Review protocol for rapid tranquillisation in the acute management of agitated or aggressive behaviour that poses a serious risk of harm to self or others

ID	Field	Content
0.	PROSPERO registration number	CRD420251127264
1.	Review title	Rapid tranquillisation in the acute management of agitated or aggressive behaviour that poses a serious risk of harm to self or others
2.	Review question	What are the benefits and harms of medication in the acute management of agitated or aggressive behaviour that poses a serious risk of harm to self or others?
3.	Objective	To determine the benefits and harms of medication in the acute management of agitated or aggressive behaviour that poses a serious risk of harm to self or others
4.	Searches	The principal search strategy will be developed in MEDLINE and then adapted, as appropriate, for use in the other sources listed, taking into account their size, search functionality and subject coverage • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE ALL • PsycInfo Database functionality will be used, where available, to exclude: • Animal studies • Editorials, letters, news items and commentaries • Conference abstracts and posters • Trial registry entries without an associated journal publication • Theses and dissertations

		• Papers not published in the English language. Date limits: Databases will be searched from inception to the date of the search with no date limits applied Search filters and classifiers: As required the following standard NICE filters will be used to limit results by study type: systematic reviews / randomised controlled trials Supplementary search techniques: • Hand-searching of inclusion lists of systematic reviews The information services team at NICE will quality assure the principal search strategy based on the PRESS 2015 Guideline Evidence Based Checklist. Any revisions or additional steps will be agreed by the review team before being implemented The full search strategies for all databases will be published in the final review
5.	Condition or domain being studied	Acute management of agitated or aggressive behaviour that poses a serious risk of harm to self or others
6.	Population	**Inclusion:** • People who are judged to be in need of medication for the acute management of agitated or aggressive behaviour that poses a serious risk of harm to self or others, and where rapid tranquillisation is necessary and proportionate **Exclusion:** • Trials of rapid tranquillisation in pregnant people • Trials that specifically recruit participants with dementia • Procedural sedation, for example, as anaesthesia for painful medical procedures or to prevent emergence agitation following anaesthesia

		If some, but not all, of a study's participants are eligible for the review, then we will include a study if at least 80% of its participants are eligible for this review
7.	Intervention	**Inclusion:** Medication used in the acute management* of agitated or aggressive behaviour that poses a serious risk of harm to self or others, including the following medications used as monotherapy or in combination with each other: • Haloperidol • Olanzapine • Aripiprazole • Risperidone • Ziprasidone • Asenapine • Loxapine • Droperidol • Levomepromazine • Lorazepam • Alprazolam • Midazolam • Clonazepam • Diazepam • Promethazine • Ketamine • Zuclopenthixol acetate (Clopixol Acuphase) • Placebo (used as a control in trials) *Acute management defined as treatment periods of 24 hours or less Drugs will be coded and entered into the network separately for different routes of administration: intramuscular (IM); intravenous (IV); oral; inhaled

		Different doses (between or within studies) will be categorised and entered into the network by medication. Categorisation of dose levels will be informed by the evidence identified and the clinical knowledge and experience of the guideline committee **Exclusion:** • Sodium valproate • Long-acting injectable antipsychotics • Oral antipsychotic medication (sometimes referred to as p.r.n medication) *to prevent the onset of* aggressive behaviour
8.	Comparator	All interventions above will be included in network meta-analysis
9.	Types of study to be included	**Inclusion:** • RCTs • Systematic reviews of RCTs (for identification of eligible RCTs) **Exclusion:** • Quasi-randomised or other non-randomised studies • Conference abstracts • Dissertations and theses • Trial registry protocols • Books and book chapters
10.	Other exclusion criteria	Non-English language papers
11.	Context	This guidance will fully update the following NICE guideline: Violence and aggression: short-term management in mental health, health and community settings (last updated 2015; NG10)
12.	Primary outcomes (critical outcomes)	**Efficacy** • Immediate adequate sedation, measured within 30 minutes of first administration of intervention (eligible timepoints ≤30 minutes), defined as:

