Supplementary materials

S1. The complete search strategy for each database

1.1. PubMed

Search Number	Query	Filters	Results	Time
#1	(((remimazolam) OR (ONO 2745)) OR (CNS 7056)) OR (methyl 3-(8-bromo-1-methyl-6-(2-pyridinyl)-4H-imidazo(1,2-a)(1,4)benzodiazepin-4-yl)propanoate)	—	425	2023/10/22 2:42:02
#2	(((((Flumazenil) OR (Flumazepil)) OR (Romazicon)) OR (Lanexat)) OR (Ro 151788)) OR (Anexate)	—	4,914	2023/10/22 2:42:36
#3	((((((((((Propofol) OR (2,6 Diisopropylphenol)) OR (2,6-Bis(1-methylethyl)phenol)) OR (Disoprofol)) OR (Diprivan)) OR (Disoprivan)) OR (Fresofol)) OR (ICI 35868)) OR (Ivofol)) OR (Recofol)) OR (Aquafol)	—	26,164	2023/10/22 2:44:09
#4	#1 AND #2 AND #3	—	16	2023/10/22 2:44:39
#5	#1 AND #2 AND #3	Randomized Controlled Trial	4	2023/10/22 2:50:32

1.2. Embase

No.	Query	Results	Date
#1.	('remimazolam'/exp OR '3 [8 bromo 1 methyl 6 (2 pyridinyl) 4h imidazo [1, 2 a] [1, 4] benzodiazepin 4 yl] propanoic acid methyl ester' OR '3 [8 bromo 1 methyl 6 (pyridin 2 yl) 4h imidazo [1, 2 a] [1, 4] benzodiazepin 4 yl] propanoic acid methyl ester' OR '8 bromo 1 methyl 6 (2 pyridinyl) 4h imidazo [1, 2 a] [1, 4] benzodiazepine 4 propanoic acid methyl ester' OR '8 bromo 1 methyl 6 (pyridin 2 yl) 4h imidazo [1, 2 a] [1, 4] benzodiazepine 4 propanoic acid methyl ester' OR 'anerem' OR 'biprazine pf' OR 'byfavo' OR 'cns 7056' OR 'cns 7056b' OR 'cns7056' OR 'cns7056b' OR 'gw 502056x' OR 'gw502056x' OR 'hr 7056' OR 'hr7056' OR 'methyl 3 [8 bromo 1 methyl 6 (2 pyridinyl) 4h imidazo [1, 2 a] [1, 4] benzodiazepin 4 yl] propanoate' OR 'methyl 3 [8 bromo 1 methyl 6 (pyridin 2 yl) 4h imidazo [1, 2 a] [1, 4] benzodiazepin 4 yl] propanoate' OR 'ono 2745' OR 'ono 2745bs' OR 'ono in251' OR 'ono2745' OR 'ono2745bs' OR 'onoin251' OR 'remimazolam' OR 'remimazolam besilate' OR 'remimazolam besylate' OR 'remimazolam bezenesulfonate' OR 'rf 10007' OR 'rf10007' OR 'ruima' OR 'sp 148.5' OR 'sp148.5') AND ('flumazenil'/exp OR '8 fluoro 5, 6 dihydro 5 methyl 6 oxo 4h imidazo [1, 5 a] [1, 4] benzodiazepine 3 carboxylic acid ethyl ester' OR '8 fluoro 5, 6 dihydro 5 methyl 6 oxoimidazo [1, 5 a] [1, 4] benzodiazepine 3 carboxylic acid ethyl ester' OR 'anexate' OR 'ethyl 8 fluoro 5, 6 dihydro 5 methyl 6 oxo 4h imidazo [1, 5 a] [1, 4] benzodiazepine 3 carboxylate' OR 'flumazenil' OR 'flumazepil' OR 'lanexat' OR 'mazicon' OR 'ro 15 1788' OR 'ro 15-1788' OR 'ro 151788' OR 'ro15 1788' OR 'ro15-1788' OR 'ro151788' OR 'romazicon' OR 'ym 684' OR 'ym684') AND ('propofol'/exp OR '2, 6 diisopropylphenol' OR 'anepol' OR 'anesia' OR 'cryotol' OR 'diisoprofol' OR 'diprivan' OR 'diprofol' OR 'disoprivan' OR 'disoprofol' OR 'fresofol' OR 'gobbifol' OR 'hiremon (propofol)' OR 'ici 35 868' OR 'ici 35, 868' OR 'ici 35868' OR 'plofed' OR 'pofol' OR 'profast' OR 'propocam' OR 'propofol' OR 'propofol lipuro' OR 'propofol-lipuro' OR 'propolipid' OR 'propoven' OR 'provive' OR 'rapinovet' OR 'rapiva' OR 'recofol' OR 'recofol n' OR 'ripol (propofol)' OR 'safol' OR 'spifol' OR 'spiva (drug)' OR 'unifol (propofol)') AND [clinical study]/lim	34	2023/10/22

1.3. Web of Science

#	Search Query	Database	Results	Date Run
1	"remimazolam (Topic) OR ONO 2745 (Topic) OR CNS 7056 (Topic) OR methyl 3-(8-bromo-1-methyl-6-(2-pyridinyl)-4H-imidazo(1,2-a)(1,4)benzodiazepin-4-yl)propanoate (Topic) and Preprint Citation Index (Exclude – Database)	All Databases	564	Sun Oct 22 2023 12:08:08 GMT+0800
2	"Flumazenil (Topic) OR Flumazepil (Topic) OR Romazicon (Topic) OR Lanexat (Topic) OR Ro 15-1788 (Topic) OR Anexate (Topic) and Preprint Citation Index (Exclude – Database)	All Databases	8270	Sun Oct 22 2023 12:11:19 GMT+0800
3	"Propofol (Topic) OR 2,6-Diisopropylphenol (Topic) OR 2,6-Bis(1-methylethyl)phenol (Topic) OR Disoprofol (Topic) OR Diprivan (Topic) OR Disoprivan (Topic) OR Fresofol (Topic) OR ICI-35,868 (Topic) OR Ivofol (Topic) OR Recofol (Topic) OR Aquafol (Topic) and Preprint Citation Index (Exclude – Database)	All Databases	47872	Sun Oct 22 2023 12:14:16 GMT+0800
4	"#1 AND #2 AND #3 and Preprint Citation Index (Exclude – Database)	All Databases	20	Sun Oct 22 2023 12:14:41 GMT+0800

