk assessment protocols reported fewer aggressive incidents when compared with usual-care units. One CRT[78] focused on lowering severe aggressive incidents; the other[87] focused on any aggressive incidents (one CRT for each outcome, low SOE).
- Cluster trials in which units employed structured risk assessment protocols reported fewer hours spent in seclusion[87] (one CRT, low SOE) and fewer coercive measures than usual-care units[78] (one CRT, low SOE).

Multimodal Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Environmental or Group Psychotherapeutic Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Medication Protocols Versus Other Medication Protocols or Alternative Strategies

- We identified no eligible studies (insufficient SOE).

In Table 5 for KQ 1a, we present our supporting judgment for our SOE grades for evidence from studies with eligible study designs (i.e., any study that we could rate for risk of bias). Supporting judgment is essentially the ratings on the main domains for grading SOE (study limitations [i.e., risk of bias], consistency, directness, and precision). The CRTs in this report did not control for clustering in their statistical analyses, which weakened the SOE grade. Table 5 has entries only for staff training (one CRT) and for risk assessment strategies (two studies); we had no relevant studies for the other three types of interventions.

Table 5. Summary of findings with strength of evidence grades: Comparative benefits of two strategies for preventing aggressive behavior[a] (Key Question 1a)

Intervention and Comparison	Primary Outcome of Interest	Outcome N of Patients Analyzed	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Staff training vs. usual care	Change in aggressive behavior	Aggressive behavior resulting in staff injury NR	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	Fewer assaults on staff occurred in unit that received the staff training vs. the control unit (4 vs. 5); no statistical testing reported.[103]
	Change in seclusion or restraint	Incidents of seclusion or restraint NR	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	Fewer incidents of seclusion or restraint on the unit that received the training vs. the control unit (84 vs. 228); no statistical testing reported.[103]
Risk assessment vs. usual care	Change in aggressive behavior	Number of aggressive patients 170 during baseline period, 458 during intervention period	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Nonsignificant 50% RR reduction with risk assessment[87]
		Aggressive incidents 170 during baseline period, 458 during intervention period	Low	Medium risk of bias, consistency unknown—single study, direct, precise	Significant 68% RR reduction with risk assessment, p<0.0001 reported; failure to control for intraclass correlations weakens the finding.[87]
		Rate of severe aggressive incidents 973 post-intervention	Low	Medium risk of bias, consistency unknown—single study, direct, precise	Significantly lower risk with structured risk assessment: (RR, 0.59; 95% CI, 0.41 to 0.83) p<0.001 reported; failure to control for intraclass correlations weakens the finding. Decrease achieved since baseline with risk assessment (-41%) vs. usual care (-15%), no statistical testing reported.[78]

Table 5. Summary of findings with strength of evidence grades: Comparative benefits of two strategies for preventing aggressive behavior[a] (Key Question 1a) (continued)

Intervention and Comparison	Primary Outcome of Interest	Outcome N of Patients Analyzed	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
		Change in physical attacks 973 post-intervention	Low	Medium risk of bias, consistency unknown—single study, direct, precise	Significantly greater decrease with risk assessment (-41%) vs. usual care (-7%), p<0.001 reported; failure to control for intraclass correlations weakens the finding.[78]
Risk assessment vs. usual care (continued)	Change in seclusion or restraint (continued)	Secluded patients 170 during baseline period, 458 during intervention period	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Nonsignificant 8% RR increase with risk assessment.[87]
		Seclusion incidents 170 during baseline period, 458 during intervention period	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Nonsignificant 15% RR reduction with risk assessment.[87]
		Hours in seclusion 170 during baseline period, 458 during intervention period	Low	Medium risk of bias, consistency unknown—single study, direct, precise	Significant 45% RR reduction with risk assessment, p<0.0001 reported; failure to control for intraclass correlations weakens the finding.[87]
		Change in coercive[b] incidents 973 post-intervention	Low	Medium risk of bias, consistency unknown—single study, indirect, precise	Significant decrease from baseline with risk assessment (-27%) vs. usual care (+10%), p<0.001 reported; failure to control for intraclass correlations weakens the finding.[78]

[a] For KQ 1a, we had no studies of eligible study design for environmental or group psychotherapeutic interventions or multimodal interventions; thus, we could not rate risk of bias.

[b] Coercive measures covered a wide range of measures, from forced injection of psychotropic medication to seclusion and mechanical restraint.[78]

CI = confidence interval; CRT = cluster randomized trial; KQ = Key Question; N = number; NR = not reported; RR = relative risk; vs. = versus.

Key Question 1b: Benefits of Strategies To De-escalate Aggressive Behavior

Staff Training Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Risk Assessment Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Multimodal Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Environmental or Group Psychotherapeutic Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Medication Protocols Versus Other Medication Protocols or Alternative Strategies

- In an inpatient psychiatric unit, effects of intramuscular haloperidol did not differ from effects of intramuscular flunitrazepam for treating patients displaying aggressive psychotic behavior[82] (one RCT, insufficient SOE).
- In a public psychiatric hospital emergency department, intramuscular droperidol for treating patients exhibiting violent and acute behavioral disturbance did not reduce the duration of aggressive behavior any more than intramuscular midazolam, but droperidol treatment did result in fewer patients requiring additional sedative medication over the ensuing 6 hours than intramuscular midazolam[77] (one RCT, insufficient SOE).
- In a hospital psychiatric emergency service, compared with intramuscular lorazepam, intramuscular lorazepam plus haloperidol for treating patients exhibiting serious, acute agitated, or aggressive behavior did not result in greater overall reduction in aggressive or agitated behavior, but the medication regimen did produce a more rapid reduction in aggressive or agitated behavior and more patients who achieved clinically significant improvement in aggressive or agitated behavior[98] (one RCT, insufficient SOE).
- In an urban university emergency department, intramuscular droperidol for intoxicated or psychiatrically ill, violently agitated patients requiring chemical restraint produced more rapid sedation and greater sedation overall than intramuscular lorazepam[102] (one RCT, insufficient SOE).
- In an inpatient psychiatric hospital setting, treatments that included any olanzapine, any risperidone, or any haloperidol for treating patients with agitation did not differ from each other in reducing aggressive behavior or suicidality[106] (one NRCT, insufficient SOE).
- In an inpatient psychiatric emergency service, oral risperidone, olanzapine, quetiapine, or haloperidol for treating patients with agitation did not differ from each other in reducing aggressive behavior[99] (one NRCT, insufficient SOE).

In Table 6 for KQ 1b, we present information (supporting judgment) for our SOE grades for evidence based on studies with an eligible study design. For this subquestion, we had no relevant studies of staff training, risk assessment, multimodal, or environmental or group psychotherapeutic interventions. All findings for the medications protocols were underpowered to test noninferiority.

Table 6. Summary of findings with strength of evidence grades: Comparative benefits of medication-based strategies for de-escalating aggressive behavior (Key Question 1b)

Intervention and Comparison	Primary Outcome of Interest	Outcome N of Patients Analyzed	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Medication protocols vs. other medication protocols	Change in aggressive behavior	Aggression response rate 28	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Nonsignificant difference in rates of OAS score reduction at 90 minutes in haloperidol vs. flunitrazepam (92% vs. 80%).[82]
		Duration of aggression 91	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Nonsignificant difference in the median duration of violent and acute behavioral disturbances with droperidol vs. midazolam vs. a combination of droperidol plus midazolam (20 vs. 24 vs. 25 minutes).[77]
		Clinically significant change in OAS scores 20	Insufficient	Low risk of bias, consistency unknown—single study, direct, imprecise	Significantly greater likelihood of improvement (decrease of four or more points) in OAS scores of aggressive or agitated behavior at 60 minutes with the combination of haloperidol plus lorazepam (100%) vs. lorazepam alone (55%), p=0.03 (note small sample size).[98]
		Time to OAS improvement 20	Insufficient	Low risk of bias, consistency unknown—single study, direct, imprecise	Significantly improvement in shorter time to OAS improvement with the combination of haloperidol plus lorazepam vs. lorazepam alone, data NR, p=0.028 (note small sample size).[98]
		Sedation score at 5, 10, 15, 30, and 60 minutes 202	Insufficient	High risk of bias, consistency unknown—single study, direct, precise	Significantly lower mean sedation scores (i.e., less combative, violent, or out of control behavior) at 10, 15, 30 and 60 minutes with droperidol vs. lorazepam, each p <0.001[102]
		Change in CGI-A scores 558	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	No differences found in changes in percentages of patients with CGI-A score ≥3 from baseline to day 6 or to last day of observation with olanzapine vs. risperidone vs. haloperidol, p=NR.[106]
		Change in MOAS total aggression scores 101	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Nonsignificant differences between risperidone vs. olanzapine vs. quetiapine vs. haloperidol in changes in mean total MOAS scores from baseline to 72 hours.[99]

CGI-A = Clinical Global Impression Severity of Illness – Aggression; MOAS = Modified Overt Aggression Scale; n = number of patients; NR = not reported; OAS = Overt Aggression Scale; vs. = versus.

Key Question 1c: Benefits of Strategies To Reduce Seclusion and Restraint Use in Aggressive Patients

Staff Training Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Risk Assessment Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Multimodal Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Environmental or Group Psychotherapeutic Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Medication Protocols Versus Other Medication Protocols or Alternative Strategies

- One RCT in an inpatient psychiatric unit involved acutely agitated and violent inpatients and compared a first choice of involuntary medication treatment with oral or intramuscular haloperidol plus promethazine with a first choice of seclusion.[86] Compared with seclusion, the medication option did not produce differences either in subsequent mechanical restraint use (one RCT, insufficient SOE) or in subsequent coercive incidents (i.e., seclusion, restraint, or involuntary medications) (one RCT, insufficient SOE).
- For treating delirium in an inpatient ICU, immediate (within 24 hours) treatment with at least one dose of an antipsychotic medication led to fewer mean days in restraints than did delayed or no treatment[85] (one retrospective cohort, insufficient SOE).

In Table 7 on KQ 1c, we present our supporting judgment for our SOE grades for each eligible study (in this case only for medication protocols).

Detailed Synthesis

We describe in separate sections the studies with benefits data relevant to KQ 1a (prevention of aggressive behavior), KQ 1b (de-escalating aggressive behavior), and KQ 1c (de-escalating aggressive behavior and reducing seclusion and restraints). We present the studies by intervention, then by study design. Appendix D presents detailed SOE tables for each KQ 1 primary outcome, organized by intervention type. Appendix E contains detailed study characteristics tables across all intervention types. Summary tables presenting all characteristics and outcomes for all pre/post studies are available in Appendix F.

Key Question 1a: Prevention of Aggressive Behavior

Evidence on prevention of aggressive behavior (Table 8) came from the following: (a) three CRTs (one staff training intervention, two risk assessment interventions), all with usual-care comparators. None of the CRTs controlled for interclass correlations, likely increasing the risk of detecting an effect that is not actually present. We also found three pre/post studies of staff training interventions and 11 pre/post studies of multimodal interventions (policies to prevent aggressive behavior); as explained earlier, however, we did not rate these types of studies for risk of bias or grade their SOE.

Table 7. Summary of findings with strength of evidence grades: Comparative benefits of medication-based strategies for reducing seclusion and restraint use in aggressive patients (Key Question 1c)

Intervention and Comparison	Primary Outcome of Interest	Outcome N of Patients Analyzed	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Medication protocols vs. other medication protocols or usual care	Change in seclusion or restraint	Seclusion incident rate 659	Insufficient	High risk of bias, consistency unknown—single study, direct, precise	Significant lower risk with involuntary medication[a] as first choice vs. seclusion as first choice (RR, 0.51; 95% CI, 0.34 to 0.79), p<0.001[86]
		Seclusion hours 659	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	Lower number of overall hours with involuntary medication[a] as first choice vs. seclusion as first choice (998 vs. 2,098), no statistical testing reported[86]
		Seclusion duration 659	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	Longer mean duration with involuntary medication[a] as first choice vs. seclusion as first choice (32 vs. 30 hours), no statistical testing reported[86]
		Seclusion duration rate 659	Insufficient	High risk of bias, consistency unknown—single study, direct, precise	Significant lower risk with involuntary medication[a] as first choice vs. seclusion as first choice (RR, 0.54; 95% CI, 0.5 to 0.58) p<0.001[86]
		Mechanical restraint incident rate 659	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	No significant difference in involuntary medication[a] as first choice vs. seclusion as first choice (RR, 1.44; 95% CI, 0.38 to 5.36).[86]
		Duration in restraints 200	Insufficient	High risk of bias, consistency unknown—single study, direct, precise	Significant decrease with single-dose delirium treatment vs. no delirium treatment, both in the first 24 hours, 3 vs. 6 days, p<0.001[85]
		Coercive incident rate[b] 659	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	No significant difference in coercive incident rate in involuntary medication[a] vs. seclusion as first choice options (RR, 0.95; 95% CI, 0.67 to 1.35)[86]

[a] "Involuntary medication" refers to singled dose haloperidol plus promethazine or lorazepam.

[b] "Coercion" refers to a sequence of coercive episodes (seclusion, mechanical restraint, or involuntary medication) for less than 24 hours.

CI = confidence interval; N = number; RR = relative risk; vs. = versus.

