Supplemental Digital Contents

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1. Panel Membership and Communication

Selection of guideline leadership

The guideline leadership was selected by the Society of Critical Care Medicine (SCCM) Board of Regents (BOR). The leadership consisted of co-chairs (M.B and M.A) and co-vice-chairs (M.M and J.L.S), all of whom are subject matter experts, which is in keeping with SCCM's BOR Standard Operating Manual. The leadership were supported by two clinician-methodologists from the Guidelines in Intensive Care, Development and Evaluation Group (GUIDE) (K.L, K.L.C). The selection process of the leadership was founded in due consideration for diversity, equity, and inclusion. Moreover, the BOR examined the candidate's Curriculum Vitae of each candidate to assess for expertise. The BOR reviewed declared conflicts of interest (COI) prior to appointment.

Selection of panelists

An additional interdisciplinary panel of 18 members from backgrounds of nursing, physicians, pharmacists, psychologists, and patient partners were appointed by the guideline leadership, with critical attention to expertise (or lived experience for the patient partners), diversity, equity and inclusion. Please see Table 1 below for the geographic distribution of the panel members. Each panel member completed a COI prior to appointment to the panel, with ongoing monitoring as per SCCMs Standard Operating Manual (i.e. annually, prior to every panel call, prior to voting, and at manuscript writing).

Table 1: Geographic Distribution of Panel Members

Country	Number of Panel Members
United States of America	19
Canada	4
France	1

Panel communication

The full panel held regular meetings to establish the scope of the guidelines, generate a series of clinical questions of interest (PICO questions), and generate recommendations using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. Meetings were facilitated originally by Zoom video-conferencing (although transitioned to Microsoft Teams), hosted by SCCM with one in-person meeting held at the annual SCCM Congress (January 2024). Guidelines leadership (co-chairs, co-vice-chairs, and clinician-methodologists) held regular video conference calls to refine processes and address barriers.

2. Conflict of Interest

SCCM maintains a commitment to trustworthy guidelines through a strict conflict of interest disclosure and management process. There were no disclosures directly related to the PICO questions within this guideline that required individual authors to abstain from voting on any recommendations. Disclosures are collected prior to voting by SCCM through a conflict of interest platform.

3. PICO Question Development

The panel formulated a series of actionable questions relevant to the scope of the guideline, following the PICO (Population, Intervention, Comparison, Outcomes) format that could potentially lead to an actionable recommendation statement.

Given that this was an update as opposed to a full guideline PICO selection was done cautiously. The leadership and panel prioritizing: 1-Updating PICOs in which new evidence had been published since the 2018 PADIS guideline was released, 2-Addressing PICOs that had not previously been addressed by a PADIS guideline, and 3-A desire to address both pharmacologic as well non-pharmacologic interventions. Possible topics that would be important to patients, their families, and clinicians were listed, and the final selection was made through discussion and consensus.

As there had been many new landmark trials published on dexmedetomidine, antipsychotics, mobilization, and melatonin since the 2018 PADIS guideline release, those areas were selected for updates. In addition, anxiety had not been previously addressed so that was selected as an area of interest. The leadership/panel acknowledge that the anxiety PICO could have been looked at in many ways (music therapy, diagnosis of anxiety, prevalence of anxiety, simply a scoping review), but it was elected to examine use of benzodiazepines for anxiety given it is such a ubiquitous intervention for likely a common issue.

For each PICO, the panel identified potential subgroups analyses of interest to be considered, subject to availability of the data during the literature review process. The members of the individual PICO questions are listed below (in alphabetical order with role indicated)

PICO 1-Anxiety treatment with benzodiazepines- Michele Balas (leadership representative), Gerald Chanques (subgroup lead), Linda Chlan (subgroup member), Jeremiah Duby (subgroup member), Erin Hall (subgroup member), Kimberley Lewis (lead methodologist)

PICO 2-Sedation with dexmedetomidine- Céline Gélinas (subgroup member), Kimberley Lewis (lead methodologist), Pratik Pandharipande (subgroup lead), Joanna Stollings (leadership representative), Judith Tate (subgroup member)

PICO 3-Delirium treatment with antipsychotics- Matt Aldrich (leadership representative), Nathan Brummel (subgroup member), Kallirroi Carayannopoulos (methodologist), Erin Hall (subgroup member), Timothy Girard (subgroup lead), Kimberley Lewis (lead methodologist), Joanna Stollings (leadership representative)

PICO 4-Enhanced mobilization- Kallirroi Carayannopoulos (lead methodologist), Michelle Kho (subgroup lead), Anna Krupp (subgroup member), Kimberley Lewis (methodologist), Molly McNett (leadership representative), Bethany Young (subgroup member)

PICO 5-Melatonin- Matt Aldrich (leadership representative), Makayla Cordoza (subgroup membered), Kimberley Lewis (lead methodologist), Patricia Louzon (subgroup member), Gerald Weinhouse (subgroup lead)

4. Outcome Prioritization

The panel identified a list of outcomes they deemed to be pertinent of the actionable PICO statements. Using the GRADE approach to outcome prioritization, each panel member independently rated each outcome on a scale of 1 to 9 (1= least important; 9 = critical to decision making). Panel members were asked to rate the importance of each of the listed outcomes **from the perspectives of patients.** Mean scores were then calculated for each outcome and categorized them based on the below 'Scoring Guide'. The final outcome ratings are displayed in the table below. Patient partners were part of the process of outcome selection.

Scoring Guide

SCORES	IMPORTANCE
1-3	**Limited Importance**
4-6	**Important**
7-9	**Critically important**

Outcome Prioritization by PICO

PICO 1-Anxiety

Outcome	Rating
Incidence of anxiety	8.0
Incidence of agitation	7.3
% of RASS measurements outside of target range	6.4
Incidence of delirium	7.5
Duration of delirium (or delirium-free days)	6.6
Duration of mechanical ventilation	7.1
ICU Length of stay	6.7
Use of mechanical restraints while in ICU	6.0
Use of additional rescue medication while in ICU	6.0
Incidence and severity of pain	5.2
Ability to communicate while in the ICU	5.8
Patient-satisfaction with care	5.3
Hospital length of stay	5.9
Mortality at 28 days	6.3
Mortality at longest follow-up	5.7
Discharge disposition	5.8
Quality of life post-ICU	6.7
Functional status post-ICU	6.2
Cognitive abilities post-ICU	6.9
Incidence of post-ICU PTSD	7.0
Incidence of post-ICU anxiety	7.4

Memory of the ICU	6.5

PICO 2-Sedation

Outcome	Rating
Incidence of agitation	8.0
% of RASS measurements outside of target range	7.3
Incidence of delirium	8.4
Duration of delirium (delirium-free days)	7.6
Duration of mechanical ventilation	8.5
ICU Length of stay	7.5
Use of mechanical restraints while in ICU	6.2
Use of additional rescue medication while in ICU	7.0
Incidence and severity of pain	5.9
Ability to communicate while in the ICU	6.5
Patient-satisfaction with care	5.6
Hospital length of stay	6.2
Mortality at 28 days	6.4
Mortality at longest follow-up	6.2
Discharge disposition	6.4
Quality of life post-ICU	6.7
Functional status post-ICU	6.5
Cognitive abilities post-ICU	6.9
Incidence of post-ICU PTSD	6.7
Incidence of post-ICU Anxeity	6.4
Memory of the ICU	6.5

PICO 3- Delirium

Outcome	Rating
Incidence of delirium	8.6
Duration of delirium (or delirium-free days)	8.3
Duration of mechanical ventilation	7.3
ICU Length of stay	7.2
Use of mechanical restraints while in ICU	6.4
Use of additional rescue medication while in ICU	6.8
Incidence and severity of pain	5.1
Hospital length of stay	6.3
Mortality at 28 days	6.6
Mortality at longest follow-up	6.0
Patient-satisfaction with care	5.2
Discharge disposition	6.2
Quality of life post-ICU	6.9
Functional status post-ICU	6.5
Cognitive abilities post-ICU	7.6

Post-ICU anxiety	6.6
Post-ICU PTSD	7.0

PICO 4-Enhanced Mobilization

Outcome	Rating
Incidence of delirium	8.0
Duration of delirium (or delirium-free days)	7.0
Incidence of anxiety	6.9
Incidence of agitation	7.1
% of RASS measurements outside of target range	5.8
Duration of mechanical ventilation	7.9
ICU Length of stay	7.7
Use of mechanical restraints while in ICU	5.7
Adverse events (e.g. unplanned extubation, line/catheter/drain dislodgement, falls, hemodynamic instability, VTE)	8.3
Incidence and severity of pain	5.9
Hospital length of stay	6.8
Mortality at 28 days	6.5
Mortality at longest follow-up	6.4
Patient-satisfaction with care	5.5
Discharge disposition	6.7
Quality of life post-ICU	7.2
Functional status post-ICU	8.0
Cognitive abilities post-ICU	7.3
Post-ICU anxiety	6.5
Post-ICU PTSD	6.5

PICO 5-Melatonin

Outcome	Rating
Incidence of anxiety	6.7
Incidence of agitation	6.7
% of RASS measurements outside of target range	5.6
Incidence of delirium	7.9
Duration of delirium (delirium-free days)	7.2
Duration of mechanical ventilation	6.5
ICU Length of stay	6.6
Use of mechanical restraints while in ICU	5.4
Use of additional rescue medication while in ICU	6.1
Incidence and severity of pain	4.7
Ability to communicate while in the ICU	5.3
Patient-satisfaction with care	6.3
Hospital length of stay	6.3
Mortality at 28 days	5.8

Mortality at longest follow-up	5.5
Discharge disposition	5.9
Quality of life post-ICU	6.5
Functional status post-ICU	6.1
Cognitive abilities post-ICU	6.7
Incidence of post-ICU PTSD	6.5
Incidence of post-ICU Anxiety	6.2
Memory of the ICU	5.8
Sleep quality/quantity	7.8

5. Literature Search Strategies

PADIS Update – Literature Search

Research Question(s):

Question	*Population*	*Intervention*	*Comparator*	*Evidence*
PICO 1 In adults admitted to the ICU, do benzodiazepines administered for anxiety vs no benzos, impact patient outcomes?	Adults with anxiety who are admitted to the ICU	A benzodiazepine of any dose, route, duration, or frequency	No benzodiazepine	RCTs Controlled observational trials
PICO 2 In adults admitted to the ICU, do antipsychotics administered for delirium vs no antipsychotics, impact patient outcomes?	Adults with delirium who are admitted to the ICU	Any antipsychotic medication, of any dose, route, duration, or frequency	No antipsychotics	RCT
PICO 3 In adults admitted to the ICU, does mobilization, vs usual care, impact patient outcomes?	Adults admitted to the ICU	Mobilization	Usual care	RCT Controlled observational trials
PICO 4 In mechanically ventilated adults admitted to the ICU, should dexmedetomidine, when compared with propofol, be used for sedation?	Adults admitted to the ICU who are mechanically ventilated and require sedation	Dexmedetomidine of any dose, route, duration, frequency	Propofol of any dose, duration, frequency	RCT Controlled observational trials
PICO 5 In adults admitted to the ICU, should melatonin vs placebo or no sleep-promoting medication impact patient outcomes?	Adults admitted to the ICU	Melatonin at any dose, duration or frequency	No melatonin	RCT Controlled observational trials

Search by: Karin Dearness (kdearnes@stjosham.on.ca)

Requestor: Kim Lewis (kimlewis83@gmail.com)

Date(s): May 12, 2023

Limits: Human, Adults (if feasible), Year of publication ≥2022 (PICO 3 only)

Databases:

- OVID Medline [medall],
- OVID Embase [oemezd],
- OVID PsycInfo [psyh],
- Cochrane Clinical Trials Register,
- www.ClinicalTrials.gov

Filters: RCTs OR observational studies (depending on PICO question)

Format: RIS output, duplicates removed

Alerts: Not automated, clients will reach out as and when update(s) needed

Additional Searching: none

Search Methods:

Electronic Search Strategy

The literature search was performed by an information specialist following PRISMA-S guidance (reference: Rethlefsen ML, et al. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev. 2021 Jan 26;10(1):39. https://doi.org/10.1186/s13643-020-01542-z) and using a peer-reviewed search strategy (Appendix 1). The search strategy was reviewed according to the methods described in McGowan, 2016 (reference: Jessie McGowan, et al. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epi. 2016(75):40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021).