		○ Number of participants adequately sedated as defined by study, commonly measured on a single-item scale where score indicates that participants are calm/tranquil or asleep ○ Number of participants for whom additional dosing of the same medication or changing to a different medication was not required • Acute agitation response, measured at 2 hours after first administration of the intervention (or if not available, at 1-2 hours) defined as: ○ Number of participants showing at least a 40% reduction in Positive and negative syndrome scale-excited component (PANSS-EC), or ○ Number of participants rated as 'much improved' or 'very much improved' (score of 1 or 2) on the Clinical Global Impression-Improvement (CGI-I) scale **Safety** • Number of participants with any (≥1) adverse events during the study period (within 24 hours of first administration of the intervention) For trials where multiple administrations of the intervention are allowed within the study period, efficacy data will be extracted before the administration of the second dose. For the safety outcome, only participants who only received one dose and type of study drug will be considered Non-imputed intention-to-treat (ITT) data is preferred (data is reported according to the intervention to which participants are assigned regardless of the actual intervention received or adherence to that intervention, and outcome data are measured for all randomised participants). If non-imputed ITT data is not reported, all randomised participants will be included in the denominator (ITT principle). For efficacy outcomes, the assumption is that participants with missing outcome data did not achieve response. For safety outcomes, the assumption is that participants with missing outcome data did not experience an adverse event
13.	Secondary outcomes (important outcomes)	None

14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI-Reviewer 5 and de-duplicated Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior systematic reviewer if necessary Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion A standardised Excel spreadsheet will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, year of trial publication, total number randomised, number of arms), participant characteristics (including mean age of total sample of randomised participants, percentage of female randomised participants, percentage of randomised participants from a BME group, primary diagnosis, baseline aggression or agitation score, proportion of participants with alcohol or substance intoxication), setting (for example, psychiatric or general emergency settings), details of the interventions (including dose, fixed/flexible dosing strategy, route of administration, additional restrictive practices used during administration of rapid tranquillisation), relevant outcome data (including timepoint of assessment, definition of adequate sedation or agitation response), and sponsorship of the study from pharmaceutical companies (yes/no/unclear/NA) Data extraction will be double-coded (one of the coders will be a senior reviewer and the double-coding will be part of the quality assurance process)
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • Cochrane RoB tool v.2 for RCTs (including cluster-randomised trials) Risk of bias assessments will be double-coded (one of the coders will be a senior reviewer and the double-coding will be part of the quality assurance process)

		Threshold analysis will be conducted to assess the robustness of intervention recommendations due to bias (Phillippo 2018)	
16.	Strategy for data synthesis	Network meta-analyses (NMAs) will be conducted within a Bayesian framework using Markov Chain Monte Carlo simulation techniques implemented in WinBUGS 1.4.3 to synthesise the data for all eligible interventions which are connected in a network of RCT comparisons The random effects assumption will be assessed by comparing the fit of fixed and random class effects models, where the former assumes intervention effects within each class are the same (i.e. no within-class variability of effects) The consistency of direct and indirect evidence will be assessed by fitting and comparing the fit of the NMA and unrelated mean effects (UME) models, the latter is equivalent to having separate, unrelated, meta-analyses for pairwise contrast (Dias 2011). Each data point's contribution to the posterior mean residual deviance for the NMA model will be plotted against that for the UME model, to visually assess if specific data points are contributing to inconsistency. If the UME suggests there is evidence of inconsistency, node-split models will be fitted to assist in identifying loops of evidence with inconsistency (Dias 2010)	
17.	Analysis of sub-groups	If the network structure allows, sensitivity analyses will be considered for: • Age (adults; children and young people) • Setting (psychiatric; general settings) • The use of additional restrictive practices (e.g. physical restraint, mechanical restraint, seclusion) during the administration of rapid tranquillisation Where sensitivity analyses have been performed, the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others	
		☒	Intervention

18.	Type and method of review	☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
19.	Language	English	
20.	Country	England	
21.	Anticipated or actual start date	July 2025	
22.	Anticipated completion date	November 2026	

23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐

		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	Named contact: National Institute for Health and Care Excellence (NICE) Named contact e-mail: violenceandaggression@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE)		
25.	Review team members	• Senior Technical Analyst • Technical Analyst • Health Economist • Information Specialist		
26.	Funding sources/sponsor	This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of		

		Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10432/documents	
29.	Other registration details	None	
30.	Reference/URL for published protocol		
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Agitation; aggression; rapid tranquillisation; sedation; emergency; acute	
33.	Details of existing review of same topic by same authors	Not applicable	
34.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35.	Additional information	None	

36.	Details of final publication	www.nice.org.uk