Table 8. Characteristics, outcomes, and risk of bias rating of three controlled studies to prevent aggressive behaviors (Key Question 1a)

Intervention First Author, Year Study Design Setting, Country	N Duration (Months)	Intervention Comparator	Aggressive Behavior	Restraint Use Seclusion Use	Seclusion and Restraint	Risk of Bias Rating
Staff Training: Smoot et al., 1995[103] CRT Inpatient psychiatric recidivist units[a] United States	NR[b] 15 months[c]	G1: Empathic interpersonal communication training program for hospital staff G2: Usual care	Percentage change from baseline in assaults on staff (n's at baseline, endpoint) G1: -20.0 (from 5 to 4) G2: -61.5 (from 13 to 5) p=NR	NR NR	Percentage change from baseline in incidents of use of seclusion and restraint G1: -30.0 G2: +100.0 p=NR	High
Risk Assessment: Abderhalden et al., 2008, 2011[78] CRT Psychiatric inpatient treatment facilities Switzerland	973 post-intervention 6 months (3 months baseline, 3 months intervention)	G1: Structured violence risk assessment, 4 unit cluster (n=390) G2: Usual care, 5-unit cluster (n=583)	Severe aggressive incidents over 3 months, total n G1: 60 G2: 100 p=NR Severe aggressive incidents, percentage change from baseline G1: -41% (RR 0.59, 95% CI, 0.41 to 0.83, p<0.001) G2: -15% (RR 0.85, 95% CI, 0.64 to 1.13) p=NR Physical attacks[e] over 3 months, total n (% change) G1: 38 (-41%) G2: 55 (-7%) p<0.001	NR NR	Coercive measures[d] over 3 months, total n G1: 135 G2: 126 p=NR Coercive measures, percentage change from baseline G1: -27% G2: +10% p<0.001	Medium
Risk Assessment: van de Sande et al., 2011[87] CRT Acute psychiatric units Netherlands	170 (baseline period), 458 (intervention period) 40 weeks (10 weeks baseline, 30 weeks intervention)	G1: Structured violence risk assessment, 2 unit cluster (n=80 [baseline period], 207 [intervention period]) G2: Usual care, 2-unit cluster (n=90 [baseline period], 251 [intervention period])	Aggressive patients over 30 weeks, total n G1: 29 G2: 62 -50% decrease in G1 vs. G2 (in comparison of change from baseline and intervention periods) p>0.05 Incidents of aggression during first 3 days, total n G1: 4 G2: 19 p=0.001	NR Patients secluded during 30 weeks, total n G1: 60 G2: 42 +8% increase in G1 vs. G2 (in comparison of change from baseline and intervention periods) p<0.10	NR	Medium

Table 8. Characteristics, outcomes, and risk of bias rating of three controlled studies to prevent aggressive behaviors (Key Question 1a) (continued)

Intervention First Author, Year Study Design Setting, Country	N Duration (Months)	Intervention Comparator	Aggressive Behavior	Restraint Use Seclusion Use	Seclusion and Restraint	Risk of Bias Rating
Risk Assessment: van de Sande et al., 2011[87] (continued)			Incidents of aggression over 30 weeks, total n G1: 52 G2: 117 -68% decrease in G1 vs. G2 (in comparison of change from baseline and intervention periods) p<0.0001	Incidents of seclusion over 30 weeks, total n G1: 93 G2: 75 -15% decrease in G1 vs. G2 (in a comparison of change between baseline and intervention periods) Unadjusted p>0.05 Duration of seclusion over 30 weeks, total hours G1: 1,624 G2: 2,149 -45% decrease in G1 vs. G2 (in comparison of change from baseline and intervention periods) p<0.0001		

[a] The two study units specialized in caring for people with a primary diagnosis of mental illness who had returned to the hospital within one year of a prior discharge.[103]

[b] Mean of 92 patients discharged per month in each unit, meaning about 184 patients were included in the study each month.[103]

[c] Baseline period was 6 months long (July to December 1990), training period was 3 months long (April to June 1991), and post-training period was 6 months long (July to December 1991).[103]

[d] Coercive measures covered a wide range of measures, from forced injection of psychotropic medication to seclusion and mechanical restraint.[87]

[e] 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.[87]

CRT = cluster randomized trial; G = group; N = number; NR = not reported; SOAS-R = Staff Observation Aggression Scale-Revised; vs. = versus.

Staff Training Interventions Versus Usual Care

Controlled Studies

One CRT (Table 8 above) tested a staff training intervention targeted at de-escalation of aggressive behavior.[103] The study was conducted on two psychiatric units in the United States; both specialized in treating adults with a primary mental health diagnosis who returned to the hospital within one year of discharge. The units were similar in size and function, and they served approximately 92 patients per month. One unit was randomized to the intervention, and the other unit served as the control. Of the 35 staff on the intervention unit, 19 received a 32-hour program in four sequential, 8-hour sessions that were held weekly. The major skill taught was accurate empathy; training (through interpersonal communication training) included both didactic and role-playing components. Outcomes included incidents of seclusion and restraints, and assaults on staff. On the intervention unit, assaults on staff declined from five in the 1-year period before the intervention to four in the year following the intervention (20.0% decrease). On the control unit, assaults on staff decreased from 13 to 5 (61.5% decrease) during this time period. Seclusion and restraint incidents declined from 120 to 84 (30.0% decrease) on the intervention unit and increased on the control unit from 114 to 228 (100.0% increase). The investigators did not report tests of statistical significance.

Pre/Post Studies

Three staff training intervention studies targeted the de-escalation of aggressive behavior using a pre/post design.[84,96,97] One study[84] took place in an urban psychiatric inpatient unit in the United States and used a recovery-oriented cognitive therapy milieu training program for 29 staff members. Staff participated in 2-hour weekly sessions for 4 weeks (8 hours total). Psychiatrists and senior psychologists received a condensed version (4 hours total). The program aimed to promote staff empathy, warmth, and genuineness and an understanding of challenging behaviors, such as aggression, and to develop tools that allow staff to prevent patients' maladaptive behavior from escalating to the point of physical or chemical intervention. Outcomes included incidents of seclusion and restraint, which declined from 19 in the 4 months before the intervention to 7 incidents in the 4 months after the intervention. Because of the limited number of cases, the investigators did not perform statistical analyses.

Another pre/post study assessed the effects of training courses in prevention and management of violence and aggression and rates of violence.[96] The intervention was conducted on 14 acute care psychiatric units in three hospitals in the United Kingdom. One unit was female only, the second was for assessments, and the remainder were mixed-gender units. Training consisted of either a 5-day foundation course or a 1-day annual update; it focused on prediction, anticipation, and prevention of violence, including response to aggression, de-escalation, communication skills, problem solving skills, and skills with restraints. Outcomes included incidents of verbal aggression, property damage, and physical aggression. Time frames for measurement of outcomes included 1- and 4-week periods. No results were reported for rates of aggression after the 5-day course, using the 4-week time frame. However, the investigators found significantly higher rates of physical (incidence rate ratio [IRR], 1.50; $p<0.001$) and verbal aggression (IRR, 1.34; $p=0.042$) in the week that staff received training in the 5-day course; the authors interpreted this as evidence that aggression increased when staff were in training. With regard to the update course, physical aggression increased 1 month after the update course (IRR, 1.17; $p<0.001$); verbal aggression dropped 1 month after the update course (IRR, 0.79; $p=0.019$) but increased 2 months after it (IRR, 1.13; $p=0.026$). Physical aggression also rose 3 weeks (IRR, 1.17; $p=0.04$)

and 4 weeks after the update course (IRR, 1.20; p=0.019); verbal aggression rose in the week that staff received the update training (IRR, 1.21; p=0.038).

Finally, a pre/post study was conducted in a psychiatric intensive care unit in the United Kingdom.[97] The intervention consisted of training in prevention of aggressive incidents, de-escalation, and restraints. Other details about the training, such as the extent (i.e., number of hours), were not specified. Outcomes included both the number of incidents and the severity of incidents. Severe incidents were those that required seclusion or increased staffing (e.g., 1:1 or 2:1) or rapid tranquilization. Outcomes were measured for the 6 months before and after the training intervention. The intervention had no effect on the rate of aggressive incidents in an unadjusted model (odds ratio [OR], 0.986; p=0.92). Similarly, the intervention had no effect on the proportion of incidents that were severe in an unadjusted model (OR, 0.577; p=0.064), or the proportion of incidents that required rapid tranquilization using an unadjusted model (OR, 0.876; p=0.704). The proportion of incidents requiring hands-on intervention was not statistically significantly different in an unadjusted model (OR, 0.517; p=0.097). Findings based on adjusted models for this study's outcomes are described in Appendix F.

Risk Assessment Interventions Versus Usual Care

Controlled Studies

Two CRTs compared the use of a structured risk assessment protocol with usual care[78,87] (Table 8 above). Both trials used the Brøset Violence Checklist as part of the protocol. However, one trial used a more comprehensive protocol that included 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.[87]

The trials also differed in the length of time over which they evaluated their risk assessment protocols. For example, the first trial[78] implemented the risk assessment protocol for the first 3 days, whereas the van de Sande et al. trial from The Netherlands[87] used the risk assessment protocol throughout each patient's stay. To measure aggressive behavior, the trials used the Staff Observation Aggression Scale-Revised (SOAS-R); however, one trial evaluated "severe" aggression (i.e., SOAS-R score $\geq$9),[78] whereas the other trial evaluated only aggression,[87] preventing us from pooling results. All patients in both trials were at least 18 years old (mean ages from 38 to 40 years); the majority of patients were male. Only van de Sande et al.[87] reported on patients' race or ethnicity. During the baseline period, the trial classified approximately one-quarter of patients as ethnic minorities; this proportion increased to approximately one-third during the intervention period.

The Swiss trial reported few baseline differences between intervention and comparison patients with regard to clinical or sociodemographic characteristics.[78] However, the Dutch trial found more substantial baseline differences,[87] including the proportion of patients involuntarily detained, the proportion of those with a psychotic or personality disorder, and the total number of seclusion hours; all comparisons showed an increased preponderance in the experimental units.[87]

These trials, both government funded, were conducted as CRTs. However, neither trial analyzed its data in a way that correctly made use of this study design.

Both trials found lower aggression incidents[87] and rates[78] when compared with the usual-care conditions. In the Abderhalden trial, both the risk assessment and usual-care conditions reported a reduction in the rate of severe aggression, but the reduction in the experimental arm (RR, 0.59; 95% CI, 0.41 to 0.83; p<0.001) was significantly larger than in the usual-care condition (RR,

0.85; 95% CI, 0.64 to 1.13).[78] The intervention arm reported fewer attacks ($p<0.001$ a decline of 41% vs. 7% in the experimental and control conditions, respectively) and use of coercive measures ($p<0.001$, decrease of 27% vs. an increase of 10% in the experimental and control conditions, respectively) when compared with usual care.[78] Finally, for evaluating any aggressive incidents (i.e., not limited to severe aggression), the van der Sande trial reported a relative risk reduction (RRR) of -68 percent ($p<0.001$).[87] Specifically, the number of incidents per week decreased from 4.9 per week to 1.7 per week in the risk assessment arm, whereas the number of incidents per week in the usual-care condition increased from 3.5 per week during the baseline to 3.9 per week during the intervention period. The risk assessment protocol led to similar reductions in the relative risk of time spent in seclusion (RRR, -45%; $p<0.05$) and the number of patients engaging in aggression (RRR, -50%; $p<0.10$) when compared with the control condition; however, the later effect was not statistically significant.[87]

Multimodal Interventions Versus Usual Care

Controlled Studies

We found no eligible controlled studies of multimodal interventions.

Pre/Post Studies

We found 11 pre/post studies on multimodal interventions that reported on preventing aggressive behavior, including seclusion and restraint use.[79,83,88-94,100,101] Please refer to Appendix F for detailed study characteristics and results; summaries appear below. Eight of these investigations demonstrated a reduction in seclusion and/or restraint use for either a component or all of the study population.[79,83,89,91-94,100] These changes ranged in magnitude from 13.8 percent[100] to 69 percent,[89] and three[89,91,93] of the eight studies reported statistically significant decreases.[79,91,93] One of the eight studies reported an increase in restraint use post-intervention, but only on the unit for individuals with chemical abuse.[94] Two additional pre/post studies looking at the same intervention, entitled City Nurse,[90,101] reported lower use of forced medication, seclusion, and restraint, but only one study had significant results.[101] The remaining study did not report on seclusion or restraint but did report a reduction in aggressive behavior.[88]

The preponderance of the data from pre/post studies does suggest the ability of multimodal interventions to reduce seclusion and restraint when that is the intention of the intervention. We cannot determine whether any *specific* component was more effective than another, because of the limitations in the design of these studies. We note, however, that 10 studies[79,88-94,100,101] did include development of the workforce as one of the intervention components. Brief summaries of the studies are presented below beginning with studies reporting on seclusion and restraint rates and ending with studies reporting solely on aggressive behavior.

Currier et al. compared restraint use before and after implementation of the guideline for the "1 hour rule" issued in 1999 by the U.S. Health Care Financing Administration. This rule required face-to-face clinician assessment of patients within 1 hour of initiation of seclusion or restraint. Although the study took place on four psychiatric units at a U.S. academic medical center, only the data from the three adult units were eligible for this review.[94] The number of calculated episodes of restraint and mean duration of episodes decreased by 85 percent and 72.1 percent, respectively, during the 3 months post-intervention on the general adult unit, and by 81 percent and 23 percent, respectively, on the neurogeriatric unit. Restraint use increased by 47 percent, while the mean duration of episodes decreased by 24.5 percent, on the chemical abusing unit. No measures of statistical significance were reported.

D'Orio et al. compared a multimodal intervention with previous usual care over 18 months in the psychiatric emergency service of a U.S. urban hospital.[93] The investigators implemented a behavioral code team, staff training that emphasized verbal de-escalation, and use of rating scales to assist in patient risk assessment. They observed a statistically significant 41.5 percent reduction in the monthly number of episodes of seclusion and restraint, when comparing the 9 months before and the 9 months after the intervention.

Forster et al. examined a multimodal quality improvement intervention (including hospital seclusion and restraint policy review, staff training, and regular discussion of seclusion and restraint use) in an acute care county psychiatric hospital in California.[100] The total annual rate of restraint decreased by 13.8 percent, and mean duration of seclusion or seclusion-and-restraint episodes also decreased by 54.7 percent, when comparing the 12 months before and the 12 months after the intervention.

Hellerstein et al. compared a multimodal intervention with usual care over 87 months in a U.S. urban psychiatric hospital.[79] The intervention had three components: (1) decreasing allowed time in restraint or seclusion before order renewal, (2) risk identification and early intervention training for staff, and (3) use of a coping questionnaire to assess patient preferences for dealing with agitation. Only data from one of the study wards were eligible for this review; showing a reduction in the mean numbers of patients per month either secluded (2.29 to 0.56) or restrained (0.19 to 0.10); results also included decreases in the mean hours per month of seclusion (28.95 to 1.45) and restraint (1.48 to 0.44). Measures of statistical significance were not reported.