Published literature was identified by searching the following bibliographic databases on May 11, 2023: MEDLINE all (1946–) via Ovid; Embase (1974–) via Ovid; PyscInfo (1807-) via Ovid, the Cochrane Clinical Trials Register, and ClinicalTrials.gov. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were: ICU, anxiety, benzodiazepines, delirium, antipsychotics, mobilization, mechanical ventilation, dexmedetomedine, propofol, melatonin.

Due to the substantial number of, and synonyms for, benzodiazepines and antipsychotic medicines, a selection of terms was used for each. MeSH entry terms were used with a selection of brand and International Nonpropiertary (generic) names (INN), as well as language variations (e.g. Spanish and Latin word endings). Chemical compositional name (e.g. 1H-1,2-benzodiazepine) was omitted for all but the highest class of drugs.

Due to the abundance of literature on physical rehabilitation and the publication of a recent review by O'Grady et al[1], PICO 3 was adapted to mirror the search terms used by O'Grady, and results limited to publication since 2022.

A methodological filter was applied to limit the retrieval to reports of randomized controlled trials (PICO 3) or observational studies (all other PICOs) excluding case series. Retrieval was limited to the human population where possible and to studies of adults only in ClinicalTrials.gov. The MEDLINE, Embase, and PsycInfo strategies were run simultaneously as a multi-file search in Ovid and the results de-duplicated using the Ovid de-duplication tool. Any additional duplicates were identified and removed in EndNote and Covidence."

Concept #1: ICU

exp *Critical Care/ use medall
*Critical Care Nursing/ use medall
exp *Critical Illness/ use medall
exp *Intensive Care Units/ use medall

O'Grady, Heather K; Reid, Julie C; Farley, Christopher; et al. Comparator Groups in ICU-Based Studies of Physical Rehabilitation: A Scoping Review of 125 Studies. Critical Care Explorations 5(5):p e0917, May 2023. | DOI: 10.1097/CCE.0000000000000917

exp *Intensive Care/ use oemezd
exp *Intensive Care Unit/ use oemezd
exp Intensive Care/ use psyh
((acute* OR intensive* OR critical* OR neurointensive* OR neuro-intensive* OR neurocritical* OR neuro-critical*) ADJ (care OR therap* OR treatment* OR unit? OR healthcare facilit* OR health-care facilit*)).ti,kf,kw.
(ICU OR MICU OR CICU OR CVICU OR CCU OR SICU OR POCCU OR ITU OR HDU OR ICUs OR MICUs OR CICUs OR CVICUs OR CCUs OR SICUs OR POCCUs OR ITUs OR HDUs).ti.
((ICU OR MICU OR CICU OR CVICU OR CCU OR SICU OR POCCU OR ITU OR HDU OR ICUs OR MICUs OR CICUs OR CVICUs OR CCUs OR SICUs OR POCCUs OR ITUs OR HDUs) AND ((acute* OR intensive* OR critical* OR neurointensive* OR neuro-intensive* OR neurocritical* OR neuro-critical*) ADJ (care OR therap* OR treatment* OR unit?))).tw,kf,kw.
(intensive care unit? OR intensive therapy unit? OR burn unit? OR coronary care unit? OR high dependency unit? OR recovery room? OR respiratory care unit? OR "acute hospital setting" OR "acute hospital settings").tw,kf,kw.

Concept #2: Anxiety

exp Anxiety/
exp Anxiety Disorders/ or exp Anxiety Disorder/
Adjustment Disorders/ or Adjustment Disorder/
Mutism/
(anxiet* or anxious* or panic* or phobi* or agoraphobi* or GAD or mute or mutism or nervous* or restless* or stress* or PTSD or obsessive compulsive or obsessive-compulsive or OCD or adjustment disorder* or neurotic or neuroses).tw,kf,kw.

Concept #3: Benzodiazepines

exp Benzodiazepines/ or Exp Benzodiazepine derivative/ use oemezd OR (Benzodiazepine or "1,2-Benzodiazepine" or 12794-10-4 or "1H-1,2-benzodiazepine" or 264-60-8 or "benzo diazepine" or benzodiazapine or benzodiazepin or benzodiazepines or CHEMBL4297264 or DB12537 or DTXSID90155730 or EN300-26945992 or M0Q7802G2B or Q27283309 or SCHEMBL8137 or UNII-M0Q7802G2B).tw,kf,kw.
Afizagabar/ or (afizagabar OR s44819 OR S-44819).tw,kf,kw.
Alprazolam/ or (Alprazolam or Alprazolan or Alprox or "Apo Alpraz" or Apo-Alpraz or Cassadan or D-65MT or D65MT or Esparon or Kalma or Novo Alprazol or Novo-Alprazol or "Nu Alpraz" or Nu-Alpraz or Ralozam or Tafil or Trankimazin or "U-31,889" or "U31,889" or Xanax).tw,kf,kw.
Amitriptyline plus chlordiazepoxide/ or ("amitriptyline plus chlordiazepoxide").tw,kf,kw.
Anthramycin/ or (Anthramycin OR Antramicina OR Antramycin OR Antramycine OR Antramycinum).tw,kf,kw.
Arfendazam/ or (Arfendazam OR Arfendazamum).tw,kf,kw.
Benzodiazepine/ or Benzodiazepine Compounds/ or Benzodiazepines/ or (Benzodiazepine OR benzo diazepine OR benzodiazapine OR benzodiazepin OR CHEMBL4297264 OR DB12537 OR DTXSID90155730 OR EN300-26945992 OR M0Q7802G2B OR Q27283309 OR SCHEMBL8137 OR UNII-M0Q7802G2B).tw,kf,kw.
exp Benzodiazepinones/ or (Benzodiazepinones or Anxyrex or "Apo Bromazepam" or Apo-Bromazepam or Bromazepam or BromaLich or "Bromaz 1A Pharma" or Bromazanil or "bromazep von ct").tw,kf,kw.
Bromazepam/ or (Bromazepam or Bromazepam-neuraxpharm or Bromazepam-ratiopharm or durazanil or Gen-Bromazepam or Lexatin or Lexomil or Lexotan or Lexotanil or "Ro 5-3350" or "Ro 53350" or "Von Ct, Bromazep").tw,kf,kw.
Camazepam/ or (Camazepam OR Albego OR "B 5333" OR Camazepamum OR Limpidon OR Nebolan OR Panevril OR Paxor OR "SB 5833" OR "S-58-33").tw,kf,kw.
Carburazepam/ or Uxepam/ or (Carburazepam OR Carburazepamum OR "Rgh 3331" OR "RGH 3331" OR RGH-3331 OR Uxepam).tw,kf,kw.
Ceclazepide/ or (Ceclazepide).tw,kf,kw.

Chlordiazepoxide/ or (Chlordiazepoxide or Chlozepid or Elenium or Librium or Methaminodiazepoxide).tw,kf,kw.
Cinolazepam/ or (Cinolazepam OR Cinolazepamum OR Gerodorm OR OX 373 OR OX-373).tw,kf,kw.
Clobazam/ or (Clobazam or Frisium or "HR 376" or "LM 2717" or LM-2717 or LM2717 or Onfi or Urbanyl).tw,kf,kw.
Clonazepam/ or (Clonazepam or "2H-1,4-Benzodiazepin-2-one, 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-" or Antelepsin or Clonazepam or Klonopin or Rivotril or "Ro 5-4023" or "Ro 54023").tw,kf,kw.
Clorazepate/ or Clorazepate Dipotassium/ or Clorazepate potassium/ or (4306-CB OR Clorazepate or Chlorazepate OR Clorazepic Acid OR Tranxene OR Tranxilium).tw,kf,kw.
Dealkylflurazepam/ or (Dealkylflurazepam OR DIDEETHYLFLURAZEPAM OR DIDESETHYLFLURAZEPAM).tw,kf,kw.
Delorazepam/ or (Delorazepam OR Chlordemethyldiazepam OR Clordesmetildiazepam OR Dadumir OR Delorazepamum OR O-CHLORODESMETHYLDIAZEPAM).tw,kf,kw.
Demoxepam/ or (Demoxepam OR Demossepam OR Demoxepamum OR "Ro 52092" OR "Ro 5-2092" OR RO5-2092 OR Ro-52092 OR RO-5-2092).tw,kf,kw.
Devazepide/ or (devazepide or je6p7qy7nh or "l 364,718" or "mk 329").tw,kf,kw.
Exp Diazepam/ or (Diazepam or "7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one" or Apaurin or Diazemuls or Faustan or Relanium or Seduxen or Sibazon or Stesolid or Valium).tw,kf,kw.
Doxefazepam/ or (Doxefazepam OR "Sas 643" OR SAS-643).tw,kf,kw.
Estazolam/ or (Estazolam or D-40TA or D40TA or Estazolam or Nuctalon or ProSom or Tasedan).tw,kf,kw.
Ethyl loflazepate/ or (Ethyl loflazepate OR CM 6912 OR CM-6912 OR "Ethyl fluclozepate" OR "ethyl loflazepate" OR "Ethylis loflazepas" OR "Loflazepate d'ethyle" OR "Loflazepato de etilo" OR Victan).tw,kf,kw.
Fludiazepam/ or (fludiazepam OR Erispan OR Fludiazepamum OR "ID 540 OR ID-540").tw,kf,kw.
Flumazenil/ or (Flumazenil or Anexate or Flumazepil or Lanexat or "Ro 15 1788" or "Ro 15-1788" or "Ro 151788" or Romazicon).tw,kf,kw.
Flunitrazepam/ or (Flunitrazepam or "Fluni 1A Pharma" or Flunibeta or Flunimerck or Fluninoc or Flunitrazepam-neuraxpharm or Flunitrazepam-ratiopharm or Flunitrazepam-Teva or flunizep or Fluridrazepam or Narcozep or RO-5-4200 or RO54200 or Rohipnol or Rohypnol).tw,kf,kw.
Flurazepam/ or (Flurazepam or Apo-Flurazepam or Dalmadorm or Dalmane or Dormodor or Staurodorm).tw,kf,kw.
Flutoprazepam/ or (Flutoprazepam OR Flutoprazepamum OR KB-509 OR Restar OR Restas).tw,kf,kw.
Fosazepam/ or (Fosazepam OR Fosazepamum).tw,kf,kw.
Gidazepam/ or (Gidazepam).tw,kf,kw.
Girisopam/ or (Girisopam OR "EGIS 5810" OR EGIS-5810 OR Girisopamum OR GYKI 51189 OR GYKI-51189).tw,kf,kw.
Halazepam/ or (Halazepam OR Halazepamum OR Halezepam OR Pacinone OR Paxipam OR "Sch 12041" OR Sch-12041).tw,kf,kw.
Loflazepate/ or (loflazepate OR CM-6913 OR "CM 6913" OR Loflazepic acid).tw,kf,kw.
Loprazolam/ or (loprazolam OR "HR 158" OR "HR 458" OR Loprazolamum OR "RU 31158" OR "RU-31158" OR Triazulenone).tw,kf,kw.
Lorazepam/ or (Lorazepam or Apo-Lorazepam or Ativan or Donix or Duralozam or Durazolam or Idalprem or Laubeel or lorazep or Lorazepam or Lorazepam-neuraxpharm or Lorazepam-ratiopharm or Novo-Lorazem or "Nu Loraz" or Nu-Loraz or "Orfidal Wyeth" or Sedicepan or Sinestron or Somagerol or Temesta or "WY 4036" or WY-4036 or WY4036 or "Wyeth, Orfidal").tw,kf,kw.
Lormetazepam/ or (Lormetazepam OR Dormagen OR Ergocalm OR Loramet OR Loretam OR Lormetazepamum OR Methyllorazepam OR N-Methyllorazepam OR Noctamid OR Noctamide).tw,kf,kw.
Lotrafiban/ or (Lotrafiban OR R-Lotrafiban OR SB 214857 OR SB-214134 OR SB-214857 OR SB-214857A).tw,kf,kw.
Meclonazepam/ or (Meclonazepam OR "Meclonazepam, (S)-isomer" OR Meclonazepamum OR "Ro 113128" OR "Ro 11-3128" OR "Ro 11-3128/002" OR Ro-113128 OR Ro-11-3128).tw,kf,kw.
Medazepam/ or (medazepam OR Nivelton OR Nobraksin OR Nobral OR Nobrium OR Resmit OR Rudotel).tw,kf,kw.
Metaclazepam/ or (Metaclazepam OR "Ka 2547" OR Ka2547 OR KA-2547 OR "KC 2547" OR KC-2547 OR Metaclazepamum OR Metaclazepan OR Metuclazepam OR Talis).tw,kf,kw.