1.4. Cochrane Library

ID	Search	Hits	Date Run
#1	(remimazolam):ti,ab,kw AND (flumazenil):ti,ab,kw AND (propofol):ti,ab,kw (Word variations have been searched)	31	22/10/2023 07:49:27

S2. PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1, 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2, 3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	2, S1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	2, 3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	3, 4

Section and Topic	Item #	Checklist item	Reported on page #
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	3, 4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	3, 4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	3, 4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	4, 5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	4, 5
Study characteristics	17	Cite each included study and present its characteristics.	5-7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7-12
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	7-12

Section and Topic	Item #	Checklist item	Reported on page #
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	12
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	12, 13
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	S3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	13
	23b	Discuss any limitations of the evidence included in the review.	14
	23c	Discuss any limitations of the review processes used.	14
	23d	Discuss implications of the results for practice, policy, and future research.	13, 14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	—
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	15
Competing interests	26	Declare any competing interests of review authors.	15
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	15

S3. Detailed results of the GRADE assessment

Author(s): Quantong Wu, Fuchao Xu, Jie Wang, and Ming Jiang.

Question: Comparison of Remimazolam-Flumazenil Versus Propofol for Recovery from General Anesthesia: A Systematic Review and Meta-Analysis.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remimazolam-flumazenil	propofol	Relative (95% CI)	Absolute (95% CI)		
Emergence time												
8	randomised trials	not serious	very serious[a]	not serious	not serious	none	259	259	—	MD 4.34 min fewer (6.88 fewer to 1.81 fewer)	⊕⊕◯◯ Low	—
Extubation time												
7	randomised trials	not serious	very serious[a]	not serious	not serious	none	244	244	—	MD 4.26 min fewer (6.81 fewer to 1.7 fewer)	⊕⊕◯◯ Low	—
Length of PACU stay												
6	randomised trials	not serious	very serious[a]	not serious	not serious	none	214	215	—	MD 4.42 min fewer (7.45 fewer to 1.38 fewer)	⊕⊕◯◯ Low	—

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remimazolam-flumazenil	propofol	Relative (95% CI)	Absolute (95% CI)		
Pain												
2	randomised trials	not serious	not serious	not serious	not serious	none	68	67	—	MD 0.01 lower (0.08 lower to 0.06 higher)	⊕⊕⊕⊕ High	—
PONV												
7	randomised trials	not serious	not serious	not serious	not serious	none	18/293 (6.1%)	21/294 (7.1%)	RR 0.87 (0.49 to 1.56)	9 fewer per 1,000 (from 36 fewer to 40 more)	⊕⊕⊕⊕ High	—
Respiratory depression												
4	randomised trials	not serious	not serious	not serious	not serious	none	0/156 (0.0%)	8/155 (5.2%)	RR 0.20 (0.04 to 0.89)	41 fewer per 1,000 (from 50 fewer to 6 fewer)	⊕⊕⊕⊕ High	—
Emergence agitation												
4	randomised trials	not serious	not serious	not serious	serious[b]	none	1/146 (0.7%)	4/145 (2.8%)	RR 0.45 (0.10 to 1.94)	15 fewer per 1,000 (from 25 fewer to 26 more)	⊕⊕⊕◯ Moderate	—

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	remimazolam-flumazenil	propofol	Relative (95% CI)	Absolute (95% CI)		
Re-sedation												
4	randomised trials	not serious	not serious	not serious	serious[b]	none	13/144 (9.0%)	2/145 (1.4%)	RR 4.15 (1.31 to 13.13)	43 more per 1,000 (from 4 more to 167 more)	⊕⊕⊕◯ Moderate	—
Delirium												
3	randomised trials	serious[c]	not serious	not serious	serious[b]	none	1/86 (1.2%)	2/86 (2.3%)	RR 0.67 (0.11 to 3.87)	8 fewer per 1,000 (from 21 fewer to 67 more)	⊕⊕◯◯ Low	—
Postoperative dizziness												
2	randomised trials	not serious	not serious	not serious	serious[b]	none	3/68 (4.4%)	7/67 (10.4%)	RR 0.42 (0.11 to 1.57)	61 fewer per 1,000 (from 93 fewer to 60 more)	⊕⊕⊕◯ Moderate	—

CI: confidence interval; MD: mean difference; RR: risk ratio; PACU: post-anesthesia care unit; PONV: postoperative nausea and vomiting.

Explanations:

a. I^2 suggested considerable heterogeneity.

b. For comparison of the incidence of rare events, the total sample size appeared insufficient, and the 95% CI was too wide.

c. The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results.

S4. Egger test of the primary outcome

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. meta bias, egger random(sjonkman)

  Effect-size label: Mean diff.
        Effect size: _meta_es
          Std. err.: _meta_se

Regression-based Egger test for small-study effects
Random-effects model
Method: Sidik–Jonkman

H0: beta1 = 0; no small-study effects
            beta1 =     -3.21
      SE of beta1 =     2.767
                z =     -1.16
       Prob > |z| =    0.2452
```