Jonikas et al. compared the implementation of a program to reduce use of physical restraints with previous usual care in three inpatient psychiatric units (the two adult units were eligible for this review) of a U.S. university hospital over a period of 30 months.[92] The intervention program had two components: collaboratively obtained (staff and patient) individualized crisis management plans and nonviolent crisis intervention staff training. Quarterly rates of restraint decreased on both adult units after the intervention. An analysis of variance demonstrated a significant effect of training; however, because the study was not controlled, the authors could not determine a definitive correlation.

Khadivi et al. compared a multimodal intervention with usual care in a large U.S. inner city community hospital.[91] The intervention, which was compatible with the mandates of Joint Commission on Accreditation of Healthcare Organizations, included staff education, addition of the history of inpatient violence to admission forms, continuous nursing monitoring to minimize the duration of episodes of seclusion and restraint, post-episode debriefing of the staff and the patient, and a review of each episode by the senior nurse and a physician. Calculated seclusion and restraint use decreased by 52 percent after the intervention; the authors noted this was statistically significant.

Melson et al. compared an alcohol withdrawal care management guideline with previous care in a large U.S. acute care hospital over 228 weeks.[83] The intervention included adding an alcohol withdrawal risk tool to the standard nursing assessment for all patients and then using another rating scale to categorize alcohol withdrawal based on symptom severity. The calculated percentage of patients with delirium tremens requiring restraint decreased by 26 percent, although changes were not statistically significant.

Pollard et al. compared the implementation of Joint Commission on Accreditation of Healthcare Organizations 2000 standards for use of seclusion or restraint for behavioral health reasons with previous usual care over 46 months on the mental health units of a VA hospital.[89] The multimodal intervention broadly included changes to facility policies and procedures,

discussions between leadership and staff about the alternatives to using seclusion and restraint, and leadership review of the use of behavioral restraints and documentation. The most important finding was that the mean hours of seclusion and restraint per patient decreased significantly even after adjusting for patient acuity. Finally, the investigators were able to demonstrate that the number of critical incidents in a 24-hour period did not increase despite significant reductions in the use of seclusion and restraint.

The City nurse multimodal intervention conducted in psychiatric wards in East End London was reported in two separate studies.[90,101] The intervention comprised two nurses working with unit staff 3 days a week, for 1 year, to move the units toward low-conflict, low-containment, high-therapy nursing. The investigators evaluated outcomes before and after the intervention. Measures included the Patient-staff Conflict Checklist Shift Report, which consists of 21 conflict behavior items and nine containment items recorded after each shift. In the first study,[90] no statistically significant reductions were seen for forced i.m. meds, seclusion, or restraint when comparing pre- and post-intervention periods; however, both verbal aggression and aggression against self and others did decrease significantly. In the later study,[101] forced medication, seclusion, and restraint significantly decreased pre and post intervention, as well as verbal aggression and aggression against others and objects.

The eleventh study did not report rates of seclusion or restraint but did address aggressive behavior.[88] Emmerson et al. compared a "4T Aggression Management Strategy" (team work, training, treatment, and tools) with previous usual care over 43 months in an Australian mental health hospital. Implementation of the strategy produced a 40 percent overall reduction and a 25.4 percent monthly reduction in aggressive incidents between patients and staff; both outcomes were statistically significant.

Environmental or Group Psychotherapeutic Interventions Versus Usual Care

Controlled Studies

We identified no eligible controlled studies.

Pre/Post Studies

Three pre/post investigations examined environmental or group psychotherapeutic efforts to de-escalate aggressive behavior. One naturalistic study compared a closed-door, locked psychiatric ICU with an open-door psychiatric ICU.[80,81] The study assessed risk and incidents of violence using the Brøset Violence Checklist. Patients presented with similar clinical profiles at baseline, and mean length of stay did not differ across the units.

During the first 3 days of the admission, the open-door psychiatric ICU reported more violent incidents, by a magnitude of almost 6, than the closed-door unit (unadjusted RR, 5.72; 95% CI, 1.69 to 19.33; p=0.001). Also, patients on the closed-door unit displayed a statistically greater reduction in risk of aggressive behavior (using the Brøset measure) than the open-door unit (p=0.02). When examining the full length of stay, the closed-door unit continued to have significantly fewer incidents of violence than the open-door unit (p<0.001). The number of patients exhibiting violent behavior in the first 3 days (p=0.08) and use of mechanical restraints over the full stay (p=NR) did not differ between units. No mean changes occurred in psychiatric symptom severity and functioning (as measured with the Positive and Negative Syndrome Scale total score and Global Assessment of Functioning Scale's function or symptom scores).

Another naturalistic study tested a practice change initiative that emphasized removing verbally and physically threatening U.S. veteran inpatients in a psychiatric ICU from stimuli before implementing seclusion alone, or seclusion and restraint interventions.[95] During the 15-month post-intervention period, a significantly lower percentage of patients received seclusion alone, or seclusion and restraint interventions than was present during the 9-month pre-intervention period (34% vs. 54%, respectively, $p < 0.05$). The benchmark goal of requiring no further intervention after "removal from stimuli" in 90 percent or more of cases was achieved in 67 percent of post-intervention months. However, in the final 6 months of the observation period, more seclusion or restraint and seclusion interventions occurred than removals from stimuli interventions.

Another naturalistic study compared a manualized cognitive-behavioral group therapy intervention with usual care for adult psychiatric inpatients.[104,105] The study took place in Italy in the psychiatric inpatient unit of a general hospital. The pre-intervention period lasted 1 year; the followup period lasted 3 years. During the post-intervention period, physical restraints were used one time each year. Physical restraints were used five times in the 1-year pre-intervention period, but no statistical tests were conducted on these differences). Additionally, ward atmosphere, which was used as an indirect measure of aggressive and violent behaviors (measured with the Ward Atmosphere Scale), significantly improved (i.e., less disturbing behavior or fewer coercive interventions required) in the post-intervention period compared to the pre-intervention period. Finally, compared with the pre-intervention period, the post-intervention period had significant decreases in the percentage of patients readmitted to the hospital and the percentage of patients readmitted under compulsory orders (both $p<0.02$) and significant improvements in patient satisfaction with care received, helpfulness and availability of professionals, information received, and ward activities ($p<0.001$).

Medication Protocols Versus Other Medication Protocols or Alternative Strategies

Controlled Studies

We identified no eligible controlled studies.

Pre/Post Studies

We identified no relevant pre/post studies.

Key Question 1b: De-escalating Aggressive Behavior

We identified six studies, all involving medication protocols (four RCTs and two NRCTs) addressing this subquestion (Table 9). We identified no relevant studies involving staff training, risk assessment, multimodal, or environmental or group psychotherapeutic interventions that addressed the comparative benefits of strategies for de-escalating aggressive behavior.

Table 9. Characteristics, outcomes, and risk of bias ratings for controlled trials of medication protocols to de-escalate aggressive behavior (Key Question 1b)

Intervention First Author, Year Study Design Setting, Country	N Duration (Months)	Intervention Comparator	Aggressive Behavior	Restraint Use Seclusion Use	Seclusion and Restraints	Risk of Bias Rating
Dorevitch et al., 1999[82] RCT (parallel) Acute inpatient psychiatric facility or facilities Israel	28 NR	G1: Single dose, i.m. 5 mg haloperidol G2: Single dose, i.m. 1 mg flunitrazepam	Rate of reduction in total OAS score at 90 mins G1: 92% G2: 80% p=0.34	NR NR	NR	Medium
Isbister et al., 2010[77] RCT (parallel) Emergency department Australia	91 44 weeks	G1: Single dose, i.m. 10 mg droperidol G2: Single dose, i.m. 10 mg midazolam G3: Single dose, i.m. 5 mg droperidol plus 5 mg midazolam	Violent and acute behavioral disturbance, median minute duration (IQR) G1: 20 (11 to 37) G2: 24 (13 to 35) G3: 25 (15 to 38) p=0.66	NR NR	NR	Medium
Bieniek et al., 1998[98] RCT (parallel) Psychiatric emergency service United States	20 3 hours	G1: Haloperidol (5 mg i.m.) + lorazepam (2 mg i.m.) (n=9) G2: Lorazepam (2 mg i.m.) (n=11)	Clinically significant improvement[a] in OAS score of aggressive or agitated behavior at 60 mins, N (%) G1: 9 (100) G2: 6 (55) p=0.03 Time to OAS improvement: Group-specific slopes of Kaplan-Meier survival curves NR, but haloperidol + lorazepam combination had a superior time to improvement p=0.028 Change in OAS scores (%) at 30 mins G1: 71 G2: 49 Change in OAS scores (%) at 60 mins G1: 85 G2: 71 Group-by-time interaction p=0.71	NR NR	NR	Low

Table 9. Characteristics, outcomes, and risk of bias ratings for controlled trials of medication protocols to de-escalate aggressive behavior (Key Question 1b) (continued)

Intervention First Author, Year Study Design Setting, Country	N Duration (Months)	Intervention Comparator	Aggressive Behavior	Restraint Use Seclusion Use	Seclusion and Restraints	Risk of Bias Rating
Richards et al., 1998[102] RCT (parallel) Large urban university emergency department United States	202 60 mins	G1: Droperidol, 2.5 mg i.v. (when weight <50 kg) or 5 mg i.v. (when weight >50 kg)[b] G2: Lorazepam, 2 mg i.v. (when weight <50 kg) or 4 mg i.v. (when weight >50 kg)[b]	Sedation scores (measure of combative, violent, and out of control behavior), mean (SD)[c] Baseline G1: 5.6 (0.6) G2: 5.3 (0.7) p=0.08 5 mins post-baseline G1: 4.8 (0.7) G2: 4.7 (0.6) p=0.3 10 mins post-baseline G1: 2.8 (0.9) G2: 4.1 (0.8) p<0.001 15 mins post-baseline G1: 2.0 (0.6) G2: 3.5 (0.8) p<0.001 30 mins post-baseline G1: 1.6 (0.5) G2: 2.9 (0.7) p<0.001 60 mins post-baseline G1: 1.5 (0.5) G2: 2.5 (0.7) p<0.001 Response time to medication in combative, violent, and out of control behavior was statistically significantly faster following droperidol than lorazepam (p=NR). No statistical difference in sedation profile between patients with different ethanol intoxications in either group (p=NR).	NR NR	NR	High

Table 9. Characteristics, outcomes, and risk of bias ratings for controlled trials of medication protocols to de-escalate aggressive behavior (Key Question 1b) (continued)

Intervention First Author, Year Study Design Setting, Country	N Duration (Months)	Intervention Comparator	Aggressive Behavior	Restraint Use Seclusion Use	Seclusion and Restraints	Risk of Bias Rating
Wilhelm et al., 2008[106] NRCT Psychiatric or forensic hospitals (n=102) Germany	558 6 days[d]	G1: Olanzapine[e] G2: Non-olanzapine medication[e] G3: Risperidone[e] G4: Non-risperidone medication[e] G5: Haloperidol[e] G6: Non-haloperidol medication[e]	CGI-A: % of patients with scores ≥3[f] % change from baseline to day 6 followup G1: -61.2 vs. G2: -67.0 G3: -67.2 vs. G4: -62.4 G5: -64.6 vs. G6: -62.4 p=NS Percentage change from baseline to last observation G1: -60.7 vs. G2: -66.0 G3: -66.4 vs. G4: -61.7 G5: -63.6 vs. G6: -61.9 p=NS CGI-SS: percentage of patients with scores ≥3[f] Percentage change from baseline to day 6 follow-up G1: -18.1 vs. G2: -22.4 G3: -20.7 vs. G4: -19.2 G5: -21.2 vs. G6: -18.9 p=NS Percentage change from baseline to last observation G1: -18.2 vs. G2: -22.0 G3: -20.8 vs. G4: -19.1 G5: -21.4 vs. G6: -18.8 p=NS	NR NR	NR	High
Villari et al., 2008[99] NRCT Psychiatric emergency service (in-hospital) Italy	101 72 hours	G1: Risperidone (2–6 mg/day PO) G2: Olanzapine (10–20 mg/day PO) G3: Quetiapine (300–800 mg/day PO) G4: Haloperidol (5–15 mg/day PO)	Changes in mean MOAS total scores from baseline to 72 hours Drug-by-drug comparisons G1: -7.3 G2: -6.3 G3: -7.9 G4: -9.4 Group-by-time interaction p=0.478 SGAs (G1 through G3 combined) vs. G4 SGAs: -7.1 G4: -9.4 Group-by-time interaction p=0.166	NR NR	NR	Medium

Table 9. Characteristics, outcomes, and risk of bias ratings for controlled trials of medication protocols to de-escalate aggressive behavior (Key Question 1b) (continued)

Intervention First Author, Year Study Design Setting, Country	N Duration (Months)	Intervention Comparator	Aggressive Behavior	Restraint Use Seclusion Use	Seclusion and Restraints	Risk of Bias Rating
Villari et al., 2008[99] (continued)			Changes in mean MOAS verbal aggression scores from baseline to 72 hours Drug-by-drug comparisons G1: -1.3 G2: -1.2 G3: -1.4 G4: -1.6 Group-by-time interaction p=0.644 SGAs (G1 through G3 combined) vs. G4 SGAs: -1.3 G4: -1.6 Group-by-time interaction p=0.222 Changes in mean MOAS physical aggression against objects scores from baseline to 72 hours Drug-by-drug comparisons G1: -1.8 G2: -2.2 G3: -1.4 G4: -2.4 Group-by-time interaction p=0.512 SGAs (G1 through G3 combined) vs. G4 SGAs: -1.8 G4: -2.4 Group-by-time interaction p=0.277 Changes in mean MOAS physical aggression against self-scores from baseline to 72 hours Drug-by-drug comparisons G1: -1.3 G2: -1.2 G3: -1.2 G4: -1.8			

Table 9. Characteristics, outcomes, and risk of bias ratings for controlled trials of medication protocols to de-escalate aggressive behavior (Key Question 1b) (continued)

Intervention First Author, Year Study Design Setting, Country	N Duration (Months)	Intervention Comparator	Aggressive Behavior	Restraint Use Seclusion Use	Seclusion and Restraints	Risk of Bias Rating
Villari et al., 2008[99] (continued)			Group-by-time interaction p=0.894 SGAs (G1 through G3 combined) vs. G4 SGAs: -1.2 G4: -1.8 Group-by-time interaction p=0.433 Changes in mean MOAS physical aggression against others scores from baseline to 72 hours Drug-by-drug comparisons G1: -3.0 G2: -1.7 G3: -3.9 G4: -3.6 Group-by-time interaction p=0.276 SGAs (G1 through G3 combined) vs. G4 SGAs: -2.8 G4: -3.6 Group-by-time interaction p=0.415			

[a] A decrease of four or more points on the OAS within 60 minutes of baseline was considered "clinically significant improvement."[98]

[b] Dosages of study drugs were selected based on patients' weight, which the treating clinician estimated visually.[102]

[c] Sedation scores were measured on a 6-point scale, ranging from 6 (combative, violent, out of control) to 1 (deep sleep).[102]

[d] 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 followup period.[106]

[e] Patients' antipsychotic treatment was categorized as including any olanzapine or not (OLZ or non-OLZ), including any risperidone or not (RIS or non-RIS), and including any haloperidol or not (HAL or non-HAL). The OLZ, RIS, and HAL cohorts thus overlap, because each cohort included all patients who received the respective drug in any amount and at any time throughout the 5-day study period.[106]

[f] CGI-A scores ≥3 correspond to at least a moderate level of aggression, and CGI-SS scores ≥3 correspond to patients who are at least moderately suicidal.[106]

CGI-A = Clinical Global Impression Severity of Illness – Aggression; CGI-SS = Clinical Global Impression Severity of Illness – Suicidality; G = group; IQR = interquartile range; i.m. = intramuscular; i.v. = intravenous; kg = kilogram; mg = milligram; mins = minutes; MOAS = Modified Overt Aggression Scale; N = number; NR = not reported; NRCT = nonrandomized controlled trial; NS = not sufficient; OAS = Overt Aggression Scale; PO = by mouth, oral medication; RCT = randomized controlled trial; SD = standard deviation; SGA = second generation antipsychotic; vs. = versus.