Midazolam/ or (Midazolam or Dormicum or "Ro 21 3981" or Ro 21-3981 or "Ro 213981" or Versed).tw,kf,kw.
n nitrosochlordiazepoxide/ or (Nitrosochlordizepoxide OR 2-N-nitrosochlordiazepoxide OR N-Nitrosochlordiazepoxide OR N-Nitrosochlorodiazepoxide).tw,kf,kw.
Nastorazepide/ or (Nastrorazepide OR "Z 360" OR Z360 OR Z-360).tw,kf,kw.
Nerisopam/ or (Nerisopam OR "Gyki 52322" OR GYKI-52322).tw,kf,kw.
Nimetazepam/ or (Nimetazepam OR Dormalon OR Hypnon OR Methylnitrazepam OR Nimetazepamum OR "S 1530" OR S-1530).tw,kf,kw.
Nitrazepam/ or (Nitrazepam or Alodorm or Dormalon or Dormo-Puren or Eatan or Imadorm or imeson or Mogadon or Nitrazadon or Nitrazep or Nitrodiazepam or Novanox or Radedorm or Remnos or Serenade or Somnite).tw,kf,kw.
Norchlordiazepoxide/ or (Norchlordiazepoxide OR Calsamin OR Calsmin OR "Dormicum (anticonvulsant)" OR Dormin-5 OR Dormo-Puren OR Dumolid OR Eatan OR Epibenzalin OR Epinelbon OR Eunoctin OR Eunoktin OR Gerson OR Hipnax OR Hipsal OR Ibrovek OR Imeson OR Imesont OR Ipersed OR Magadon OR Megadon OR Mitidin OR Mogadan OR Mogadon OR Mogadone OR N-Desmethylnimetazepam OR Nelbon OR Nelmat OR Neozepam OR Neuchlonic OR Nitrados OR Nitravet OR Nitrazepamum OR Nitrempax OR Nitrenpax OR Noctesed OR Pacisyn OR Paxisyn OR Pelson OR Persopit OR Radedorm OR Relact OR Remnos OR Somitran OR Somnased OR Somnibel OR Somnite OR Sonebon OR Sonnolin OR Trazenin OR Unisomnia).tw,kf,kw.
Norclobazam/ or (Norclobazam OR "CLOBAZAM IMPURITY A" OR "CLOBAZAM METABOLITE M9" OR "Clobazam-M nor" OR Clofazin OR Demethylclobazam OR N-Demethylclobazam OR N-Desmethyl Clobazam-d5 OR NOR-CLOBAZAM).tw,kf,kw.
Nordazepam/ or (Nordezepam or Calmday or Dealkylprazepam or Demethyldiazepam or Deoxydemoxepam or Desmethyldiazepam or Desalkylhalazepam or "Descyclopropylmethyl Prazepam" or Descyclopropylmethylprazepam or Destrifluoroethylhalazepam or N-Desalkylhalazepam or N-Descyclopropylmethyl-Prazepam or N-Descyclopropylmethylprazepam or N-Destrifluoroethylhalazepam or Nordaz or Nordazepam or Nordiazepam or Norprazepam or "Ro 5 2180" or "Ro 5-2180" or "Ro 52180" or Tranxilium or Vegesan).tw,kf,kw.
Norfludiazepam/ or (Norfludiazepam OR "CM 7116" OR CM-7116 OR Descarbethoxyloflazepate OR "MIDAZOLAM IMPURITY F" OR norflurazepam OR nor-Flurazepam OR Norflutoprazepam OR "Ro 5-3367" OR "Ro-053367" OR "Ro-05-3367").tw,kf,kw.
Norflunitrazepam/ or (Norflunitrazepam OR Demethylflunitrazepam OR Desmethylflunitrazepam OR N-Desmethylflunitrazepam OR Nor-Flunitrazepam).tw,kf,kw.
Olanzapine/ or (Olanzapine or "2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno(2,3-b)(1,5)benzodiazepine" or "LY 170052" or "LY 170053" or LY-170052 or LY170052 or Zolafren or Zyprexa).tw,kf,kw.
Osugacestat/ or (Osugacestat OR "BMS 906024" OR BMS-906024).tw,kf,kw.
Oxazepam/ or (Oxazepam OR Abboxapam OR Adumbran OR Alepam OR Ansioxacepam OR Anxiolit OR Aplakil OR Astress OR Azutranquil OR Drimuel OR Droxacepam OR Durazepam OR Lederpam OR Limbial OR Nesontil OR Noctazepam OR Nortemazepam OR Nozepam OR Ossazepam OR Oxanid OR Oxa-puren OR Oxazepamum OR Oxazipam OR Oxozepam OR Pacienx OR Praxiten OR Propax OR Psicopax OR Psiquiwas OR Quilibrex OR Sedigoa OR Serax OR Serenid OR Serenid-D OR Serepax OR Seresta OR Serpax OR Sigacalm OR Sobril OR Tacepam OR Tarchomin OR Tazepam OR Uskan OR Vaben OR Zaxopam).ti,kf,kw.
Pamozirine/ or (Pamozirine OR 1343476-98-1 OR NF6U5U2UEB OR SC-DR002 OR SCHEMBL18541706 OR UNII-NF6U5U2UEB).tw,kf,kw.
Phenazepam/ or (Phenazepam OR Fenazepam OR PHENZITAT).tw,kf,kw.
Pinazepam/ or (Pinazepam OR Domar OR Duna OR Pinazepamum OR Z-905).tw,kf,kw.
Pirenzepine/ or (Pirenzepine or Gastrotsepin or Gastrozepin or "L-S 519" or "LS 519" or "LS-519" or LS519 or "Piren basan" or Piren-basan or Pirenzepin or PPirenzepin-ratiopharm or Pyrenzepine or Ulcoprotect or Ulgescum).tw,kf,kw.
Prazepam/ or (Prazepam or Centrax or Demetrin or Lysanxia or Reapam).tw,kf,kw.
Quazepam/ or (Quazapam OR Doral OR Dormalin OR Oniria OR Prosedar OR Quazepamum OR Quazium OR Sch 16134 OR Sch-161 OR Sch-16134).tw,kf,kw.
Remimazolam/ OR (Remimazolam OR CNS 7056 OR CNS-7056 OR ONO 2745 OR ONO2745 OR ONO-2745).tw,kf,kw.

Talampanel/ or (Talampanel OR GYKI 53773 OR GYKI 537773 OR GYKI-53773 OR Kinampa OR LY 300164 OR LY300164 OR LY-300164 OR "talampanel(ly300164)").tw,kf,kw.
Talirine/ or (Talirine OR 1Y234W15BL OR UNII-1Y234W15BL).tw,kf,kw.
Tampramine/ or (Tampramine OR UNII-47GSE5RM8N).tw,kf,kw.
Tarazepide/ or (Tarazepide OR UNII-RK2972YZ2U).tw,kf,kw.
Temazepam/ or (Temazepam or "3 Hydroxydiazepam" or 3-Hydroxydiazepam or Dasuen or Euhypnos or Hydroxydiazepam or Levanxol or Methyloxazepam or Nocturne or "Norkotral Tema" or Normison or Normitab or Nortem or Oxydiazepam or Planum or "Pronervon T" or Remestan or Restoril or "Ro 5 5345" or Ro-5-5345 or Ro55345 or "SaH 47 603" or "SaH 47-603" or "SaH 47603" or Signopam or "Tema, Norkotral" or Temaze or "temazep von ct" or Temtabs or "Tenox or Von Ct, Temazep" or "WY 3917" or WY-3917 or WY3917).tw,kf,kw.
Tibezonium iodide/ or (Tibezonium iodide OR "Iodure de tibezonium" OR "Ioduro de tibezonio" OR Maxoral OR "REC-15/0691" OR Thiabenzazonium OR Tibenzonio ioduro OR Tibenzonium iodide OR Tibezonii iodidum OR "Tibezonium (iodide)").tw,kf,kw.
Tifluadom/ or (Tifluadom OR "KC 5103" OR KC-5103 OR "KC 5911" OR "KC 6128" OR KC-5911 OR KC-6128 OR KC5103 OR "Tifluadom/KC-5103" OR titfluadom OR UNII-TF8X866L0I).tw,kf,kw.
Tofisopam/ or (tofisopam OR dextofisopam OR EGYT-341 OR Emandaxin OR Grandaxin OR levotofisopam OR Tofisopamum OR tofizopam).tw,kf,kw.
Tomaymycin/ or (Tomaymycin).tw,kf,kw.
Tuclazepam/ or (Tuclazepam OR Tuclazepamum OR UNII-343211YULR).tw,kf,kw.

Concept #4: Delirium

exp Delirium/ use medall or exp *Delirium/ use oemezd or Delirium/ use psyh
Confusion/ use medall or exp *Confusion/ use oemezd or Mental Confusion/ use psyh
Hallucinations/ use medall or exp *Hallucination/ use oemezd or exp Hallucinations/ use psyh
(bewilderment OR confusion* OR deliria* OR delirious* OR delirium* OR disorientation OR hallucinat*).tw,kf,kw,id.

Concept #5: Antipsychotics

exp Antipsychotic Agents/ use medall
exp Neuroleptic Agent/ use oemezd
exp Neuroleptic Drugs/ use psyh
(antipsychotic* or anti-psychotic* or ((neuroleptic or neuroleptics) ADJ (agent or agents or drug or drugs)) or ((butyrophenone or major or phenothiazine) ADJ (tranquilis* or tranquiliz*)) or neuroleptic*).tw,kf,kw,id.
("1,2,3,6 tetrahydro 4 phenyl 1 [(3 phenyl 3 cyclohexen 1 yl)methyl]pyridine" or "ci 1007" or ci1007 or "pd 143188" or pd143188 or "150013−70−0").tw,kf,kw.
("2 [4 [4 (7,9 dioxo 6 thia 8 azaspiro[4.4]nonan 8 yl)butyl] 1 piperazinyl] 3 pyridinecarbonitrile" or "2 [4 [4 (7,9 dioxo 6 thia 8 azaspiro[4.4]nonan 8 yl)butyl] 1 piperazinyl] 3 pyridinecarbonitrile hydrochloride" or "2 [4 [4 (7,9 dioxo 6 thia 8 azaspiro[4.4]nonan 8 yl)butyl] 1 piperazinyl]pyridine 3 carbonitrile" or "bmy 13980" or "bmy 13980 1" or bmy13980 or bmy139801 or "mj 13980 1" or "mj 13980−1" or "mj 139801" or "mj13980 1" or "mj13980−1" or mj139801 or "85581−65−3").tw,kf,kw.
("2 chloro 12 (3 dimethylamino 2 methylpropyl)dibenzo[d,g][1,3,6]dioxazocined" or "2 chloro 12 (2 methyl 3 dimethylaminopropyl) 12h dibenzo[d,g][1,3,6]dioxazocine monohydrochloride" or "2 chloro 12 (3 dimethylamino 2 methylpropyl)dibenzo[d,g][1,3,6]dioxazocine hydrochloride" or "egyt 2509" or egyt2509 or "70133−85−6").tw,kf,kw.
("2 chloro n [alpha (2 piperidinyl)benzyl] 3 trifluoromethylbenzamide" or "2 chloro n [phenyl(piperidin 2 yl)methyl] 3 trifluoromethylbenzamide" or "ssr 504734" or ssr504734).tw,kf,kw.
("2 cyclopropyl 5 [1 (2 fluoro 3 pyridinyl) 5 methyl 1h 1,2,3 triazol 4 yl] 2,3 dihydro 1h isoindol 1 one" or CFMTI or "864864−17−5").tw,kf,kw.
"2,3,3a,12b tetrahydro 3 methyl 1h dibenzo[b,f]oxepino[10,11 c]pyrrole".tw,kf,kw.
("3 [3 (methylsulfonyl)phenyl] 1 propylpiperidine" OR "3 (3 methylsulfonyl phenyl) 1 propyl piperidine" OR "3 (3 methylsulfonyl phenyl) 1 propyl piperidine hydrochloride" OR "3 [3 (methylsulfonyl)phenyl] 1