Medication Protocols Versus Other Medication Protocols or Alternative Strategies

Controlled Studies

We found four RCTs and two NRCTs meeting the eligibility criteria (Table 9 above). Two of the RCTs involved haloperidol. In one RCT involving 20 emergency service patients, 5 mg i.m. haloperidol plus 2 mg i.m. lorazepam resulted in a shorter time to achieve clinically significant reductions in aggressive behavior (4+ point reduction in OAS score) and clinician-rated agitation and hostility; the combined medication regimen did not produce a significantly greater reduction in aggressive behavior or agitation and hostility overall than 2 mg i.m. lorazepam alone.[98] In a second RCT, single-dose 5 mg i.m. haloperidol did not yield a greater reduction in aggressive behavior than 1 mg i.m. flunitrazepam in 28 patients in an acute inpatient psychiatric facility.[82]

The other two RCTs investigated the comparative efficacy of droperidol with another medication or combination of medications. One double-blind RCT compared single-dose 10 mg i.m. midazolam (considered the standard treatment) with 10 mg i.m. droperidol and with 5 mg i.m. midazolam plus 5 mg i.m. droperidol in 79 patients who presented a total of 91 times to the emergency department.[77] After study drug administration, the treatment groups did not differ significantly in median duration of aggressive behavior (p=0.66); however, over the ensuing 6 hours, more midazolam-treated patients required additional sedative medication than droperidol-treated patients (hazard ratio [95% CI], 2.31 [1.01 to 4.71]). In contrast, patients treated with midazolam plus droperidol were no more likely to require additional sedative medication than droperidol-treated patients (hazard ratio [95% CI], 1.18 [0.46 to 2.5]). This trial also collected data on the number of calls to security staff for additional assistance and the percentage of patients sedated after 20 minutes of receiving sedative medication, but it did not statistically compare between-group differences for either outcome. Another RCT compared i.v. lorazepam with i.v. droperidol in 202 acutely agitated adult emergency department patients.[102] Physician-estimated body weight (< or > 50 kg) determined dose of lorazepam (2 mg or 4 mg) and droperidol (2.5 mg or 5 mg), and sedation (i.e., used to measure reduction in combative, violent, and out-of-control behavior) was rated on a 6-point scale (1 = deep sleep, 6 = combative, violent, out of control). Droperidol resulted in faster time to sedation than lorazepam (2.8 ± 0.9 vs. 4.1 ± 0.8 at minute 10, p<0.001) and greater sedation overall than lorazepam (1.5 ± 0.5 vs. 2.5 ± 0.7 at minute 60, p<0.001). In addition, patients who were discharged home spent significantly (p<0.001) fewer hours in the emergency department if treated with droperidol (5.9 ± 1.3) than those treated with lorazepam (8.6 ± 1.4).

The two NRCTs both involved haloperidol. In one NRCT, involving 101 psychiatric inpatients requiring emergency medication to control agitation, oral daily doses of 5 mg to 15 mg haloperidol did not result in greater reductions in aggressive behavior over 72 hours than either one of three second-generation antipsychotics (6 mg risperidone, 10 mg–20 mg olanzapine, or 300 mg–800 mg quetiapine).[99] However, risperidone did result in greater reduction in anergia. The comparison of haloperidol with the second-generation antipsychotics collectively also did not yield any significant differences in the reduction in aggressive behavior. The other NRCT of 558 acutely agitated psychiatric inpatients compared three cohorts of patients: those who received any olanzapine vs. any risperidone vs. any haloperidol as part of their treatment over a 5-day period.[106] Oral dosing was most common, but some patients received i.v. and i.m. formulations. The three treatment cohorts exhibited similar reductions in aggressive behavior and suicidality.

Key Question 1c: Reducing Seclusion and Restraint Use

We identified two controlled trials involving medication protocols (one RCT, one retrospective cohort study). Both investigations targeted actively aggressive individuals in an attempt to reduce seclusion and restraint use (Table 10). We also identified one pre/post medication protocol study. We found no eligible studies that compared staff training, risk assessment, multimodal interventions, or environmental or group psychotherapeutic interventions with other strategies to reduce seclusion or restraints for those with active aggression.

Table 10. Characteristics, outcomes, and risk of bias ratings for controlled trials of medication protocols to de-escalate aggressive behavior and reduce use of seclusion or restraints (Key Question 1c)

Intervention First Author, Year Study Design Setting, Country	N Duration (Months)	Intervention Comparator	Aggressive Behavior	Restraint Use	Seclusion Use	Seclusion and Restraints	Risk of Bias Rating
Georgieva et al., 2013[86] RCT (parallel) Psychiatric hospital (no other details reported) Netherlands	659 34 months	G1: Involuntary medication as first choice (single dose oral, 10 mg haloperidol plus 100 mg promethazine or 2.5–5 mg lorazepam, or single-dose i.m. 5 mg haloperidol plus 50 mg promethazine or 2.5–5 mg lorazepam) G2: Seclusion as first choice	NR	Mechanical restraint incidents, n per 1,000 admission days G1: 1.3 G2: 0.9 (RR, 1.44; 95% CI, 0.38 to 5.36) p=NS Involuntary medication incidents (overall) G1: 47 G2: 21 p=NR Involuntary medication incidents (per 1000 admission days) G1: 4.6 G2: 11.8 (RR, 2.58; 95% CI, 1.54 to 4.31) p<0.001	Seclusion incidents (per 1,000 admission days): G1: 15 G2: 7.8 (RR, 0.51; 95% CI, 0.34 to 0.79) p<0.001 Seclusion hours (overall) G1: 988 G2: 2,098 p=NR Seclusion hours (per 1,000 admission days) G1: 10 G2: 19.1 (RR, 0.54; 95% CI, 0.5 to 0.58) p<0.001 Duration of seclusion incidents in hours, mean (SD) G1: 32 (40) G2: 30 (44) p=NR	Coercive[a] incidents (individual or combined), n per 1,000 admission days G1: 14.6 G2: 15.3 (RR, 0.95; 95% CI, 0.67 to 1.35) p=NS	High

Table 10. Characteristics, outcomes, and risk of bias ratings for controlled trials of medication protocols to de-escalate aggressive behavior and reduce use of seclusion or restraints (Key Question 1c) (continued)

Intervention First Author, Year Study Design Setting, Country	N Duration (Months)	Intervention Comparator	Aggressive Behavior	Restraint Use	Seclusion Use	Seclusion and Restraints	Risk of Bias Rating
Michaud et al., 2014[85] Retrospective cohort Intensive care unit United States	200 35 months	G1: Single dose, delirium txt in 24 hours G2: No delirium txt in 24 hours	NR	Median days in restraints (range) G1: 3 (1 to 12) G2: 6 (1 to 21) p<0.001	NR	NR	High

[a] "Coercion" refers to a sequence of coercive episodes (seclusion, mechanical restraint, or involuntary medication) for less than 24 hours.

CI = confidence interval; G = group; i.m. = intramuscular; mg = milligram; n = number; NR = not reported; NS = not significant; RCT = randomized controlled trial; RR = relative risk; SD = standard deviation; txt = treatment.

Medication Protocols Versus Other Medication Protocols or Alternative Strategies

Controlled Studies

One RCT compared a first-choice treatment of involuntary medication with a first-choice treatment of seclusion (considered "treatment as usual" in the Netherlands) in 520 patients (who accounted for 659 admissions covering 8,544 hospitalization days).[86] Involuntary medication comprised 10 mg haloperidol plus either 100 mg promethazine or 2.5 mg lorazepam, given orally; if patients refused, they received i.m. 5 mg haloperidol plus either 50 mg promethazine or 2.5 to 5 mg lorazepam. During seclusion, further administration of "as needed" medications were considered "involuntary medication." Per 1,000 admission days, for those assigned to first-choice involuntary medication, both the use of seclusion (RR, 0.51; 95% CI, 0.34 to 0.79; p<0.001) and the duration of seclusion (RR, 0.54; 95% CI, 0.50 to 0.58; p<0.001) were significantly lower. Because the use of involuntary medication was also allowable in the seclusion group and because the choice and dosing of medications used potentially could have been equivalent to those in the first-choice involuntary medication group, the authors compared the use of involuntary medications in the two groups. Use of involuntary medication was significantly higher (RR, 2.58; 95% CI, 1.54 to 4.31; p<0.001) in patients assigned to first-choice involuntary medication than in those in first-choice seclusion. In contrast, neither use of mechanical restraint nor coercive incidents (defined as a sequence of coercive episodes including seclusion, mechanical restraint, or involuntary medication over a 24-hour period) differed significantly between groups.

One retrospective cohort study compared pharmacological delirium treatment with no treatment in 200 intubated patients with delirium.[85] The delirium treatment group comprised 98 patients that received at least one dose of quetiapine, olanzapine, risperidone, ziprasidone, haloperidol, or dexmedetomidine within 24 hours of their first positive delirium screen; the no treatment group comprised 102 patients who received delirium treatment more than 24 hours

after screening (n=18) or received no pharmacological intervention during their delirium course (n=84). The treatment group spent significantly fewer days in restraint compared with the no treatment group (median of 3 vs. 6 days, p<0.001).

Pre/Post Studies

One retrospective pre/post study reported changes in the use of seclusion and restraint following implementation of a hospital-wide ban on p.r.n. ("when necessary") orders for psychotropic medications.[76] During the 3-month baseline period when p.r.n. medications were permitted, 8 incidents of restraint and 48 incidents of seclusion occurred during 223 admissions. During the subsequent 3-month period when p.r.n medications were not permitted, fewer incidents of restraint (4) and seclusion (41) occurred among 224 admissions, although the mean duration of seclusion was higher (13.1 vs. 19.2 hours). None of these observed differences was statistically significant.

Comparative Harms of Strategies (Key Question 2)

We describe in separate sections the studies that reported harms data relevant to KQ 2a (preventing aggressive behavior); KQ 2b (de-escalating aggressive behavior); and KQ 2c (reducing restraints or seclusion). In Appendix D, we present detailed SOE tables for each primary outcome, organized by intervention type. Summary tables presenting characteristics and outcomes for all pre/post studies are available in Appendix F.

Table 11. Summary of findings with strength of evidence: Comparative harms of staff training strategies for preventing aggressive behavior (KQ 2a)

Intervention and Comparison	Primary Outcome of Interest	Outcome N of Patients Analyzed	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Staff training vs. usual care	Staff distress	Change in staff resignations and transfers NR	Insufficient	High risk of bias, consistency unknown—single study, indirect, imprecise	Fewer staff resignations and transfers in unit that received the staff training than in control unit (4 vs. 9), no statistical testing reported[103]
		Change in staff sick leave NR	Insufficient	High risk of bias, consistency unknown—single study, indirect, imprecise	Greater percentage decrease in number of sick leave hours in unit that received the staff training than in control unit (-28.2% vs. +7.7%), no statistical testing reported[103]
	Patient distress	Change in patients' rights complaints NR	Insufficient	High risk of bias, consistency unknown—single study, indirect, imprecise	Fewer patients' rights complaints occurred in unit that received the staff training than in control unit (from 6 to 2 vs. from 1 to 4), no statistical testing reported[103]

N = number; NR = not reported; vs. = versus.

Key Points

Key Question 2a: Harms of Strategies To Prevent Aggressive Behavior

Staff Training Interventions Versus Usual Care

- One CRT (Table 11) addressed staff training. A unit on which staff received interpersonal communication training had fewer patient rights complaints, staff resignations and transfers, and sick leave compared to a control unit. Further, the intervention unit experienced a greater decrease in these outcomes during the study period, compared to the control unit[103] (one CRT, insufficient SOE).

Risk Assessment Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Multimodal Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Environmental or Group Psychotherapeutic Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Medication Protocols Versus Other Medication Protocols or Alternative Strategies

- We identified no eligible studies (insufficient SOE).

Key Question 2b: Harms of Strategies to De-escalate Aggressive Behavior

Staff Training Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Risk Assessment Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Multimodal Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Environmental or Group Psychotherapeutic Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Medication Protocols Versus Other Medication Protocols or Alternative Strategies

- Four RCTs provided harms data for medication protocols for de-escalating aggressive behavior; all reported small numbers of events and performed no statistical testing (all

insufficient SOE). These studies (Table 12) generally reported their harms findings as indicating no differences, but they were underpowered to test noninferiority.

- One RCT examined three possible harms: incidence of staff injury; drug-related adverse effects; and incidence of abnormal QT (QRS complex to T wave interval) interval after use of midazolam, droperidol, or their combination for patients with active aggression[77] (one RCT, insufficient SOE).
- Another RCT reported on acute extrapyramidal events and incidence of marked sedation in a comparison between haloperidol and flunitrazepam[82] (one RCT, insufficient SOE).
- A third RCT reported the incidence of side effects of i.m. 2 mg lorazepam alone or in combination with i.m. 5 mg haloperidol for 20 adults treated in a psychiatric emergency service setting[98] (one RCT, insufficient SOE).
- Finally, one RCT reported the incidence of differences in changes in vital signs in 202 acutely agitated emergency department patients treated with intravenous droperidol or lorazepam[102] (one RCT, insufficient SOE).

- One NRCT (Table 12) reported the incidence of extrapyramidal events in 101 adult inpatients with psychosis receiving either risperidone, olanzapine, quetiapine, or haloperidol[99] (one NRCT, insufficient SOE).
- Another NRCT (Table 12) reported the incidence of treatment-emergent side effects, including extrapyramidal events, for patients receiving olanzapine, risperidone, or haloperidol [106] (one NRCT, insufficient SOE).

Table 12. Summary of findings with strength of evidence: Comparative harms of medication protocols for addressing aggressive behavior (Key Question 2b)

Intervention and Comparison	Primary Outcome of Interest	Outcome of Interest N of Patients Analyzed	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Medication protocols vs. other medication protocols	Staff harm	Staff injury 91	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Very small numbers of events with no statistical testing for detecting differences in droperidol vs. midazolam vs. a combination of droperidol plus midazolam (3 vs. 1 vs. 2, p=NR).[77]
	Adverse effects from medication	Acute extra-pyramidal events 28	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	No acute extrapyramidal events[a] with either in haloperidol vs. flunitrazepam at 90 minutes.[82]
		Marked sedation 28	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Very few events at 90 minutes with either haloperidol vs. flunitrazepam, no statistical testing reported (3 vs. 3, p=NR).[82]
		Drug-related adverse events 91	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Very small numbers of events with no statistical testing for detecting differences in droperidol vs. midazolam vs. a combination of droperidol plus midazolam (2 vs. 8 vs. 2, p=NR).[77]

Table 12. Summary of findings with strength of evidence: Comparative harms of medication protocols for addressing aggressive behavior (Key Question 2b) (continued)

Intervention and Comparison	Primary Outcome of Interest	Outcome of Interest N of Patients Analyzed	Strength of Evidence[a]	Supporting Judgment	Findings and Direction of Effect
Medication protocols vs. other medication protocols (continued)	Adverse effects from medication (continued)	Abnormal QT interval 91	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Very small numbers of abnormal QT intervals with no statistical testing for detecting differences in droperidol vs. midazolam vs. a combination of droperidol plus midazolam (2 vs. 2 vs. 4, p=NR).[77]
		Medication side effects 20	Insufficient	Low risk of bias, consistency unknown—single study, direct, imprecise	No medication side effects reported with either haloperidol plus lorazepam vs. lorazepam.[98]
		Reduction in vital signs 202	Insufficient	High risk of bias, consistency unknown—single study, direct, precise	No significant difference for any reduced vital signs between droperidol vs. lorazepam.[102]
		Overall treatment-emergent adverse events 558	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	Few overall treatment-emergent adverse events with olanzapine vs. risperidone vs. haloperidol vs. other comparator groups (p=NR).[106]
		Adverse events considered related to primary antipsychotic medication 558	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	Very few events considered related to primary antipsychotic medication with olanzapine vs. risperidone vs. haloperidol (p=NR).[106]
		Extra-pyramidal symptoms 558	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	No significant difference (very few events) with olanzapine vs. risperidone vs. haloperidol vs. other comparator groups.[106]
		Discontinu-ation due to clinically significant adverse events 558	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	No significant difference in discontinuation due to clinically significant adverse events with olanzapine vs. risperidone vs. haloperidol vs other comparator groups.[106]
		Extra-pyramidal events 101	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Significant difference but very few extrapyramidal events in risperidone vs. olanzapine vs. quetiapine vs. haloperidol (p=0.012).[99]

[a] Also no excitation or disinhibition in patients receiving flunitrazepam, not reported for the haloperidol.[82]

N = number; NR = not reported; NS = not significant; QT = QRS complex to T wave interval; vs. = versus.

Key Question 2c: Harms of Strategies To Reduce Seclusion and Restraint Use

Staff Training Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Risk Assessment Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Multimodal Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Environmental or Group Psychotherapeutic Interventions Versus Usual Care

- We identified no eligible studies (insufficient SOE).

Medication Protocols Versus Other Medication Protocols or Alternative Strategies

- We identified no eligible studies (insufficient SOE).

Detailed Synthesis

We identified 15 studies in 16 articles for this KQ with harms data: seven controlled trials and eight pre/post studies. Below, we detail the results by subquestion, then by intervention, and then by study design. In Appendix D, we present detailed SOE tables for each KQ 2 primary outcome, organized by intervention type. Appendix E contains detailed study characteristics tables across all intervention types. Appendix F provides a summary of findings for the pre/post studies.

Key Question 2a: Prevention of Aggressive Behavior

This section describes the eight included studies evaluating the effectiveness of interventions designed to prevent aggressive behavior in those without active aggression. One study was a controlled trial using a CRT design to assess staff training interventions;[103] seven (reported in eight articles) used a pre/post design.[80,81,88,90,91,94,100,101] Of those seven pre/post studies, six evaluated the implementation of a multimodal intervention,[88,90,91,94,100,101] and one evaluated an environmental or group psychotherapeutic intervention.[80,81]

We did not identify any studies that addressed the comparative harms of either risk assessment interventions or medication protocols with other early intervention techniques or usual care for preventing aggressive behavior or use of seclusion and restraints.

Staff Training Interventions Versus Usual Care

Controlled Studies

The staff training CRT (see Table 8 for de-escalating aggressive behavior), which focused on empathy training, also investigated patient complaints, staff resignations and transfers, and sick leave.[103] On the intervention unit, patients' rights complaints declined from 6 in the 1-year period before the intervention to 2 in the year following the intervention (66.7% decrease). On the

control unit, patients' rights complaints increased from 1 to 4 (300.0% increase) during the same period. Staff resignation and transfers declined from 11 to 4 (63.6% decrease) on the intervention unit; these outcomes increased on the control unit from 8 to 9 (12.5% increase). Sick leave (in hours) declined from 1,470 hours to 1,056 (28.2% decrease) on the intervention unit and increased on the control unit from 1,404 to 1,512 (7.7% increase). The investigators did not report tests of statistical significance.

Multimodal Interventions Versus Usual Care

Controlled Studies

We identified no eligible controlled studies.

Pre/Post Studies

Six pre/post studies addressed harms related to preventing aggression in those without active aggression.[88,90,91,94,100,101] We discussed these studies in detail for KQ 1a (with additional details in Appendix F); data relevant to KQ 2a are presented here with studies in alphabetical order. Both the initial and followup studies of the City Nurse intervention, by Bowers et al.,[90,101] compared the rate of suicide attempts before and after intervention implementation. The overall rate of suicide attempts was very low in both studies (0.004 and 0.008 mean attempts per shift pre-intervention, respectively); neither study showed a statistically significant reduction after the intervention. Currier et al.[94] reported that the rate of injuries to staff by patients did not increase after the intervention (designed to reduce seclusion and restraint), although the investigators did not present data by unit or report any specific numbers or measures of statistical significance. They also reported that the number of patient falls increased on the neurogeriatric unit post-intervention, but they simultaneously noted that these falls were without injuries. Emmerson et al.,[88] for their 4T aggression Management Strategy, reported statistically significant overall and mean monthly reductions in staff injuries and a lack of a potentially anticipated harm from medication protocols to decrease aggression (no significant increase in sedation-related adverse effects). Forster et al.[100] reported that the rate of staff injuries were reduced by 18.8 percent, when comparing the 12 months before and the 12 months after the multimodal quality improvement intervention. Finally, Khadivi et al.[91] reported a statistically significant decrease in assaults on staff and assaults on patients after reducing seclusion and restraint; they also observed a nonsignificant decrease in self-destructive behavior. Although the pre/post design of these studies does not allow causal inference, this available information is consistent with evidence suggesting that multimodal interventions lower seclusion and restraint use and aggressive behavior without harms.

Environmental or Group Psychotherapeutic Interventions Versus Usual Care

Controlled Studies

We identified no eligible studies.

Pre/Post Studies

One pre/post study comparing a closed-door, locked psychiatric ICU with an open-door psychiatric ICU examined suicide as a potential harm to patients (see KQ 1 for a more detailed study description).[80,81] A single serious suicide attempt took place in the open-door ICU. The

investigators did not statistically compare the risk of suicidal behaviors between the two units and did not report any other harms.

Medication Protocols Versus Other Medication Protocols or Alternative Strategies

Controlled Studies

We identified no eligible studies.

Pre/Post Studies

We identified no relevant studies.

Key Question 2b: De-escalating Aggressive Behavior

No studies of staff training, risk assessment, multimodal, or environmental or group psychotherapeutic interventions reported on the comparative harms of strategies for de-escalating aggressive behavior. All six eligible studies addressed the use of medication protocols (Table 13).

Table 13. Characteristics, main outcomes, and risk of bias ratings for harms from medication protocol studies to de-escalate aggressive behaviors (Key Question 2b)

Intervention First Author, Year Study Design Setting, Country	N Duration (Months)	Intervention Comparator	Staff Injury	Medication Side Effects	Risk of Bias Rating
Isbister et al., 2010[77] RCT (parallel) Public psychiatric hospital Australia	91 6 hours	G1: Droperidol: 10 mg i.m. G2: Midazolam: 10 mg i.m. G3: Droperidol (5 mg i.m.) plus Midazolam (5 mg i.m.)	Staff injury, n (%) [95% CI] G1: 3 (9%) [2 to 25%] G2: 1 (3%) [0 to 20%] G3: 2 (7%) [1 to 24%] p=NR	Drug-related adverse events, n (%) [95% CI] G1: 2 (6%) [1 to 22%] G2: 8 (28%) [13 to 47%] G3: 2 (7%) [1 to 24%] p=NR Abnormal QT interval, n (%) [95% CI] G1: 2 (6%) [1 to 23%] G2: 2 (7%) [1 to 24%] G3: 4 (14%) [5 to 33%] p=NR	Medium
Dorevitch et al., 1999[82] RCT (parallel) Acute inpatient psychiatric facility or facilities Israel	28 90 mins	During aggressive event: G1: Haloperidol (5 mg i.m.) G2: Flunitrazepam (1 mg i.m.)	NR	Acute extrapyramidal events[a], n G1: 0 G2: 0 p=NR Incidence of marked sedation, n G1: 3 G2: 3 p=NR	Medium
Bieniek et al., 1998[98] RCT (parallel) Psychiatric emergency service United States	20 3 hours	G1: Haloperidol (5 mg i.m.) + lorazepam (2 mg i.m.) (n=9) G2: Lorazepam (2 mg i.m.) (n=11)	NR	Medication side effects, n G1: 0 G2: 0	Low

Table 13. Characteristics, main outcomes, and risk of bias ratings for harms from medication protocol studies to de-escalate aggressive behaviors (Key Question 2b) (continued)

Intervention First Author, Year Study Design Setting, Country	N Duration (Months)	Intervention Comparator	Staff Injury	Medication Side Effects	Risk of Bias Rating
Richards et al., 1998[102] RCT (parallel) Large urban university emergency department United States	202 60 mins	G1: Droperidol, 2.5 mg i.v. (when weight <50 kg) or 5 mg i.v. (when weight >50 kg)[b] G2: Lorazepam, 2 mg i.v. (when weight <50 kg) or 4 mg i.v. (when weight >50 kg)[b]	NR	Acute dystonic reaction G1: 1[c] G2: 0 p=NR Patients in both groups experienced statistically significant reductions in vital signs within 60 mins of receiving drugs, including pulse, SBP, and respiratory rate (all p's <0.001), but not body temperature (p=0.2 after droperidol and 0.4 after lorazepam). However, no statistically significant between-group differences for any vital sign (all p's >0.05). Additionally, no adverse events with respect to vital signs in either group. No acute allergic reactions to either drug, and no patient required airway intervention.	High
Villari et al., 2008[99] NRCT Psychiatric emergency service (in-hospital) Italy	101 72 hours	G1: Risperidone (2–6 mg/day PO) G2: Olanzapine (10–20 mg/day PO) G3: Quetiapine (300–800 mg/day PO) G4: Haloperidol (5–15 mg/day PO)	NR	Abnormal gait, n (%) G1: 2 (7.4) G2: 2 (8.3) G3: 1 (4.6) G4: 2 (7.1) p=0.964 Dizziness, n (%) G1: 1 (3.7) G2: 3 (12.5) G3: 4 (18) G4: 1 (3.6) p=0.204 EPS, n (%) G1: 2 (7.4) G2: 0 (0) G3: 0 (0) G4: 6 (21.4) p=0.012 Headache, n (%) G1: 1 (3.7) G2: 2 (8.3) G3: 1 (4.6) G4: 2 (7.1) p=0.888 Hypotension, n (%) G1: 2 (7.4) G2: 4 (17) G3: 3 (14) G4: 4 (14) p=0.78	Medium

Table 13. Characteristics, main outcomes, and risk of bias ratings for harms from medication protocol studies to de-escalate aggressive behaviors (Key Question 2b) (continued)