propylpiperidine hydrochloride" OR "osu 6162" OR osu6162 OR "pnu 0096391" OR "pnu 96391" OR "pnu 96391a" OR pnu0096391 OR pnu96391 OR pnu96391a OR "156907−84−5").tw,kf,kw.
"6 n (2,2 diphenylethyl)adenosine".tw,kf,kw.
"7 hydroxychlorpromazine".tw,kf,kw.
"8 ethyl 7,8 dihydro 1,3,5 trimethyl 1h imidazo[1,2 c]pyrazolo[3,4 e]pyrimidine".tw,kf,kw.
aceperone/ or (aceperone OR Aceperona OR Aceperonum OR Acetabuton OR ACETABUTONE).tw,kf,kw.
Acepromazine/ or acepromazine maleate/ or (acepromazine or acetazine or acetopromazine or acetylpromazine or calmivet or plegicil or vetranquil).tw,kf,kw.
aceprometazine/ OR (aceprometazine OR UNII-984N9YTM4Y).tw,kf,kw.
acetophenazine/ OR acetophenazine dimaleate/ OR (acetophenazine OR UNII-8620H6K4QH).tw,kf,kw.
adoprazine/ OR (adoprazine OR "SLV 313" OR SLV313 OR SLV-313 OR UNII-7SNB18Q89D).tw,kf,kw.
alimemazine/ OR alimemazine tartrate/ OR (alimemazine OR Isobutrazine OR Methylpromazine OR Nedeltran OR Panectyl OR Repeltin OR Repetin OR Spansule OR Temaril OR Teralen OR Teralene OR Theralen OR Theralene OR Trimeperazine OR trimeprazine OR Trimeprazine-d6 OR UNII-76H78MJJ52 OR Vallergan OR Vanectyl OR Variargil).tw,kf,kw.
"alpha (4 fluorophenyl) 4 (5 fluoro 2 pyrimidinyl) 1 piperazinebutanol"/ OR (UNII-A5NB5G07JO).tw,kf,kw.
"alpha [1 [2 (1,4 benzodioxan 5 yloxy)ethyl] 3 pyrrolidinyl] 4 fluoroacetophenone"/
amitriptyline plus perphenazine/ OR ("amitriptyline, perphenazine drug combination" OR "Anxipress D" OR Deprelio OR Elavil Plus OR Longopax OR Mutabon OR "Perphenazine and amitriptyline hydrochloride" OR "Perphenazine-amitriptyline combination" OR Pertriptyl OR "TRIAVIL 2-10" OR "TRIAVIL 2-25" OR "TRIAVIL 4-10" OR "TRIAVIL 4-25" OR "TRIAVIL 4-50" OR Triptafe).tw,kf,kw.
aplindore/ OR (aplindore OR UNII-Q5O76TA0ML).tw,kf,kw.
Amisulpride/ or (amisulpride or barnetil or "dan 2163" or "lin 1418" or solian or sultopride).tw,kf,kw.
Aripiprazole/ or (aripiprazole or "7-(4-(4-(2,3-dichlorophenyl)-1-piperazinyl)butyloxy)-3,4-dihydro-2(1H)-quinolinone" or Abilify or Aripiprazol or "OPC 14597" or OPC-14597).tw,kf,kw.
Azaperone/ or (Azaperone or R-1929 or R1929 or Stresnil).tw,kf,kw.
balipodect/ or (balipodect OR "TAK 063" OR TAK063 OR TAK-063 OR UNII-6650W303H0).tw,kf,kw.
benperidol/ or (Benperidol OR Anquil OR Benperidolo OR Benperidolum OR Benquil OR Benzeridol OR Benzoperidol OR Benzperidol OR Frenactil OR Frenactyl OR Glianimon).tw,kf,kw.
berupipam/ or (berupipam OR UNII-420895MAOC).tw,kf,kw.
bitopertin/ or (bitopertin OR "R 1678" OR R-1678 OR "RG 1678" OR RG1678 OR RG-1678 OR UNII-Q8L6AN59YY).tw,kf,kw.
blonanserin/ or (blonanserin OR "AD 5423" OR AD5423 OR AD-5423 OR Lonasen OR UNII-AQ316B4F8C).tw,kf,kw.
brofoxine/ or (brofoxine OR Brofossina OR Brofoxina OR Brofoxinum OR Dimethabrone).tw,kf,kw.
bromospiperone/ or (bromospiperone OR 4-Bromospiperone OR 4-Bromospiroperidol OR p-bromospiperone OR p-Bromospiroperidol).tw,kf,kw.
bromperidol/ or (bromperidol OR Azurene OR Bromoperidol OR Bromperidolum OR Impromen OR Tesoprel).tw,kf,kw.
Butaclamol/ or (butaclamol or "AY 23,028" or "AY-23,028" or "AY23,028").tw,kf,kw.
butaperazine/ or (butaperazine OR Butaperazina OR Butaperazinum OR Butyrylperazine OR Megalectil OR Randolectil OR Repoise OR Tyrylen).tw,kf,kw.
carfenazine/ or (carfenazine OR Carfenazina OR Carfenazinum OR Carphenazin OR Carphenazine OR Procethazine OR Proketazine).tw,kf,kw.
cariprazine/ or (cariprazine OR cis-Cariprazine OR Vraylar).tw,kf,kw.
carpipramine/ or (carpipramine or Carbadipimidine OR Carpipramina OR Carpipraminum OR Defekton OR Prazinil).tw,kf,kw.
carvotroline/ or (carvotroline).tw,kf,kw.
centbutindole/ or (centbutindole OR Biriperona OR Biriperone OR Biriperonum).tw,kf,kw.
chlorphenethazine/ or (chlorphenethazine OR Chlorfenethazine OR Chlorphenethazine OR Ethyl chlorpromazine OR Elroquil OR Marophen).tw,kf,kw.
chlorproethazine/ or (chlorproethazine OR Chlorproethazinum OR Clorproetazina OR Neuriplege).tw,kf,kw.
Chlorpromazine/ or (Chlorpromazine or Aminazine or Chlorazine or Chlordelazine or Contomin or Fenactil or Largactil or Propaphenin or Thorazine).tw,kf,kw.

Chlorprothixene/ or (Chlorprothixene or Chlorprotixen or Taractan).tw,kf,kw.
cinuperone/ OR (Cinuperone OR Cinuperonum).tw,kf,kw.
clocapramine/ OR (clocapramine OR Clocapramina OR Clocapraminum).tw,kf,kw.
cloflumide mesilate/ OR (cloflumide).tw,kf,kw.
clofluperol/ OR (clofluperol or Clofluperidol OR Clofluperolum).tw,kf,kw.
Clopenthixol/ or (Clopenthixol or alpha-Clopenthixol or Cisordinol or Clopenthixol or Zuclopenthixol).tw,kf,kw.
clopimozide/ OR (clopimozide OR Clopimozida OR Clopimozidum OR "R 29,764" OR "R 29764" OR R-29764).tw,kf,kw.
clopipazan/ OR (clopipazan).tw,kf,kw.
clospipramine/ OR (clospipramine OR Clospipramine OR Cremin OR Mosapramine dihydrochloride OR mosapramine hydrochloride).tw,kf,kw.
clotiapine/ OR (clotiapine OR Clothiapine OR Clotiapina OR Clotiapinum OR Entumin OR Entumine OR Etumine).tw,kf,kw.
Clozapine/ or (Clozapine OR Clorazil OR Clozapin OR Clozapina OR Clozapinum OR CLOZARIL OR Leponex OR Lepotex).tw,kf,kw.
cyamemazine/ OR (cyamemazine OR Ciamatil OR Ciamemazina OR Cianatil OR Cyamemazin OR Cyamemazinum OR Cyamepromazine OR Kyamepromazin OR Kyamepromazine OR Tercian).tw,kf,kw.
dimetotiazine/ OR (dimetotiazine OR Banistyl OR Dimethiotazine OR Dimethodin OR Dimethothiazine OR Dimetiotazine OR Dimetothiazine OR Dimetotiazin OR Dimetotiazina OR Dimetotiazinum OR Migristene OR Promaquid).tw,kf,kw.
dixyrazine/ OR (dixyrazine OR Dixyrizine OR Esocalm OR Esucos OR Metronal OR Roscal).tw,kf,kw.
dolasetron mesilate/ OR (dolasetron mesilate OR Anemet OR Anzemet OR Dalasetron Mesylate Hydrate OR Dolasetron mesilate OR Dolasetron methanesulfonate OR Dolasetronmesylate).tw,kf,kw.
Droperidol/ or (Dehidrobenzperidol or Dehydrobenzperidol or Droleptan or Droperidol or Inapsine).tw,kf,kw.
duoperone/ OR (duoperone OR Duoperona OR Duoperonum).tw,kf,kw.
Etazolate/ or (Etazolate or "SQ 20009" or SQ-20009 or SQ20009).tw,kf,kw.
etymemazine/ OR (etymemazine OR Ethotrimeprazine OR Ethyl isobutrazine OR Ethylisobutrazine).tw,kf,kw.
evenamide/ OR (evenamide OR Evenamid).tw,kf,kw.
farampator/ OR (farampator OR "CX 691" OR CX691 OR CX-691 OR Org 24448 OR Org24448 OR Org-24448).tw,kf,kw.
fluanisone/ OR (fluanisone OR Fluanison OR Fluanisona OR Fluanisonum OR Haloanisone).tw,kf,kw.
Flupenthixol/ or (alpha-Flupenthixol or cis-Flupenthixol or Emergil or Fluanxol or Flupentixol).tw,kf,kw.
flupentixol decanoate/ OR (flupentixol decanoate or Depixol).tw,kf,kw.
Fluphenazine/ or (Flufenazin or Fluphenazine or Lyogen or Prolixin).tw,kf,kw.
fluphenazine decanoate/ OR (fluphenazine decanoate OR Flufenazine decanoate OR Fluorophenazine decanoate OR Fluphenaline decanoate OR Fluphenazine depot OR FLUPHENAZINE ENANTHATE IMPURITY C OR Fluphenazine O-decanoate OR Fluphenazinedecanoate OR fluphenazine-decanoate OR Fluphenazini decanoas OR liogen OR Lyogen OR Mirenil OR Modecate OR Moditen depot OR Moditen-depo OR Prolixin decanoate).tw,kf,kw.
fluphenazine enanthate/ OR (Fluphenazine Enanthate OR Enanthic acid fluphenazine OR Eutimox OR Flufenan OR Moditen enanthate OR Moditen-retard OR Prolixin Enanthate).tw,kf,kw.
Fluspirilene/ or (Fluspirilene or Fluspirilen or Fluspi or Imap or kivat or Redeptin or Spirodiflamine).tw,kf,kw.
flutroline/ OR (Flutroline OR Flutrolino OR Flutrolinum OR Fluspi OR fluspirilen OR Fluspirilene or Imap OR Kivat OR Redeptin OR Spirodiflamine).tw,kf,kw.
gevetroline/ OR (gevetroline).tw,kf,kw.
Haloperidol/ or haloperidol decanoate/ OR (haloperidol OR Aloperidin OR Aloperidol OR Aloperidon OR Aloperidolo OR Bioperidolo OR Brotopon OR Dozic OR Duraperidol OR Einalon OR Eukystol OR Fortunan OR Galoperiodol OR Halidol OR Haldol OR Halojust OR Halol OR Halomonth OR Halopal OR Haloperidolum OR Halopidol OR Halopoidol OR Halosten OR Keselan OR Linton OR Mixidol OR Neurodol OR Pekuces OR Peluces OR Pernox OR Sernas OR Serenace OR Serenase OR Sigaperidol OR Ulcolind OR Uliolind).tw,kf,kw.
iclepertin/ OR (Iclepertin OR "BI 425809" OR BI425809 OR BI-425809).tw,kf,kw.

isofloxythepin/ OR (isofloxythepin).tw,kf,kw.
isomolpan/ OR (isomolpan).tw,kf,kw.
Lamotrigine/ or (lamotrigine or "BW 430C" or BW-430C or BW430C or Crisomet or Labileno or Lamictal or Lamiktal).tw,kf,kw.
landipirdine/ OR (landipirdine).tw,kf,kw.
lenperone/ OR (lenperone OR AHR 2277 OR AHR2277 OR AHR-2277 OR Lenperona OR Lenperonum).tw,kf,kw.
Loxapine/ or (loxapine or "CL 71,563" or "CL-71,563" or "CL71,563" or Cloxazepine or Loxapinsuccinate or loxapine succinate OR Oxilapine).tw,kf,kw.
Lurasidone Hydrochloride/ or (Lurasidone or latuda).tw,kf,kw.
luvadaxistat/ OR (luvadexistat).tw,kf,kw.
mardepodect/ OR (mardepodect).tw,kf,kw.
maroxepine/ OR (Maroxepine OR Maroxepin OR Maroxepina OR Maroxepinum).tw,kf,kw.
mazapertine/ OR (mazapertine).tw,kf,kw.
mepiprazole/ OR (mepiprazole OR Mepiprazol OR Mepiprazolum OR Quiadon).tw,kf,kw.
mesoridazine besylate/ OR (Mesoridazine besylate OR Lidanar OR Lidanil OR Mesoridazine benzenesulfonate OR mesoridazine monobenzenesulfonate OR Serentil).tw,kf,kw.
Methiothepin/ or (Methiothepin or Methiothepine or Metitepine).tw,kf,kw.
methopromazine/ OR (Methopromazine OR Methopromazinum OR Methoxypromazine OR Metopromazina OR Mopazin OR Mopazine OR Neoproma).tw,kf,kw.
Methotrimeprazine/ or (Methotrimeprazine or Levomeprazin or Levomepromazine or Levopromazine or Tisercin or Tizercine or Tizertsin).tw,kf,kw.
metofenazate/ OR (metofenazate OR Frenolone OR Methophenazine OR Metofenazato OR Metofenazatum OR metophenazate OR Phrenolon).tw,kf,kw.
Molindone/ or (Molindone or Moban).tw,kf,kw.
moperone/ OR (Moperone OR Luvatren OR Luvatrena OR Meperon OR Methylperidol OR Moperona OR Moperonum OR Mopiperone).tw,kf,kw.
neboglamine/ OR (neboglamine OR CR 2249 OR Cr2249 OR CR-2249).tw,kf,kw.
noctran/ OR (Noctran OR 78355-48-3 OR "FA 522 A").tw,kf,kw.
norchlorpromazine/ OR (Norchlorpromazine OR Demethylchlorpromazine OR Demonomethylchlorpromazine OR Desmethylchloropromazine OR Desmethylchlorpromazine OR MONODESMETHYLCHLORPROMAZINE OR N-Desmethylchlorpromazine OR N-Monodesmethylchlorpromazine OR NOR1CHLORPROMAZINE OR NOR1-CHLORPROMAZINE).tw,kf,kw.
Olanzapine/ or (Olanzapine or "LY 170052" or "LY 170053" or LY-170052 or LY170052 or Zolafren or Zyprexa).tw,kf,kw.
oxiperomide/ OR (oxiperomide OR Oxiperomida OR Oxiperomidum OR Oxyperomide OR Peromide).tw,kf,kw.
oxypertine/ OR (oxypertine OR Equipertine OR Forit OR Opertil OR Oxipertina OR Oxipertine OR Oxipertinum OR Oxypertin OR Oxypertinum).tw,kf,kw.
oxyprothepine/ OR oxyprothepine decanoate/ OR (oxyprothepine).tw,kf,kw.
Paliperidone Palmitate/ or (paliperidone or "9 Hydroxy risperidone" or "9 Hydroxyrisperidone" or "9 OH risperidone" or 9-hydroxy-risperidone or 9-hydroxyrisperidone or 9-OH-risperidone or Invega).tw,kf,kw.
pecazine/ OR (pecazine OR Lacumin OR mepasin OR Mepazin OR MEPAZINE OR Meprazine OR Mesapin OR Pacatal OR Pacatol OR Pakatal OR Paxital OR Pecatal OR Pecazina OR Pecazinum).tw,kf,kw.
Penfluridol/ or (Penfluridol OR Penfluridolum OR Semap).tw,kf,kw.
perazine/ OR (perazine OR Perazin OR Pernazine OR Taxilan).tw,kf,kw.
periciazine/ OR (Periciazine OR Aolept OR Nelactil OR Nemactil OR Neulactil OR Neuleptil OR Periciazin OR Periciazina OR Periciazinum OR PERICYAZINE).tw,kf,kw.
perimetazine/ OR (Perimetazine OR leptryl OR Perimetazin OR Perimetazina OR Perimetazinum OR Perimethazine).tw,kf,kw.
Perphenazine/ or perphenazine decanoate/ OR (Perphenazine or Chlorperphenazine OR Chlorpiprazine OR Emesinal OR Etaperazin OR Etaperazine OR Ethaperazine OR Etrafon OR Perfenazina OR Perfenil OR Perphenan OR Perphenazin OR Perphenazinum OR Thilatazin OR Tranquisan OR Trifaron OR Trilafon OR Trilifan OR Triphenot).tw,kf,kw.

pf 217830/ OR (PF-00217830 OR PF-217830).tw,kf,kw.
pf 3463275/ OR (PF 03463275 OR PF-0346275 OR PF-03463275 OR PF-3463275).tw,kf,kw.
picobenzide/ OR (Picobenzide OR Picobenzida OR Picobenzidum).tw,kf,kw.
piflutixol/ OR (piflutixol OR Piflutixolum OR "trans piflutixol-(E)" OR trans-Piflutixol).tw,kf,kw.
pimavanserin/ OR (pimavanserin OR Nuplazid).tw,kf,kw.
pimethixene/ OR (Pimethixene OR Calmixen OR Calmixene OR Mepithiathene OR Pimethixen OR Pimethixenum OR PIMETIXENE OR Pimetixeno).tw,kf,kw.
Pimozide/ or (Pimozide OR Antalon OR Opiran OR Orap OR "R 623" OR "R 6238" OR R-623 OR R6238 OR R-6238).tw,kf,kw.
pipamperone/ OR (pipamperone OR Dipiperal OR Dipiperon OR Dipiperone OR Floropipamide OR Fluoropipamide OR Pipamperon OR Pipamperona OR Pipamperonum OR Pipaneperone OR Piperonil OR Piperonyl OR Propitan OR "R 3345" OR R-3345).tw,kf,kw.
piperacetazine/ OR (piperacetazine OR Piperacetazina OR Piperacetazinum OR Piperazetazina OR Psymod OR Quide).tw,kf,kw.
pipotiazine/ OR (pipotiazine OR Lonseren OR Piportil OR Pipothiazine OR Pipotiazina OR Pipotiazinum OR RP 19366 OR RP-19366).tw,kf,kw.
pipotiazine palmitate/ OR (Pipotiazine palmitate OR Piportil depot OR Pipothiazin palmitate OR Pipothiazine palmitate OR Pipotiazin Retard OR Pipotiazine Palmitic Ester OR pipotiazine-palmitate).tw,kf,kw.
pirenperone/ OR (pirenperone OR Pirenperona OR Pirenperonum OR R 47465 OR "R-47,465" OR R-47465).tw,kf,kw.
pomaglumetad methionil/ OR (pomaglumetad methionil OR LY 2140023 OR LY2140023 OR LY-2140023).tw,kf,kw.
Prochlorperazine/ or prochlorperazine edisylate/ OR prochlorperazine maleate/ OR (Prochlorperazine or CHLOPERAZINE OR Chlormeprazine OR Chloropernazine OR Chlorperazine OR Proazine OR Prochloroperazine OR Prochlorpemazine OR Prochlorperazin OR Prochlorperazinum OR Prochlorpermazine OR Procloperazine OR Proclorperazina OR Proclorperazine OR Tementil OR Temetid OR Vertigon).tw,kf,kw.
profenamine/ OR (profenamine OR Ethapropazine OR Ethopromazine OR ethopropazine OR Etopropezina OR Fempropazine OR Fenpropazina OR Isopthazine OR Isotazin OR Isothazine OR Isothiazine OR Lysivane OR Pardisol OR Parfezine OR Parkin OR Parphezein OR Parsidol OR Parsitan OR Parsotil OR Phenopropazine OR Phenoprozine).tw,kf,kw.
Promazine/ or (Promazine or Prazin OR Prazine OR Promazin OR Promazina OR Promazinum OR Promwill OR Propazinum OR Protactyl OR Sinophenin OR Sparine).tw,kf,kw.
propiomazine/ OR propiomazine maleate/ OR (propiomazine OR Largon OR Phenoctyl OR Propavan OR Propiomazina OR Propiomazinum OR Propionylpromethazine).tw,kf,kw.
propionylpromazine/ OR (propionylpromazine OR Combilen OR Propionpromazine OR Propionylpromazone OR Propiopromazine).tw,kf,kw.
prothipendyl/ OR (prothipendyl OR Dominal OR Largophren OR Phrenotropin OR Prothipendylum OR Protipendilo OR Timoval OR Timovan OR Tolnate OR Tumovan).tw,kf,kw.
Quetiapine Fumarate/ or (quetiapine or Seroquel).tw,kf,kw.
Raclopride/ or raclopride tartrate/ or (Raclopride or "FLA 870" or FLA-870 or FLA870 or "FLB 472" or FLB-472 or FLB472).tw,kf,kw.
ralmitaront/ OR (ralmitaront).tw,kf,kw.
Remoxipride/ or (Remoxipride).tw,kf,kw.
Reserpine/ or (Reserpine or Raunervil or Raupasil or Rausedil or Rausedyl or Serpasil or Serpivite or "V Serp" or V-Serp).tw,kf,kw.
rimcazole/ OR (rimcazole OR BW 234U OR BW-234U OR Rimcazol OR Rimcazolum).tw,kf,kw.
Risperidone/ or (Risperidone or Risperdal or "R 64,766" or "R 64766" or "R-64,766" or R-64766 or "R64,766" or R64766 or Risperidone).tw,kf,kw.
Ritanserin/ or (Ritanserin or "6-(2-(4-(Bis(4-fluorophenyl)methylene)-1-piperidinyl)ethyl)-7-methyl-5H-thiazolo(3,2-a)pyrimidin-5-one" or "R 55667" or R-55667 or R55667).tw,kf,kw.
roluperidone/ OR (roluperidone OR MIN-101 OR Roluperidon).tw,kf,kw.
romergoline/ OR (Romergoline).tw,kf,kw.
savoxepine/ OR (savoxepine OR Cipazoxapine OR Savoxepin OR Savoxepina OR Savoxepinum).tw,kf,kw.