Intervention First Author, Year Study Design Setting, Country	N Duration (Months)	Intervention Comparator	Staff Injury	Medication Side Effects	Risk of Bias Rating
Medication Protocol Villari et al., 2008[99] (continued)				Somnolence, n (%) G1: 3 (11.1) G2: 5 (21) G3: 7 (32) G4: 5 (18) p=0.338	
Wilhelm et al., 2008[106] NRCT Psychiatric or forensic hospitals (n=102) Germany	558 6 days[d]	G1: Olanzapine G2: Non-olanzapine medication G3: Risperidone G4: Non-risperidone medication G5: Haloperidol G6: Non-haloperidol medication	NR	AEs considered related to primary antipsychotic medication, n (%) G1: 21 (5.4) vs. G2: 12 (7.1) G3: 8 (11.1) vs. G4: 25 (5.1) G5: 12 (9.1) vs. G6: 21 (4.9) p=NS Discontinuation due to clinically significant AEs, n (%) G1: 1 (0.3) vs. G2: 1 (0.6) G3: 1 (1.4) vs. G4: 1 (0.2) G5: 0 (0.0) vs. G6: 2 (0.5) p=NS Overall treatment-emergent AEs, n (%)[e] G1: 24 (6.2) vs. G2: 13 (7.7) G3: 8 (11.1) vs. G4: 29 (6.0) G5: 13 (9.8) vs. G6: 24 (5.6) p=NS Serious AEs considered related to primary antipsychotic medication, n (%) G1: 1 (0.3) vs. G2: 1 (0.6) G3: 0 (0.0) vs. G4: 2 (0.4) G5: 2 (1.5) vs. G6: 0 (0.0) p=NS Overall serious AEs, n (%) G1: 2 (0.5) vs. G2: 2 (1.2) G3: 0 (0.0) vs. G4: 4 (0.8) G5: 3 (2.3) vs. G6: 1 (0.2) p=NS Dyskinesia[f], n (%) G1: 2 (0.5) vs. G2: 2 (1.2) G3: 0 (0.0) vs. G4: 4 (0.8) G5: 3 (2.3) vs. G6: 1 (0.2) p=NS EPS[g], n (%) G1: 1 (0.3) vs. G2: 3 (1.8) G3: 1 (1.4) vs. G4: 3 (0.6) G5: 2 (1.5) vs. G6: 2 (0.5) p=NS	High

Table 13. Characteristics, main outcomes, and risk of bias ratings for harms from medication protocol studies to de-escalate aggressive behaviors (Key Question 2b) (continued)

Intervention First Author, Year Study Design Setting, Country	N Duration (Months)	Intervention Comparator	Staff Injury	Medication Side Effects	Risk of Bias Rating
Wilhelm et al., 2008[106] (continued)				Sedation, n (%) G1: 3 (0.8) vs. G2: 1 (0.6) G3: 1 (1.4) vs. G4: 3 (0.6) G5: 2 (1.5) vs. G6: 2 (0.5) p=NS Postural dizziness, n (%) G1: 3 (0.8) vs. G2: 0 (0.0) G3: 0 (0.0) vs. G4: 3 (0.6) G5: 2 (1.5) vs. G6: 1 (0.2) p=NS Increased weight, n (%) G1: 3 (0.8) vs. G2: 0 (0.0) G3: 1 (1.4) vs. G4: 2 (0.4) G5: 0 (0.0) vs. G6: 3 (0.7) p=NS Akathisia, n (%) G1: 2 (0.5) vs. G2: 0 (0.0) G3: 1 (1.4) vs. G4: 1 (0.2) G5: 0 (0.0) vs. G6: 2 (0.5) p=NS Oculogyric crisis, n (%) G1: 2 (0.5) vs. G2: 0 (0.0) G3: 1 (1.4) vs. G4: 1 (0.2) G5: 0 (0.0) vs. G6: 2 (0.5) p=NS Salivary hypersecretion, n (%) G1: 1 (0.3) vs. G2: 1 (0.6) G3: 1 (1.4) vs. G4: 1 (0.2) G5: 0 (0.0) vs. G6: 2 (0.5) p=NS Very few discontinuations due to clinically significant adverse events with olanzapine vs. risperidone vs. haloperidol medication, p=NR.	

[a] Also no excitation or disinhibition in patients receiving flunitrazepam, not reported for the haloperidol.[82]

[b] Dosages of study drugs were selected based on patients' weight, which the treating clinician estimated visually.[102]

[c] The one case of dystonic reaction occurring in the droperidol group was characterized by torticollis and tongue protrusion. The patient responded well to i.v. diphenhydramine.[102]

[d] 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 followup period.[106]

[e] A total of 37 patients experienced one or more treatment-emergent adverse events, but some patients were included in more than one category of adverse event.[106]

[f] Included early (n=3) and perioral dyskinesias (n=1).[106]

[g] Extrapyramidal symptoms were described as "extrapyramidal disorder" by study authors.[106]

AE = adverse event; CI = confidence interval; EPS = extrapyramidal symptoms; G = group; i.m. = intramuscular; i.v. = intravenous; kg = kilogram(s); mg = milligram; mins = minutes; n = number of events; NR = not reported; NS = not significant; PO = orally; QT = Q and T wave intervals; RCT = randomized controlled trial; SBP = systolic blood pressure; vs. = versus.

Medication Protocols Versus Other Medication Protocols or Alternative Strategies

Controlled Studies

Four RCTs[77,82,98,102] and two NRCTs[99,106] reported medication side effects (Table 13).

One double-blind RCT compared single-dose 10 mg i.m. midazolam (considered the standard treatment) with 10 mg i.m. droperidol and with 5 mg i.m. midazolam plus 5 mg i.m. droperidol in 79 patients. Midazolam resulted in a higher incidence of medication side effects (n=8) compared with droperidol (n=2) or with a lower-dose combination of the two (n=2); and the medication regimens did not differ in the incidence of abnormal QT interval (n=2 vs. 2 and 4, respectively). The investigators did not report statistical significance of these findings.

A second RCT compared single-dose intravenous droperidol (2.5 mg or 5 mg if weight < or > 50 kg) with lorazepam (2 mg or 4 mg if weight < or > 50 mg) in 202 acutely agitated patients in an emergency department who were at risk of placing themselves and staff at danger and required constant supervision.[102] No patients experienced an acute allergic reaction or needed airway intervention, but one droperidol-treated patient experienced an acute dystonic reaction. Between-group differences in reductions in vital signs (pulse, respiratory rate, blood pressure, and body temperature) were not statistically significant.

Two RCTs compared i.m. haloperidol with a different psychotropic medication in actively psychotic patients. One compared single-dose 5 mg i.m. haloperidol plus 2 mg lorazepam (considered the standard treatment) with lorazepam alone in 20 adults treated in a psychiatric emergency service setting.[98] The other compared 5 mg i.m. haloperidol with 1 mg i.m. flunitrazepam in 28 patients.[82] Neither trial reported any statistically different incidences of medication-related adverse events or side effects.

One NRCT reported no statistically significant differences in the incidence of abnormal gait, dizziness, extrapyramidal events, headache, hypotension, or somnolence in 101 adult inpatients with psychosis who were treated for 72 hours with one of three oral second-generation antipsychotics (2–6 mg/day risperidone, 10–20 mg/day olanzapine, 300–800 mg/day quetiapine) or with oral 5–15 mg/day haloperidol.[99]

One naturalistic, observational NRCT of 588 agitated psychiatric inpatients reported the percentage of adverse events considered related to primary antipsychotic medication as 5.4 percent for olanzapine, 11.1 percent for risperidone, and 9.1 percent for haloperidol. The percentage of serious medication adverse events was low for all treatments: haloperidol (1.5%), olanzapine (0.3%), and risperidone (0.0%).[106]

Key Question 2c: Reducing Seclusion and Restraint Use

No studies provided information on the comparative harms of staff training, risk assessment, multimodal, or environmental or group psychotherapeutic interventions to reduce use of seclusion and restraint for patients with active aggression. We identified one study, a pre/post study, that addressed the use of medication protocol interventions to reduce the use of seclusion and restraint for actively aggressive patients. Thus, all SOE grades were insufficient.

Medication Protocols Versus Other Medication Protocols or Alternative Strategies

Controlled Studies

We identified no eligible studies.

Pre/Post Studies

One pre/post study compared the number of employee injuries before and after implementation of a hospital-wide ban on p.r.n. orders for psychotropic medications.[76] Fourteen staff injuries occurred during the 3-month period when p.r.n orders were permitted, and 12 staff injuries occurred during the 3-month period when p.r.n. orders were not permitted.

Key Question 3. Characteristics Modifying the Comparative Benefits or Harms of Strategies

For this KQ, we had intended to evaluate potential moderators of the benefits or harms of strategies to prevent or de-escalate aggressive behavior or reduce the use of seclusion or restraints. However, we found no eligible studies of staff training, risk assessment, environmental or group psychotherapeutic, multimodal, or medication protocol interventions for KQ 3. SOE is, therefore, insufficient in all cases.

Discussion

Our review aims to address two gaps in the available literature involving the effectiveness of strategies to de-escalate aggressive behavior. We synthesized available data about (1) the effectiveness of different alternative strategies to *prevent aggressive behavior* and (2) the effectiveness of alternative strategies compared with each other or with seclusion and restraints to *de-escalate aggressive behaviors* or *improve health outcomes for those who are acutely aggressive*.

This chapter summarizes key findings and how they relate to published findings and current clinical practices and policies. We also briefly examine the applicability of our findings and their implications for decisionmaking. We comment on limitations of both the review process and the entire evidence base as a segue into our discussion of research gaps in this field.

Key Findings and Strength of Evidence

Identifying and implementing effective strategies to de-escalate aggressive behaviors in acute care and emergency department settings is a key concern for patients, clinicians and policymakers. The emphasis is on safe and effective means of limiting the use of seclusion and restraints. Alternative strategies include staff training, risk assessment, multimodal interventions (which include multiple components that may be part of other strategies), environmental interventions (including group psychotherapeutic options), and use of medications. Our report provides a comprehensive summary of the available evidence on the comparative benefits and harms of alternatives to seclusion and restraints versus each other and versus the use of seclusion and restraints.

In this review, we focus on three key issues that decisionmakers commonly face:

1. What is the comparative effectiveness of general strategies that can be applied unit-wide to prevent aggressive behavior?
2. Once patients are actively aggressive, what is the comparative effectiveness of strategies, including the use of seclusion and restraints, to de-escalate aggressive behavior?
3. Once patients are actively aggressive, what is the comparative effectiveness of strategies to reduce the use of seclusion and restraints?

Overall, the evidence base is extremely limited. What evidence was available came largely from pre/post studies. Their inherent high risk of bias precludes drawing inferences of causality (and so we did not grade strength of evidence [SOE] for such studies), but we note the existence of these studies in the text below.

No Key Questions (KQs) had data supporting a SOE grade that exceeded low SOE (based on criteria as described in the Evidence-based Practice [EPC] Methods Guide).[74] Although 15 of 29 studies involved acute inpatient psychiatric settings, most of which involved serious mental illness diagnoses, the majority of articles did not give the proportion of patients with agitated or aggressive behavior. Consequently, we are not able to describe clinical demographics.

We focus here on the 11 studies (mainly randomized controlled trials [RCTs] or cluster randomized trials [CRTs]) for which we could grade SOE of one or more outcomes. Of these, three were CRTs (for KQ 1. We rated all as medium risk of bias, most commonly because of failure to control either for potential confounding or for intraclass correlations in the CRTs that were eligible for inclusion. No KQs had comparative data supporting an SOE grade that exceeded low strength of evidence. By definition, all findings were of unknown inconsistency

(because they were single studies), but all provided direct evidence. In most cases, however, the data reported were imprecise. Thus, we graded these findings as insufficient SOE. In a very small number of cases in which data were precise, we graded SOE as low.

The tables below summarize *only* those findings with low SOE and those outcomes with eligible studies but with an SOE grade of insufficient. The variety of measures used to assess aggressive behavior and seclusion and restraint use prevented quantitative synthesis of the meager data that were available.

Most evidence addressed preventive, unit-wide programs rather than interventions specifically targeting actively aggressive patients; this focus essentially represents the core difference between the CRTs and the RCTs. Moreover, these analyses could involve samples of patients who were not actively aggressive as well as those who were. These factors prevented us from attributing reduction of aggressive behavior in actively aggressive patients to any particular intervention.

Furthermore, the inexact description of many interventions made it difficult to attribute a change to a particular component. For example, multimodal interventions had components of risk assessment and staff training, and distinguishing between them was sometimes challenging.

We report on our findings, by benefits and harms for each subquestion (e.g., KQs 1a and 2a) together, organized by intervention and specific outcomes. We also summarize our SOE findings for each subquestion in accompanying tables. If an eligible study provided relevant data, but we graded SOE as insufficient, we note this in the text and the table. If no eligible studies provided relevant data, we graded the SOE as insufficient and mention it in the text but not in the table.

As noted earlier, some SOE grades for KQ 1 were low (when we could assign a grade other than insufficient). Findings from eligible studies for KQ 2 were all insufficient. We had no studies for KQ 3.

Table 13 documents benefits and harms for risk assessment and staff training for preventing aggressive behaviors (KQs 1a and 2a); Table 14 documents benefits and harms of medication protocols for decreasing aggressive behaviors (KQs 1b and 2b); and Table 15 documents benefits and harms of medication protocols for reducing seclusion or restraints (KQs 1c and 2c).

The low confidence in these SOE grades (very few low grades; mainly insufficient grades that are not included in these tables because we had no relevant studies) reflects a critical limitation of the reviewed research. This pattern also calls into question both the reproducibility or replicability and the generalizability of results. Subsequent studies, assuming they are well designed and take statistical issues accurately into account, are likely to affect these findings substantially, although in what direction remains unclear. Future research, with the same assumptions, may confirm some findings but provide more information that might lead to higher SOE grades.

Strategies To Prevent Aggressive Behavior: Benefits (KQ 1a) and Harms (KQ 2a)

Two of the interventions had eligible studies, only one of which (risk protocol assessment) led primarily to low SOE findings (Table 14). For units implementing structured risk assessment protocols, which matches needs to identified risks to reduce the likelihood of aggressive behavior, we graded the SOE as low that these protocols produced fewer aggressive incidents and a reduction in the use of seclusion and restraints compared with usual care. This low SOE rating was attributable, in the main, to a small number of trials; other issues involved diverse operationalizations of key concepts across studies, which precluded direct comparisons; and the

failure of analyses of the CRTs to account for intra-class correlations.[107] We identified no data addressing the harms of such an intervention (so the SOE rating of insufficient).

Table 14. Summary of findings with strength of evidence grades: Comparative benefits and harms of two strategies for preventing aggressive behavior[a] (KQs 1a and 2a)

Intervention and Comparison	Primary Outcome of Interest	Outcome N of Patients Analyzed	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Staff training vs. usual care	Change in aggressive behavior	Aggressive behavior resulting in staff injury NR	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	Fewer assaults on staff occurred in unit that received the staff training vs. the control unit (4 vs. 5); no statistical testing reported.[103]
	Change in seclusion or restraint	Incidents of seclusion or restraint NR	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	Fewer incidents of seclusion or restraint on the unit that received the training vs. the control unit (84 vs. 228); no statistical testing reported.[103]
	Staff distress	Change in staff resignations and transfers NR	Insufficient	High risk of bias, consistency unknown—single study, indirect, imprecise	Fewer staff resignations and transfers in unit that received the staff training than in control unit (4 vs. 9), no statistical testing reported.[103]
		Change in staff sick leave NR	Insufficient	High risk of bias, consistency unknown—single study, indirect, imprecise	Greater percentage decrease in number of sick leave hours in unit that received the staff training than in control unit (-28.2% vs. +7.7%), no statistical testing reported.[103]
	Patient distress	Change in patients' rights complaints NR	Insufficient	High risk of bias, consistency unknown—single study, indirect, imprecise	Fewer patients' rights complaints occurred in unit that received the staff training than in control unit (from 6 to 2 vs. from 1 to 4), no statistical testing reported.[103]
Risk assessment vs. usual care	Change in aggressive behavior	Number of aggressive patients 170 during baseline period, 458 during intervention period	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Nonsignificant 50% RR reduction with risk assessment.[87]
		Aggressive incidents 170 during baseline period, 458 during intervention period	Low	Medium risk of bias, consistency unknown—single study, direct, precise	Significant 68% RR reduction with risk assessment, p<0.0001 reported; failure to control for intraclass correlations weakens the finding.[87]
		Rate of severe aggressive incidents 973 post-intervention	Low	Medium risk of bias, consistency unknown—single study, direct, precise	Significantly lower risk with structured risk assessment: (RR, 0.59; 95% CI, 0.41 to 0.83) p<0.001 reported; failure to control for intraclass correlations weakens the finding. Decrease achieved since baseline with risk assessment (-41%) vs. usual care (-15%), no statistical testing reported.[78]

Table 14. Summary of findings with strength of evidence grades: Comparative benefits and harms of two strategies for preventing aggressive behavior[a] (KQs 1a and 2a) (continued)

Intervention and Comparison	Primary Outcome of Interest	Outcome N of Patients Analyzed	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Risk assessment vs. usual care (continued)	Change in seclusion or restraint (continued)	Change in physical attacks 973 post-intervention	Low	Medium risk of bias, consistency unknown—single study, direct, precise	Significantly greater decrease with risk assessment (-41%) vs. usual care (-7%), p<0.001 reported, failure to control for intraclass correlations weakens the finding.[78]
		Secluded patients 170 during baseline period, 458 during intervention period	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Nonsignificant 8% RR increase with risk assessment.[87]
		Seclusion incidents 170 during baseline period, 458 during intervention period	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Nonsignificant 15% RR reduction with risk assessment.[87]
		Hours in seclusion 170 during baseline period, 458 during intervention period	Low	Medium risk of bias, consistency unknown—single study, direct, precise	Significant 45% RR reduction with risk assessment, p<0.0001 reported; failure to control for intraclass correlations weakens the finding.[87]
		Change in coercive[b] incidents 973 post-intervention	Low	Medium risk of bias, consistency unknown—single study, indirect, precise	Significant decrease from baseline with risk assessment (-27%) vs. usual care (+10%), p<0.001 reported; failure to control for intraclass correlations weakens the finding.[78]

[a] For KQ 1a, we had no studies of eligible study design for environmental or group psychotherapeutic interventions or multimodal interventions; thus, we could not rate risk of bias.

[b] Coercive measures covered a wide range of measures from forced injection of psychotropic medication to seclusion and mechanical restraint.[78]

CI = confidence interval; KQ = Key Question; N = number; NR = not reported; RR = relative risk; vs. = versus.

For staff training, for environmental interventions, and for medication use, we graded the evidence base addressing benefits and harms as insufficient. We identified no controlled trials or interrupted time-series studies to provide data for an SOE rating for either question.

Strategies To Address Aggressive Behavior: Benefits (KQ 1b) and Harms (KQ 2b)

We identified no eligible studies for strategies involving staff training, risk assessment interventions, multimodal interventions, or environmental interventions. As a result, we rated all these strategies as having insufficient SOE for both benefit and harms. Although some of these strategies may have been applied to actively aggressive patients, reported data did not stratify by whether the outcomes happened specifically in the aggressive subgroup; rather, the data were

reported for the group involving both those actively aggressive and those not, so we could not determine the effect specifically on the aggressive subgroup.

The interventions to address the comparative effectiveness of strategies to de-escalate aggressive behavior focused on medications. These studies provided the only direct comparisons of two active strategies (rather than with usual care). Here, too, the evidence was limited. For both benefits and harms, we graded SOE as insufficient for each comparison assessing whether any specific medication or programmatic approach involving the timing of medication use emerged as a superior method for de-escalating aggressive behavior (Table 15). All comparisons occurred in single trials only, and the metric used to assess aggressive behavior differed across studies. All studies assessing benefits were underpowered to test noninferiority, and those studies reporting harms reported small numbers of events, preventing any statistical comparisons.

Table 15. Summary of findings with strength of evidence grades: Comparative benefits and harms of medication protocols for de-escalating aggressive behavior (KQs 1b and 2b)

Intervention and Comparison	Primary Outcome of Interest	Outcome N of Patients Analyzed	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Medication protocols vs. other medication protocols: Benefits	Change in aggressive behavior	Aggression response rate 28	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Nonsignificant difference in rates of OAS score reduction at 90 minutes in haloperidol vs. flunitrazepam (92% vs. 80%).[82]
		Duration of aggression 91	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Nonsignificant difference in the median duration of violent and acute behavioral disturbances with droperidol vs. midazolam vs. a combination of droperidol plus midazolam (20 vs. 24 vs. 25 minutes).[77]
		Clinically significant change in OAS scores 20	Insufficient	Low risk of bias, consistency unknown—single study, direct, imprecise	Significantly greater likelihood of improvement (decrease of four or more points) in OAS scores of aggressive or agitated behavior at 60 minutes with the combination of haloperidol plus lorazepam (100%) vs. lorazepam alone (55%), p=0.03 (note small sample size).[98]
		Time to OAS improvement 20	Insufficient	Low risk of bias, consistency unknown—single study, direct, imprecise	Significantly shorter time to OAS improvement with the combination of haloperidol plus lorazepam vs. lorazepam alone, data NR, p=0.028 (note small sample size).[98]
		Sedation score at 5, 10, 15, 30, and 60 minutes 202	Insufficient	High risk of bias, consistency unknown—single study, direct, precise	Significantly lower mean sedation scores (i.e., less combative, violent, or out of control behavior) at 10, 15, 30, and 60 minutes with droperidol vs. lorazepam, each p <0.001[102]
		Change in CGI-A scores 558	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	No differences in changes in percentages of patients with CGI-A score ≥3 from baseline to day 6 or to last day of observation with olanzapine vs. risperidone vs. haloperidol, p=NR.[106]

Table 15. Summary of findings with strength of evidence grades: Comparative benefits and harms of medication protocols for de-escalating aggressive behavior (KQs 1b and 2b) (continued)

Intervention and Comparison	Primary Outcome of Interest	Outcome N of Patients Analyzed	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Medication protocols vs. other medication protocols: Benefits (continued)	Change in aggressive behavior (continued)	Change in MOAS total aggression scores 101	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Nonsignificant differences between risperidone vs. olanzapine vs. quetiapine vs. haloperidol in changes in mean total MOAS scores from baseline to 72 hours.[99]
Medication protocols vs. other medication protocols: Harms	Staff harm	Staff injury 91	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Very small numbers of events with no statistical testing for detecting differences in droperidol vs. midazolam vs. a combination of droperidol plus midazolam (3 vs. 1 vs. 2, p=NR).[77]
	Adverse effects from medication	Acute extra-pyramidal events 28	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	No acute extrapyramidal events[a] with either in haloperidol vs. flunitrazepam at 90 minutes.[82]
		Marked sedation 28	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Very few events at 90 minutes with either haloperidol vs. flunitrazepam, no statistical testing reported (3 vs. 3, p=NR).[82]
		Drug-related adverse events 91	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Very small numbers of events with no statistical testing for detecting differences in droperidol vs. midazolam vs. a combination of droperidol plus midazolam (2 vs. 8 vs. 2, p=NR).[77]
		Abnormal QT interval 91	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Very small numbers of abnormal QT intervals with no statistical testing for detecting differences in droperidol vs. midazolam vs. a combination of droperidol plus midazolam (2 vs. 2 vs. 4, p=NR).[77]
		Medication side effects 20	Insufficient	Low risk of bias, consistency unknown—single study, direct, imprecise	No medication side effects reported with either haloperidol plus lorazepam vs. lorazepam.[98]
		Reduction in vital signs 202	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	No significant difference for any reduced vital signs between droperidol vs. lorazepam.[102]
		Overall treatment-emergent adverse events 558	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	Few overall treatment-emergent adverse events with olanzapine vs. risperidone vs. haloperidol p=NR.[106]

Table 15. Summary of findings with strength of evidence grades: Comparative benefits and harms of medication protocols for de-escalating aggressive behavior (KQs 1b and 2b) (continued)

Intervention and Comparison	Primary Outcome of Interest	Outcome N of Patients Analyzed	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Medication protocols vs. other medication protocols: Harms (continued)	Adverse effects from medication (continued)	Adverse events considered related to primary antipsychotic medication 558	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	Very few events considered related to primary antipsychotic medication with olanzapine vs. risperidone vs. haloperidol p=NR.[106]
		Extrapyramidal symptoms 558	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	No significant differences (very few events) with olanzapine vs. risperidone vs. haloperidol vs or comparator groups.[106]
		Discontinu-ation due to clinically significant adverse events 558	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	No significant difference in discontinuation due to clinically significant adverse events with olanzapine vs. risperidone vs. haloperidol vs or comparator groups.[106]
		Extrapyramidal events 101	Insufficient	Medium risk of bias, consistency unknown—single study, direct, imprecise	Very small numbers of dizziness events in risperidone vs. olanzapine vs. quetiapine vs. haloperidol, p=0.012.[99]

[a] Also no excitation or disinhibition in patients receiving flunitrazepam, not reported for the haloperidol.[82]

CGI-A = Clinical Global Impression Severity of Illness – Aggression; KQ = Key Question; MOAS = Modified Overt Aggression Scale; N, n = number of patients; NR = not reported; NS = not significant; OAS = Overt Aggression Scale; QT = QRS complex to T wave interval; vs. = versus.

Strategies To Address Aggressive Behavior: Benefits (KQ 1c) and Harms (KQ 2c)

We identified no eligible studies for strategies involving staff training, risk assessment interventions, multimodal interventions, or environmental interventions. We graded SOE for all these strategies as insufficient for both benefit and harms.

Again, only medication interventions addressed this question and provided any direct comparisons of strategies (Table 16). Although involuntary medication as a first choice in actively aggressive patients did decrease the use of seclusion compared with first choice of seclusion, this single study's high risk of bias led to a grade of insufficient SOE. This study reported no harms data, leading to an SOE grade of insufficient regarding the comparative harms of these strategies.

Table 16. Summary of findings with strength of evidence grades: Comparative benefits of medication-based strategies for reducing seclusion and restraint use in aggressive patients (KQ 1c)

Intervention and Comparison	Primary Outcome of Interest	Outcome N of Patients Analyzed	Strength of Evidence	Supporting Judgment	Findings and Direction of Effect
Medication protocols vs. other medication protocols or usual care	Change in seclusion or restraint	Seclusion incident rate 659	Insufficient	High risk of bias, consistency unknown—single study, direct, precise	Significant lower risk with involuntary medication[a] as first choice vs. seclusion as first choice (RR, 0.51; 95% CI, 0.34 to 0.79), p<0.001.[86]
		Seclusion hours 659	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	Lower number of overall hours with involuntary medication[a] as first choice vs. seclusion as first choice (998 vs. 2,098), no statistical testing reported.[86]
		Seclusion duration 659	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	Longer mean duration with involuntary medication[a] as first choice vs. seclusion as first choice (32 vs. 30 hours), no statistical testing reported.[86]
		Seclusion duration rate 659	Insufficient	High risk of bias, consistency unknown—single study, direct, precise	Significant lower risk with involuntary medication[a] as first choice vs. seclusion as first choice (RR, 0.54; 95% CI, 0.5 to 0.58), p<0.001.[86]
		Mechanical restraint incident rate 659	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	No significant difference in involuntary medication[a] as first choice vs. seclusion as first choice (RR, 1.44; 95% CI, 0.38 to 5.36).[86]
		Coercive incident rate[b] 659	Insufficient	High risk of bias, consistency unknown—single study, direct, imprecise	No significant difference in coercive incident rate in involuntary medication[a] vs. seclusion as first choice options (RR, 0.95; 95% CI, 0.67 to 1.35).[86]
		Duration in restraints 200	Insufficient	High risk of bias, consistency unknown—single study, direct, precise	Significant decrease with single-dose delirium treatment vs. no delirium treatment, both in the first 24 hours, 3 vs. 6 days, p<0.001.[85]

[a] "Involuntary medication" refers to single dose haloperidol plus promethazine or lorazepam.[86]

[b] "Coercion" refers to a sequence of coercive episodes (seclusion, mechanical restraint, or involuntary medication) for less than 24 hours.[86]

CI = confidence interval; KQ = Key Question; N = number; RR = relative risk; vs. = versus.

Finally, in treating delirium in an intensive care setting, immediate treatment with psychotropic medications led to shorter time in restraints compared with delayed or no treatment. We graded this as insufficient SOE because the data came from a high risk of bias study. Again, the study reported no harms data, leading to an insufficient SOE grade.

Characteristics of Patient, Intervention Components, or Settings Modifying Outcomes (KQ 3)

We identified no eligible studies that addressed whether these characteristics modified these results.