sb 773812/ OR ("sb 773812").tw,kf,kw.
seridopidine/ OR (seridopidine).tw,kf,kw.
setoperone/ OR (setoperone OR SEPTOPERONE OR Setoperona OR Setoperonum).tw,kf,kw.
Spiperone/ or (Spiperone OR Espiperona OR Spiperonum OR Spiroperidol OR Spiroperidone OR Spiropitan).tw,kf,kw.
sulforidazine/ OR (sulforidazine OR Psychoson OR Solforidazina OR Sulforidazina OR Sulforidazinum OR Thioridazine 2-Sulfone Thioridazine sulfone OR Thioridazine sulphone OR Thioridazine-2-sulfone).tw,kf,kw.
suvecaltamide/ OR (suvecaltamide OR Suvecaltamide).tw,kf,kw.
Sulpiride/ or (Sulpiride or Aiglonyl or Arminol or Deponerton or Desisulpid or Digton or Dogmatil or Dolmatil or Eglonyl or Ekilid or Guastil or Lebopride or Meresa or neogama or Pontiride or Psicocen or Sulp or Sulperide or Sulpitil or Sulpivert or Sulpor or Synedil or Tepavil or "Vertigo Meresa" or "vertigo neogama" or Vertigo-Meresa or vertigo-neogama).tw,kf,kw.
Tefludazine/ OR (tefludazine OR Tefludazina OR Tefludazinum).tw,kf,kw.
Tetrabenazine/ OR deutetrabenazine/ OR (tetrabenazine OR Nitoman OR tetra Benazin OR Tetrabenazin OR Tetrabenazina OR Tetrabenazinum OR Tetrabenzaine OR Tetrabenzine OR Xenazine).tw,kf,kw.
Thiopropazate/ OR (thiopropazate OR Dartal OR Dartalan OR Perphenazine acetate OR Thiopropazat OR Thiopropazatum OR Tiopropazato).tw,kf,kw.
Thioproperazine/ OR (Thioproperazine OR Sulfenazin OR Thioperazine OR Thioproperazin OR Thioproperazinum OR Thiproperazine OR Tioproferazina OR Tioproperazin OR Tioproperazina OR Vontil).tw,kf,kw.
thioproperazine methanesulfonate/ OR (thioproperazine methanesulfonate OR Mageptyl OR Majeptil OR Thioperazine dimethanesulfonate OR Thioperazine mesylate OR Thioproperasine dimesylate OR Thioproperazine bis-methanesulfonate OR Thioproperazine dimesilate OR Thioproperazine dimesylate OR Thioproperazine dimethanesulfonate OR THIOPROPERAZINE DIMETHANESULPHONATE OR Thioproperazine mesilate OR Thioproperazine mesylate OR Thioproperazine methanesulfonate OR Thioproperazinum).tw,kf,kw.
Thioridazine/ or (Thioridazine or Aldazine or Apo-Thioridazine or ApoThioridazine or Meleril or Mellaril or Melleretten or Melleril or Melleryl or Melzine or Rideril or Sonapax or Thioridazine-neurazpharm or Thioridazineneurazpharm or Thiozine).tw,kf,kw.
Thiothixene/ or (Thiothixene OR cis-Thiothixene OR Navan OR Navane OR Navaron OR Orbinamon OR Tiotixene OR Tiotixeno OR Tiotixenum).tw,kf,kw.
Tiapride Hydrochloride/ or (Tiapride or Equilium or "FLO 1347" or FLO-1347 or FLO1347 or Tiapridal or Tiapridex or Tiaprizal).tw,kf,kw.
Tilapertin/ OR (Tilapertin).tw,kf,kw.
Timiperone/ OR (timiperone OR Timiperona OR Timiperonum OR Tolopelon).tw,kf,kw.
Trifluoperazine/ or (Trifluoperazine or Apo-Trifluoperazine or ApoTrifluoperazine or Eskazine or Flupazine or Stelazine or Terfluzine or Trifluoroperazine or Triftazin).tw,kf,kw.
Trifluperidol/ or (Trifluperidol or Trisedil).tw,kf,kw.
Triflupromazine/ or (Triflupromazine or Fluopromazine or Siquil or Triflupromazine).tw,kf,kw.
tulrampator/ OR (tulrampator).tw,kf,kw.
ulotaront/ OR (ulotaront).tw,kf,kw.
umespirone/ OR (umesprione).tw,kf,kw.
vabicaserin/ OR (vabicaserin).tw,kf,kw.
zetidoline/ OR (zetidoline OR Zetidolina OR Zetidolinum).tw,kf,kw.
zicronapine/ OR (zicronapine).tw,kf,kw.
zoloperone/ OR (zoloperone OR Zoloperona OR Zoloperonum).tw,kf,kw.

Concept #6: Mobilization

exp Early ambulation/
exp Exercise therapy/ or exp kinesiotherapy/
exp Movement or exp "movement(physiology)"/
exp Musculoskeletal Manipulations or exp *musculoskeletal manipulation/
exp Physical therapy modalities/ or exp physiotherapy/
Activities of daily living/ OR Daily life activity/

Rehabilitation/
Rehabilitation, vocational/ or vocational rehabilitation/
"Physical and rehabilitation medicine"/
Exercise/
Physical therapy modalities/
Range of motion, articular/
Recovery of function/
Muscle strength/
Exp Mobilization/ use oemezd
Joint mobilization/ use oemezd
Physical activity/ use oemezd
Physical Mobility/ use psyh

(Mobili* or physical therapy* or physiotherap* or physical function* or exercis* or activit* of daily living OR ADL or rehab* or range of motion or ROM or recovery of function OR muscle strength OR physical activit* OR recovery of function OR ambulate or ambulation or mobilise or mobilize or mobilisation or mobilization or mobility or movement).tw,kf,kw.

Concept #7: Mechanical Ventilation

exp Respiration, Artificial/ or exp artificial ventilation/
exp Ventilators, Mechanical/ or exp mechanical ventilator/
((artificial* or mechanical* or invasive* or high-frequency or positive-pressure or "positive pressure" or negative-pressure or "negative pressure") adj3 (respirat* or ventilat*)).tw,kf,kw.
(artificial airway? OR controlled ventilation).tw,kf,kw.

Concept #8: Dexmedetomidine

exp Dexmedetomidine/ or (Dexmedetomidine or "(+)-4-((S)-.ALPHA.,2,3-TRIMETHYLBENZYL)IMIDAZOLE" or "(+)-4-((S)-alpha,2,3-Trimethylbenzyl)imidazole" or "(S)-4-(1-(2,3-dimethylphenyl)ethyl)-1H-imidazole" or "(S)-4-[1-(2,3-Dimethylphenyl)ethyl]-1H-imidazole" or "(S)-5-(1-(2,3-Dimethylphenyl)ethyl)-1H-imidazole" or 108D583 or 113775-47-6 or "1H-Imidazole, 4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-" or "1H-Imidazole, 5-[(1S)-1-(2,3-dimethylphenyl)ethyl]-" or "4-[(1~{S})-1-(2,3-dimethylphenyl)ethyl]-1~{H}-imidazole" or "4-[(1S)-1-(2,3-Dimethylphenyl)ethyl]-1H-imidazol" or "4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole" or "4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-3H-imidazole" or "4-[(s)-1-(2,3-dimethyl-phenyl)-ethyl]-1h-imidazole" or "5-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole" or 67VB76HONO or AB01566872_01 or AB01566872_02 or AKOS025149503 or AKOS026750524 or AS-68685 or "bxcl 501" or bxcl501 BDBM50085683 or C07450 or CCG-266586 or "CHEBI:4466" or CHEMBL778 or CS-0012295 or cepedex or D00514 or DB00633 or "da 9051" or da9051 or delos or Dexdor or Dexmedetomidina or "DexmedetomidineHclC13H16N2.Hcl" or Dexmedetomidinum or dexdomitor or dexdor or DTXSID10873388 or EN300-127736 or GTPL521 or HMS3885M07 or HY-12719 or Igalmi or Medetomidine or MFCD00880557 or "MPV 1440" or MPV-1440 or NCGC00025347-01 or NCGC00371080-02 or NCGC00371080-09 or Precedex or primadex or Q412133 or s3075 or SCHEMBL26433 or sedadex or sileo or SW219607-1 or Tocris-2023 or "TPU 006" or tpu006 or UNII-67VB76HONO or ZINC4632106).tw,kf,kw.

Concept #9: Propofol

Propofol/ or ("2, 6-Diisopropylphenol" or "2,6 Diisopropylphenol" or "2,6-Bis(1-methylethyl)phenol" or "2,6-bis(Isopropyl)phenol" or "2,6-bis(propan-2-yl)phenol" or "2,6-di isopropyl phenol" or "2,6-di(propan-2-yl)phenol" or "2,6-Diisopropyl phenol" or "2,6-diisopropyl-phenol" or "2,6-Diisopropylphenol" or "2,6-Di-iso-propylphenol-d18" or "2,6-dipropan-2-ylphenol" or "BIDD:GT0436" or "CHEBI:44915" or "BRN 1866484" or "EINECS 218-206-6" or "ghl.PD_Mitscher_leg0.558" or "HSDB 7123" or "ICI 35,868" or "ICI 35868" or "ICI 35-868" or "ICI35,868" or "MLS-0318084.P017" or "NSC 5105" or "Pharmakon1600-01505022" or "Phenol, 2, 6-bis(1-methylethyl)-" or "Phenol, 2,6-bis(1-methylethyl)" or "Phenol, 2,6-bis(1-methylethyl)-"

or "Phenol, 2,6-diisopropyl-" or "Phenol,6-bis(1-methylethyl)-" or "Phenol,6-diisopropyl-" or "SDCCGMLS-0318084.P029" or "SDCCGSBI-0050422.P002" or 2078-54-8 or 3f33 or 3p50 or A814898 or AB00513968 or AB00513968_08 or AB00513968-07 or AC-2038 or AC8633 or AI3-26295 or AKOS009159417 or ALBB-036351 or AM90311 or Ampofol or Anepol or Anesia or Aquafo or Aquafol or AS-13299 or BCP02920 or BCP0726000298 or BDBM50058046 or Biomol-NT_000248 or BPBio1_000950 or BPBio1_000969 or BRD-K82255054-001-03-5 or BRD-K82255054-001-08-4 or BSPBio_000862 or C07523 or CAS-2078-54-8 or CCG-204529 or "CCRIS 9000" or CHEMBL526 or cryotol or CS-W020057 or D00549 or D0617 or D126608 or DB00818 or DDS-04F or diisoprofol or Diisopropylphenol or Dipravan or Diprifusor or Diprivan or Diprofol or Disoprivan or Disoprofol or DTXSID6023523 or EN300-52468 or EU-0100437 or Fresofol or gobbifol or GTPL5464 or hiremon or HMS1570L04 or HMS2089O21 or HMS2094E17 or HMS2097L04 or HMS2231E16 or HMS3259E03 or HMS3261G16 or HMS3369I16 or HMS3714L04 or HY-B0649 or "ici 35 868" or "ici 35868" or ICI-35868 or Ivofol or Lipuro or Lopac0_000437 or Lopac-D126608 or LP00437 or MFCD00008885 or MLS001066348 or MLS001335999 or MLS002454360 or MLS-0318084 or NC00449 or NCGC00015389-01 or NCGC00015389-02 or NCGC00015389-03 or NCGC00015389-04 or NCGC00015389-05 or NCGC00015389-06 or NCGC00015389-07 or NCGC00015389-08 or NCGC00015389-09 or NCGC00015389-10 or NCGC00015389-11 or NCGC00015389-14 or NCGC00015389-17 or NCGC00091538-01 or NCGC00091538-02 or NCGC00091538-03 or NCGC00091538-04 or NCGC00091538-05 or NCGC00091538-06 or NCGC00257228-01 or NCGC00260670-01 or NCGC00261122-01 or NSC5105 or NSC-5105 or NSC758909 or NSC-758909 or plofed or Pofol or Prestwick0_000931 or Prestwick1_000931 or Prestwick2_000931 or Prestwick3_000931 or profast or propocam or "propofol lipuro" or Propofol-Lipuro or Propofolum or propolipid or Propovan or Propoven or provive or rapinovet or Q-201631 or Q422740 or Rapinovet or rapiva or recofol or "recofol n" or ripol or safol or SCHEMBL36245 or SMR000059151 or SPBio_003031 or SPECTRUM1505022 or spifol or spival SR-01000075468 or SR-01000075468-1 or SR-01000075468-4 or SR-01000075468-6 or SY013479 or Tox21_110134 or Tox21_110134_1 or Tox21_201371 or Tox21_303225 or Tox21_500437 or unifol or UNII-YI7VU623SF or YI7VU623SF or ZD-0859 or ZINC968303).tw,kf,kw.

Concept #10: Melatonin

Melatonin/ or (melatonin or "5-methoxy n-acetyl-tryptamine" or "BRN 0205542" or "CCRIS 3472" or "EINECS 200-797-7" or "J5.258B" or "NSC 113928" or "3-N-Acetyl-5-methoxyl tryptamine" or "BIDD:ER0618" or "SDCCGMLS-0065812.P001" or "SDCCGMLS-0065812.P002" or "SDCCGSBI-0050765.P003" or 005M655 or 0E2B08C1-B325-45B1-8939-6F9081EFDFA4 or 5-22-12-00042 or 5-methoxy-N-acetyltryptamine or A929721 or AB00053279 or AB00053279_12 or AB00053279-10 or AC-10019 or Acetamide or ACT03490 or adaflex or AKOS000276269 or AMY33320 or "apl 510" or apl510 or aritonin or BA164660 or "bci 049" or bci049 or BCI-049 or BCP28154 or BDBM9019 or BPBio1_000590 or BRD-K97530723-001-07-6 or BRD-K97530723-001-11-8 or BSPBio_000536 or BSPBio_003006 or C01598 or CAS-73-31-4 or CCG-38837 or celton or ceyestaeusom or ceyesto CHEMBL45 or ChemDiv2_003916 or circadin or civasta or CS-1769 or D08170 or DB01065 or DivK1c_000353 or DTXSID1022421 or EN300-6486827 or EU-0100787 or eusom or F1929-1777 or FT-0628191 or FT-0658928 or FT-0670984 or GLXC-25215 or GTPL1357 or GTPL224 or Guna-dermo or HMS1380B22 or HMS1569K18 or HMS1921E04 or HMS2089F09 or HMS2096K18 or HMS2233D23 or HMS3262M16 or HMS3370J20 or HMS3413P14 or HMS3654A22 or HMS3677P14 or HMS3713K18 or HMS3884M05 or HMS501B15 or HSCI1_000400 or HSDB 7509 or HY-B0075 or IDI1_000353 or IDI1_002631 or "jan 13004" or jan13004 or jl5dk93rcl or KBio1_000353 or KBio2_000665 or KBio2_003233 or KBio2_005801 or KBio3_002226 or KBioGR_000591 or KBioSS_000665 or "ki 1001" or ki1001 or KS-1454 or L001261 or lestinora or Lopac0_000787 or Lopac-M-5250 or LP00787 or M 5250 or M1105 or M-1200 or M-1250 or Melapure or Melatobel or mallozen or mecastrin or melabiorytm or melatal or melatan or melatol or melatonina or melatonine or melatonite or mellaras or mellozzan or melovine or MFCD00005655 or MLS000859594 or MLS001055382 or MLS001240204 or mucomel or N-Acetyl-5-methoxytryptamine or N-acetyl-5-methoxy-tryptamine or NCGC00015680-01 or NCGC00015680-02 or NCGC00015680-03 or NCGC00015680-04 or NCGC00015680-05 or NCGC00015680-06 or NCGC00015680-07 or NCGC00015680-08 or NCGC00015680-09 or NCGC00015680-10 or NCGC00015680-11 or NCGC00015680-12 or NCGC00015680-13 or NCGC00015680-14 or NCGC00015680-15 or NCGC00015680-16 or NCGC00015680-18 or NCGC00015680-35 or NCGC00090727-01 or

NCGC00090727-02 or NCGC00090727-03 or NCGC00090727-04 or NCGC00090727-05 or NCGC00090727-06 or NCGC00090727-07 or NCGC00090727-08 or NCGC00090727-09 or NCGC00256404-01 or NCGC00259077-01 or NCGC00261472-01 or NCI60_004378 or NINDS_000353 or noxarem or NSC113928 or NSC-113928 or NSC56423 or NSC-56423 or oniria or Oprea1_104553 or Oprea1_814234 or orlogin or Posidorm or Prestwick_312 or Prestwick0_000458 or Prestwick1_000458 or Prestwick2_000458 or Prestwick3_000458 or Primex or Q180912 or regulin or S1204 or SCHEMBL19018 or sental or slenyto or sloremina or SMP2_000309 or SMR000326666 or "sp 13004" or sp13004 or SPBio_001527 or SPBio_002475 or Spectrum_000185 or SPECTRUM1500690 or Spectrum2_001344 or Spectrum3_001393 or Spectrum4_000066 or Spectrum5_001745 or SR-01000075559 or SR-01000075559-1 or SR-01000075559-6 or SR-01000075559-7 or SR-01000075559-8 or STK386880 or SW196607-4 or SY051401 or syncrodin or TNP00300 or Tox21_110195 or Tox21_110195_1 or Tox21_201527 or Tox21_302926 or Tox21_500787 or UNII-JL5DK93RCL or waferest or Z1191880499 or ZINC57060).tw,kf,kw.

Filter 1: RCTs – MEDLINE, Embase and PsycInfo

Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
Randomized Controlled Trial/
exp Randomized Controlled Trials as Topic/
"Randomized Controlled Trial (topic)"/
Controlled Clinical Trial/
exp Controlled Clinical Trials as Topic/
"Controlled Clinical Trial (topic)"/
Randomization/
Random Allocation/
Double-Blind Method/
Double Blind Procedure/
Double-Blind Studies/
Single-Blind Method/
Single Blind Procedure/
Single-Blind Studies/
Placebos/
Placebo/
Control Groups/
Control Group/
(random* or sham or placebo*).ti,ab,hw,kf,kw.
((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.
(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
allocated.ti,ab,hw.
((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.
((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.

Filter 2: Observational Studies (excluding case studies) – MEDLINE and Embase

epidemiologic methods/
epidemiologic studies/
observational study/
observational studies as topic/

clinical studies as topic/
controlled before-after studies/
cross-sectional studies/
historically controlled study/
interrupted time series analysis/
exp seroepidemiologic studies/
national longitudinal study of adolescent health/
cohort studies/
cohort analysis/
longitudinal studies/
longitudinal study/
prospective studies/
prospective study/
follow-up studies/
follow up/
followup studies/
retrospective studies/
retrospective study/
case-control studies/
exp case control study/
cross-sectional study/
observational study/
quasi experimental methods/
quasi experimental study/
(observational study OR validation studies OR clinical study).pt.
(observational adj3 (study OR studies OR design OR analysis OR analyses)).ti,ab,kf,kw.
cohort*.ti,ab,kf,kw.
(prospective adj7 (study OR studies OR design OR analysis OR analyses)).ti,ab,kf,kw.
((follow up OR followup) adj7 (study OR studies OR design OR analysis OR analyses)).ti,ab,kf,kw.
((longitudinal OR longterm OR (long adj term)) adj7 (study OR studies OR design OR analysis OR analyses OR data)).ti,ab,kf,kw.
(retrospective adj7 (study OR studies OR design OR analysis OR analyses OR data OR review)).ti,ab,kf,kw.
((case adj control) OR (case adj comparison) OR (case adj controlled)).ti,ab,kf,kw.
(case-referent adj3 (study OR studies OR design OR analysis OR analyses)).ti,ab,kf,kw.
(population adj3 (study OR studies OR analysis OR analyses)).ti,ab,kf,kw.
(descriptive adj3 (study OR studies OR design OR analysis OR analyses)).ti,ab,kf,kw.
((multidimensional OR (multi adj dimensional)) adj3 (study OR studies OR design OR analysis OR analyses)).ti,ab,kf,kw.
(cross adj sectional adj7 (study OR studies OR design OR research OR analysis OR analyses OR survey OR findings)).ti,ab,kf,kw.
((natural adj experiment) OR (natural adj experiments)).ti,ab,kf,kw.
(quasi adj (experiment OR experiments OR experimental)).ti,ab,kf,kw.
((non experiment OR nonexperiment OR non experimental OR nonexperimental) adj3 (study OR studies OR design OR analysis OR analyses)).ti,ab,kf,kw.
(prevalence adj3 (study OR studies OR analysis OR analyses)).ti,ab,kf,kw.

Filter 3: Observational Studies – PsycInfo

((case* adj5 control*) or (case adj3 comparison*) or case-comparison or control group*).ti,ab,id. not "Literature Review".md.
((cohort or longitudinal or prospective or retrospective).ti,ab,id. or longitudinal study.md. or prospective study.md. or retrospective study.md.) not "Literature Review".md.
(cross section* or "prevalence study").ti,ab,id.

Filter 4: Animal studies – MEDLINE, Embase and PsycInfo

exp animals/
exp animal experimentation/ or exp animal experiment/
exp models animal/
nonhuman/
exp vertebrate/ or exp vertebrates/
exp humans/
exp human experimentation/ or exp human experiment/

Search strategies as run

Database: Embase <1974 to 2023 May 10>, APA PsycInfo <1806 to May Week 1 2023>, Ovid MEDLINE(R) ALL <1946 to May 10, 2023>
Search Strategy:
1 exp *Critical Care/ use medall (38205)
2 *Critical Care Nursing/ use medall (2049)
3 exp *Critical Illness/ use medall (19388)
4 exp *Intensive Care Units/ use medall (44221)
5 exp *Intensive Care/ use oemezd (284720)
6 exp *Intensive Care Unit/ use oemezd (60463)
7 exp Intensive Care/ use psyh (7016)
8 (((acute* or intensive* or critical* or neurointensive* or neuro-intensive* or neurocritical* or neuro-critical*) adj (care or therap* or treatment* or unit?)) or healthcare facilit* or health-care facilit*).ti,kf,kw. (256452)
9 (ICU or MICU or CICU or CVICU or CCU or SICU or POCCU or ITU or HDU or ICUs or MICUs or CICUs or CVICUs or CCUs or SICUs or POCCUs or ITUs or HDUs).ti. (40311)
10 ((ICU or MICU or CICU or CVICU or CCU or SICU or POCCU or ITU or HDU or ICUs or MICUs or CICUs or CVICUs or CCUs or SICUs or POCCUs or ITUs or HDUs) and ((acute* or intensive* or critical* or neurointensive* or neuro-intensive* or neurocritical* or neuro-critical*) adj (care or therap* or treatment* or unit?))).tw,kf,kw. (165519)
11 (intensive care unit? or intensive therapy unit? or burn unit? or coronary care unit? or high dependency unit? or recovery room? or respiratory care unit? or "acute hospital setting" or "acute hospital settings").tw,kf,kw. (416132)
12 or/1-11 (820201)
13 exp Anxiety/ (485436)
14 exp Anxiety Disorders/ or exp anxiety disorder/ (446311)
15 Adjustment Disorders/ or adjustment disorder/ (9773)
16 Mutism/ (4823)
17 (anxiet* or anxious* or panic* or phobi* or agoraphobi* or GAD or mute or mutism or nervous* or restless* or stress* or PTSD or obsessive compulsive or obsessive-compulsive or OCD or adjustment disorder* or neurotic or neuroses).tw,kf,kw. (4489702)
18 or/13-17 (4702373)
19 exp Benzodiazepines/ or exp Benzodiazepine derivative/ use oemezd or (Benzodiazepine or "1,2-Benzodiazepine" or 12794-10-4 or "1H-1,2-benzodiazepine" or 264-60-8 or "benzo diazepine" or benzodiazapine or benzodiazepin or benzodiazepines or CHEMBL4297264 or DB12537 or DTXSID90155730 or EN300-26945992 or M0Q7802G2B or Q27283309 or SCHEMBL8137 or UNII-M0Q7802G2B).tw,kf,kw. (373604)
20 Afizagabar/ or (afizagabar or s44819 or S-44819).tw,kf,kw. (33)
21 Alprazolam/ or (Alprazolam or Alprazolan or Alprox or "Apo Alpraz" or Apo-Alpraz or Cassadan or D-65MT or D65MT or Esparon or Kalma or Novo Alprazol or Novo-Alprazol or "Nu Alpraz" or Nu-Alpraz or Ralozam or Tafil or Trankimazin or "U-31,889" or "U31,889" or Xanax).tw,kf,kw. (26303)
22 Amitriptyline plus chlordiazepoxide/ or "amitriptyline plus chlordiazepoxide".tw,kf,kw. (22)
23 Anthramycin/ or (Anthramycin or Antramicina or Antramycin or Antramycine or Antramycinum).tw,kf,kw. (439)
24 Arfendazam/ or (Arfendazam or Arfendazamum).tw,kf,kw. (5)
25 Benzodiazepine/ or Benzodiazepine Compounds/ or Benzodiazepines/ or (Benzodiazepine or benzo