Findings in Relationship to What Is Already Known

This limited body of evidence is consistent with prior findings. Older reviews emphasized the lack of high quality and effective intervention studies to prevent the development of aggressive behavior in acute-care settings.[12,15,108,109] The absence of relevant literature has been similarly reported for patients with actively aggressive behavior, whether alternative strategies were being compared with seclusion and restraints[12,15] or whether alternatives to seclusion and restraints were being compared with each other.[12,13,15,108] The lack of literature about comparative harms of these interventions has also been identified.[110] Our review updates and confirms these findings, and it additionally includes potentially relevant pharmacologic interventions.

What our review adds is the finding that a general application to all individuals on a inpatient psychiatric units (i.e., not just to those who are actively aggressive) of a strategy that involves a risk assessment component to can decrease subsequent *aggressive* behavior. Earlier reviews of risk assessments assessed whether they could decrease *agitation*, which is often considered a lower-level precursor to aggression. However, CRTs in both trials that evaluated the effectiveness of risk assessment had data analytic limitations related to using a cluster randomized design. Specifically, investigators had not analyzed their data to account appropriately for the clustered nature of the data; this drawback likely affected each trial's results (e.g., increased the risk of a type I error). Finally, our results can be considered in the context of prior research about the impact of risk assessment practice on patients' agitation.[111] Specifically, our review identified a potential relationship between using risk assessment and lower aggression in acute care settings (albeit with the statistical limitations we noted); earlier research had found that using risk assessment is associated with reduced agitation.

Applicability

The scope of our review encompassed adults with a diagnosed psychiatric disorder, including delirium, in an acute care hospital setting and adults with severe psychiatric symptomatology in an emergency department setting. In addition, we included studies of patients for whom attempts were made to prevent aggressive behavior or to de-escalate that behavior if they became actively aggressive.

The populations and settings in the included studies were relevant to those we were targeting. When reported, mean ages generally ranged from 38 to 40 years. Studies varied widely in the percentages of patients who were male or female. We found little information on other sociodemographic or clinical characteristics of patients.

Interventions were in line with clinical practice in acute care units. However, the specifics of how investigators implemented their interventions were not always clear; hence, how to reproduce or replicate them is also uncertain. This point is especially relevant to the multimodal protocols, where varying fidelity to multiple components makes it difficult to attribute benefits to specific components.

Studies generally compared interventions with usual care. Usual-care practices appeared to be consistent with standard practice on psychiatric and medical units. The only studies directly

comparing alternative strategies with each other involved medication protocols. Only one study compared an alternative strategy (first choice involuntary medication) directly with seclusion (considered usual care in that country).

Outcomes measured were quite diverse; this fact precluded any kind of quantitative synthesis of data. For example, changes in any aggressive incidents versus changes in severe aggressive incidents were not regarded as combinable outcomes. Also, most studies reported short-term, but not long-term, outcomes. One study reported long-term outcomes such as quality of life, patient experience, and subsequent aggressive behavior. Two studies reported on use of services and economic outcomes.

Nineteen studies addressed individuals on an acute care psychiatric unit (rather than a medical or emergency department setting). Approximately half of the total number of identified studies were conducted in the United States. However, of the 11 eligible studies, only 4 were from U.S. settings (1 high risk of bias CRT in inpatient psychiatric settings,[103] 1 high risk of bias retrospective cohort study addressing delirium in an intensive care unit,[85] and 1 high risk of bias RCT[102] and 1 low risk of bias RCT[98] both addressing aggression in an emergency department). Indeed, 5 of the 6 eligible studies involving inpatient psychiatric settings were conducted in countries other than the United States. The 2 studies forming the basis for the single low SOE intervention, risk assessment,[78,87] were both conducted outside the United States. How substantially clinical practice in sites outside the United States differs from current U.S. practice is not clear. This finding implies that the applicability of findings from outside the United States may be questioned.

Implications for Clinical and Policy Decisionmaking

The paucity of evidence means that most of our implications are for future research rather than clinical or policy judgments. Still, the handful of findings that we graded as low SOE may provide some implications for clinical practice or policy judgments.

In particular, a limited number of risk assessment interventions subsequently led to less aggressive behavior (low SOE) and reduced the subsequent use of seclusion and restraints (low SOE). These findings suggest the need for clinicians to consider carefully the role of these strategies as interventions on psychiatric inpatient units. Specifically, acute care practitioners and administrative staff will need to 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. The questions that may arise, for example, include: Is the limited evidence currently available sufficient for evaluating effectiveness? Should implementation decisions be delayed until more evidence becomes available? What is the role of quality measures designed to create incentives to improve the quality of care when the evidence base for those measures is unclear?

We are unaware of any ongoing trials that will add to the current sparse body of evidence regarding the benefits of risk assessments and multimodal interventions. Furthermore, we cannot comment on potential harms or costs associated with implementing risk assessment protocols. Indeed, with only one study (rated as high risk of bias) from U.S. inpatient psychiatric settings, determining how these interventions might be applied in and what modifications might be necessary are key next steps.

Limitations of the Systematic Review Process

To find eligible studies, we employed an intensive search process in multiple electronic databases; we also conducted searches for gray literature. Because of time and monetary

limitations, however, we limited eligible studies to those published in English. Methods research indicates that such an approach can introduce language bias; in general, however, it may also lead to overestimates of the effectiveness of interventions.[61]

We also limited the scope to focus on data relevant to adults in acute care settings. This restriction followed the request of the topic nominator, but our Key Informants and stakeholders supported this approach as we developed the scope of the review. This focus left out consideration of data in chronic care and psychiatric residential settings; it also omitted treatment of children and adolescents. In both these clinical areas, however use of seclusion and restraints is common and potentially concerning.[22] Further, this focus on acute care settings (rather than psychiatric hospitals, which can involve both acute and longer-term lengths of stay) prevented inclusion of the few otherwise eligible studies that addressed the use of the Six Core Strategies,[32] a key strategy in widespread use in psychiatric units worldwide. For example, some evidence of longer-stay psychiatric hospitals suggests benefit of multimodal interventions.[112]

Our review does not address those with a primary diagnosis of dementia in an acute care setting. Although systematic review evidence addressing the use of seclusion and restraints in patients with dementia in chronic care settings exists,[54,55] we did not identify any reviews of the use of these approaches in acute care facilities treating patients with dementia.

To allow a meaningful synthesis of outcomes, we required that studies report at least one of our main outcomes—change in aggressive behavior or change in seclusion and restraint use. This restriction may have reduced the number of eligible studies and limited the number of patient-centered outcomes (e.g., improved quality of life and improved therapeutic relationship) we could examine. However, synthesizing such data with the other collected outcomes would have been difficult and would be unlikely to affect our SOE findings.

Distinguishing between benefits (KQ 1) and harms (KQ 2) in comparative effectiveness reviews can be challenging. For example, a benefit of a particular alternative strategy (e.g., decreased injury to staff) could be seen as a harm of the comparator (e.g., increased injury to staff). Given the limited evidence identified in our review, we do not think this difficulty affects interpretation of our results, but it is an important issue to consider in this work. Furthermore, although we group intervention types in our results section for ease of reporting, these types were not established a priori. The lack of a generally accepted nomenclature for types of interventions aimed at de-escalating aggressive behavior in psychiatric patients is another limitation of our review.

Publication bias and selective outcome reporting are potential limitations. Although we searched for gray and unpublished literature, the extent and impact of publication and reporting bias in this body of evidence are impossible to determine.

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.[111] This exclusion limited consideration of interventions to reduce agitation, which may also lead to a decrease in aggression. An evidence base for reducing agitation does exist[113,114] and may inform aggression management. This decision to focus on aggression and not agitation, while 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.

Our review addressed only interventions for which an evidence base exists. Newer interventions, which might deal with aggressive behavior but for which data have not yet generated, were not ones we could have identified for this review.

Finally, our scope did not allow us to evaluate the accuracy of risk assessment tools. Risk assessment is an essential step to identify patients at high risk of aggressive behavior (i.e., those to whom interventions to de-escalate aggressive behavior need to be targeted).[109] We found no systematic review of the psychometric evidence of these tools for identifying those at risk of aggressive behavior.

Limitations of the Evidence Base

Overall, several major limitations characterize this body of evidence. First, the number and quality of eligible studies are quite low. We identified a small number of eligible trials, and for those eligible, all but one had medium or high risk of bias assessments, leading to only one intervention—risk assessment—with SOE greater than low. Most of the available evidence was from pre/post studies with designs that precluded conclusions of causal inference. Further, we were surprised that no eligible trials tested application of the Six Core Strategies for decreasing aggressive behavior, given its influence on practices both in the United States and internationally.[115-117] This evidence base leaves clinicians, administrators, policymakers, and patients without clear guidance on how to best prevent and de-escalate aggressive behaviors in acute care settings.

Second, the analytic approaches employed to handle CRTs, particularly for evaluating risk assessment protocols, had substantial limitations that affected the assigned SOE ratings. More information in each primary study, including the standard error of each intraclass correlation coefficient, the average cluster size for each outcome, and the within- and between- variation for the outcomes, would have made it easier to determine how much the data clustering affected the results; this in turn which would have made for more precise SOE ratings.

Third, limited description of the nonmedication interventions in the articles and the lack of a reference standard for specific interventions made it difficult to clarify which specific parts of an intervention were being applied. This lack of clarity may have led to our inaccurately classifying interventions (e.g., components of staff training may overlap with environmental interventions, so that the difference between the two interventions may not be that substantial) and made it difficult to determine what specific components were effective. Similarly, this limited description makes it difficult to determine how to successfully replicate effective interventions, such as the implementation of risk assessment protocols, in an inpatient U.S. acute care setting.

Fourth, reporting on the relevant outcomes is varied. Although studies report on variables reflecting aggressive behavior and use of seclusion and restraint use, they use many different measures to do so, making synthesis of the data challenging. For example, aggressive behavior might be reported as a total count of aggressive incidents, or as a mean rate of aggressive incidents per 100 treatment days; such diversity prevents analysts from doing a clear quantitative synthesis of the results to determine a magnitude of effect. Similarly, seclusion and restraint outcomes might be measured in total counts, or rates per 100 treatment days, or duration in seclusion. Additionally, seclusion and restraints were sometimes reported as single summary measure; other times reported them separately. Determining which outcomes are more important, and then collecting them systematically (consistently), would be important future steps in research on these topics.

Fifth, some of the available interventions were targeted at slightly different populations, making the SOE assessment difficult. For example, the violence risk assessment studies evaluated not only different risk assessment protocols but also different classifications of

aggression (i.e., severe aggression and any aggression). Therefore, for most outcomes, we graded the SOE as either low or insufficient.

Sixth, many relevant outcomes are not reported. In our eligible studies, we found limited reporting of patient-centered outcomes, such as improved quality of life or patient experience, and improved therapeutic relationship, that are key guides to selecting a strategy. Similarly, we found only limited information on harms and no information on costs or resource utilization. However, data on each of these issues are necessary to determine whether the balance of benefits and harms supports the use particular strategies, such as risk assessment interventions.

Seventh, most of the available acute care evidence is from inpatient psychiatric settings, with little eligible evidence for inpatient medical/surgical units and emergency departments.

Finally, we found no eligible evidence to guide decisionmakers about how these comparative effects might differ by key moderating variables, such as age, specific psychiatric diagnosis, and specific treatment component.

Research Recommendations

Major evidence gaps exist in this important and 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 decisionmaking in this area are minimal. A major gap is well-designed, adequately powered, properly analyzed comparative trials that address questions of prevention and de-escalation. The validity of findings from the three reasonably well-designed CRTs was severely limited 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 that may need to be addressed first.

Head-to-head trials that move beyond a usual-care comparator to examine various interventions against each other are needed to guide decisionmaking. The critical element is identifying the “right” interventions to compare, to make the most efficient use of research time and funding on this topic. More evidence that can speak to differential effectiveness of various interventions would allow clinicians and administrators to balance effectiveness with implementation and resource costs.

Investigators leading trials in the future 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 may be the most (or least) effective. Risk assessment strategies, which have some evidence for preventing aggressive behavior, need to be described in more detail to enable them to be compared with each other and allow variations within these approaches to be compared.

Currently, clinicians and investigators do not know the accuracy of risk assessment tools. These are necessary to identify patients at high risk of aggressive behavior and, hence, to develop an effective plan to manage potential or real aggressive behavior. For that reason, more work on documenting the measurement properties of these tools is needed.

All future trials must report on consistently defined and clinically meaningful outcomes, both short term and long term. Selection of these outcomes needs to be informed by key stakeholders, including patients. 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 (CONSORT) statement regarding the reporting of clinical trials (including cluster randomized trials).

Key long-term outcomes must involve more patient-centered outcomes, including, for instance, quality of life or other patient-reported outcomes. Patient perspectives of harms, including treatment preferences, are largely missing from the literature in acute care settings, and this gap should be remedied. Measures of the use of health services are important, as are cost implications and data. Investigators should incorporate implementation factors, 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 from settings outside the United States. In the latter case, standard practices, patient populations, insurance coverage, costs, and various other variables may differ, perhaps considerably. Future well-designed studies of inpatient psychiatric settings need to 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 clearly had no useful data on modifiers of treatment effectiveness. Thus, future studies (including comparative trials) need to assess how variables such as age and other sociodemographic or economic factors, specific diagnosis (and perhaps coexisting conditions), and specific treatment components modify or mediate the effects of the interventions studied. Consideration of effect modifiers must be powered appropriately, although we acknowledge that in this clinical area achieving adequate sample sizes for comparative trials of these types of interventions (perhaps apart from medication protocols) may prove challenging.

Conclusions

Given the ethical imperative for treating 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 decisionmaking for 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 individual setting.

The current evidence base leaves clinicians, administrators, policymakers, and patients without clear guidance on how to best prevent and de-escalate aggressive behaviors in acute care settings. Only risk assessment had any evidence that they can decrease aggression and reduce seclusion and restraint; however, the strength of that evidence was, at best, low. Evidence for de-escalating aggressive behavior is even more limited. More research is needed to guide clinicians, administrators, and policymakers on how to best prevent and de-escalate aggressive behavior in acute care settings.

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