diazepine or benzodiazapine or benzodiazepin or CHEMBL4297264 or DB12537 or DTXSID90155730 or EN300-26945992 or M0Q7802G2B or Q27283309 or SCHEMBL8137 or UNII-M0Q7802G2B).tw,kf,kw. (140011)
26 exp Benzodiazepinones/ or (Benzodiazepinones or Anxyrex or "Apo Bromazepam" or Apo-Bromazepam or Bromazepam or BromaLich or "Bromaz 1A Pharma" or Bromazanil or "bromazep von ct").tw,kf,kw. (296613)
27 Bromazepam/ or (Bromazepam or Bromazepam-neuraxpharm or Bromazepam-ratiopharm or durazanil or Gen-Bromazepam or Lexatin or Lexomil or Lexotan or Lexotanil or "Ro 5-3350" or "Ro 53350" or "Von Ct, Bromazep").tw,kf,kw. (4657)
28 Camazepam/ or (Camazepam or Albego or "B 5333" or Camazepamum or Limpidon or Nebolan or Panevril or Paxor or "SB 5833" or "S-58-33").tw,kf,kw. (320)
29 Carburazepam/ or Uxepam/ or (Carburazepam or Carburazepamum or "Rgh 3331" or "RGH 3331" or RGH-3331 or Uxepam).tw,kf,kw. (17)
30 Ceclazepide/ or Ceclazepide.tw,kf,kw. (0)
31 Chlordiazepoxide/ or (Chlordiazepoxide or Chlozepid or Elenium or Librium or Methaminodiazepoxide).tw,kf,kw. (17931)
32 Cinolazepam/ or (Cinolazepam or Cinolazepamum or Gerodorm or OX 373 or OX-373).tw,kf,kw. (46)
33 Clobazam/ or (Clobazam or Frisium or "HR 376" or "LM 2717" or LM-2717 or LM2717 or Onfi or Urbanyl).tw,kf,kw. (10989)
34 Clonazepam/ or (Clonazepam or "2H-1,4-Benzodiazepin-2-one, 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-" or Antelepsin or Clonazepam or Klonopin or Rivotril or "Ro 5-4023" or "Ro 54023").tw,kf,kw. (36538)
35 Clorazepate/ or Clorazepate Dipotassium/ or Clorazepate potassium/ or (4306-CB or Clorazepate or Chlorazepate or Clorazepic Acid or Tranxene or Tranxilium).tw,kf,kw. (4866)
36 Dealkylflurazepam/ or (Dealkylflurazepam or DIDEETHYLFLURAZEPAM or DIDESETHYLFLURAZEPAM).tw,kf,kw. (263)
37 Delorazepam/ or (Delorazepam or Chlordemethyldiazepam or Clordesmetildiazepam or Dadumir or Delorazepamum or O-CHLORODESMETHYLDIAZEPAM).tw,kf,kw. (592)
38 Demoxepam/ or (Demoxepam or Demossepam or Demoxepamum or "Ro 52092" or "Ro 5-2092" or RO5-2092 or Ro-52092 or RO-5-2092).tw,kf,kw. (299)
39 Devazepide/ or (devazepide or je6p7qy7nh or "l 364,718" or "mk 329").tw,kf,kw. (2575)
40 exp Diazepam/ or (Diazepam or "7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one" or Apaurin or Diazemuls or Faustan or Relanium or Seduxen or Sibazon or Stesolid or Valium).tw,kf,kw. (112308)
41 Doxefazepam/ or (Doxefazepam or "Sas 643" or SAS-643).tw,kf,kw. (44)
42 Estazolam/ or (Estazolam or D-40TA or D40TA or Estazolam or Nuctalon or ProSom or Tasedan).tw,kf,kw. (1981)
43 Ethyl loflazepate/ or (Ethyl loflazepate or CM 6912 or CM-6912 or "Ethyl fluclozepate" or "ethyl loflazepate" or "Ethylis loflazepas" or "Loflazepate d'ethyle" or "Loflazepato de etilo" or Victan).tw,kf,kw. (373)
44 Fludiazepam/ or (fludiazepam or Erispan or Fludiazepamum or "ID 540 OR ID-540").tw,kf,kw. (208)
45 Flumazenil/ or (Flumazenil or Anexate or Flumazepil or Lanexat or "Ro 15 1788" or "Ro 15-1788" or "Ro 151788" or Romazicon).tw,kf,kw. (16016)
46 Flunitrazepam/ or (Flunitrazepam or "Fluni 1A Pharma" or Flunibeta or Flunimerck or Fluninoc or Flunitrazepam-neuraxpharm or Flunitrazepam-ratiopharm or Flunitrazepam-Teva or flunizep or Fluridrazepam or Narcozep or RO-5-4200 or RO54200 or Rohipnol or Rohypnol).tw,kf,kw. (13163)
47 Flurazepam/ or (Flurazepam or Apo-Flurazepam or Dalmadorm or Dalmane or Dormodor or Staurodorm).tw,kf,kw. (6615)
48 Flutoprazepam/ or (Flutoprazepam or Flutoprazepamum or KB-509 or Restar or Restas).tw,kf,kw. (83)
49 Fosazepam/ or (Fosazepam or Fosazepamum).tw,kf,kw. (40)
50 Gidazepam/ or Gidazepam.tw,kf,kw. (80)
51 Girisopam/ or (Girisopam or "EGIS 5810" or EGIS-5810 or Girisopamum or GYKI 51189 or GYKI-51189).tw,kf,kw. (48)
52 Halazepam/ or (Halazepam or Halazepamum or Halezepam or Pacinone or Paxipam or "Sch 12041" or Sch-12041).tw,kf,kw. (459)
53 Loflazepate/ or (loflazepate or CM-6913 or "CM 6913" or Loflazepic acid).tw,kf,kw. (253)

54 Loprazolam/ or (loprazolam or "HR 158" or "HR 458" or Loprazolamum or "RU 31158" or "RU-31158" or Triazulenone).tw,kf,kw. (3039)
55 Lorazepam/ or (Lorazepam or Apo-Lorazepam or Ativan or Donix or Duralozam or Durazolam or Idalprem or Laubeel or lorazep or Lorazepam or Lorazepam-neuraxpharm or Lorazepam-ratiopharm or Novo-Lorazem or "Nu Loraz" or Nu-Loraz or "Orfidal Wyeth" or Sedicepan or Sinestron or Somagerol or Temesta or "WY 4036" or WY-4036 or WY4036 or "Wyeth, Orfidal").tw,kf,kw. (37778)
56 Lormetazepam/ or (Lormetazepam or Dormagen or Ergocalm or Loramet or Loretam or Lormetazepamum or Methyllorazepam or N-Methyllorazepam or Noctamid or Noctamide).tw,kf,kw. (2097)
57 Lotrafiban/ or (Lotrafiban or R-Lotrafiban or SB 214857 or SB-214134 or SB-214857 or SB-214857A).tw,kf,kw. (211)
58 Meclonazepam/ or (Meclonazepam or "Meclonazepam, (S)-isomer" or Meclonazepamum or "Ro 113128" or "Ro 11-3128" or "Ro 11-3128/002" or Ro-113128 or Ro-11-3128).tw,kf,kw. (181)
59 Medazepam/ or (medazepam or Nivelton or Nobraksin or Nobral or Nobrium or Resmit or Rudotel).tw,kf,kw. (1617)
60 Metaclazepam/ or (Metaclazepam or "Ka 2547" or Ka2547 or KA-2547 or "KC 2547" or KC-2547 or Metaclazepamum or Metaclazepan or Metuclazepam or Talis).tw,kf,kw. (228)
61 Midazolam/ or (Midazolam or Dormicum or "Ro 21 3981" or Ro 21-3981 or "Ro 213981" or Versed).tw,kf,kw. (82331)
62 n nitrosochlordiazepoxide/ or (Nitrosochlordizepoxide or 2-N-nitrosochlordiazepoxide or N-Nitrosochlordiazepoxide or N-Nitrosochlorodiazepoxide).tw,kf,kw. (14)
63 Nastorazepide/ or (Nastrorazepide or "Z 360" or Z360 or Z-360).tw,kf,kw. (150)
64 Nerisopam/ or (Nerisopam or "Gyki 52322" or GYKI-52322).tw,kf,kw. (41)
65 Nimetazepam/ or (Nimetazepam or Dormalon or Hypnon or Methylnitrazepam or Nimetazepamum or "S 1530" or S-1530).tw,kf,kw. (245)
66 Nitrazepam/ or (Nitrazepam or Alodorm or Dormalon or Dormo-Puren or Eatan or Imadorm or imeson or Mogadon or Nitrazadon or Nitrazep or Nitrodiazepam or Novanox or Radedorm or Remnos or Serenade or Somnite).tw,kf,kw. (8795)
67 Norchlordiazepoxide/ or (Norchlordiazepoxide or Calsamin or Calsmin or "Dormicum (anticonvulsant)" or Dormin-5 or Dormo-Puren or Dumolid or Eatan or Epibenzalin or Epinelbon or Eunoctin or Eunoktin or Gerson or Hipnax or Hipsal or Ibrovek or Imeson or Imesont or Ipersed or Magadon or Megadon or Mitidin or Mogadan or Mogadon or Mogadone or N-Desmethylnimetazepam or Nelbon or Nelmat or Neozepam or Neuchlonic or Nitrados or Nitravet or Nitrazepamum or Nitrempax or Nitrenpax or Noctesed or Pacisyn or Paxisyn or Pelson or Persopit or Radedorm or Relact or Remnos or Somitran or Somnased or Somnibel or Somnite or Sonebon or Sonnolin or Trazenin or Unisomnia).tw,kf,kw. (1744)
68 Norclobazam/ or (Norclobazam or "CLOBAZAM IMPURITY A" or "CLOBAZAM METABOLITE M9" or "Clobazam-M nor" or Clofazin or Demethylclobazam or N-Demethylclobazam or N-Desmethyl Clobazam-d5 or NOR-CLOBAZAM).tw,kf,kw. (329)
69 Nordazepam/ or (Nordezepam or Calmday or Dealkylprazepam or Demethyldiazepam or Deoxydemoxepam or Desmethyldiazepam or Desalkylhalazepam or "Descyclopropylmethyl Prazepam" or Descyclopropylmethylprazepam or Destrifluoroethylhalazepam or N-Desalkylhalazepam or N-Descyclopropylmethyl-Prazepam or N-Descyclopropylmethylprazepam or N-Destrifluoroethylhalazepam or Nordaz or Nordazepam or Nordiazepam or Norprazepam or "Ro 5 2180" or "Ro 5-2180" or "Ro 52180" or Tranxilium or Vegesan).tw,kf,kw. (3902)
70 Norfludiazepam/ or (Norfludiazepam or "CM 7116" or CM-7116 or Descarbethoxyloflazepate or "MIDAZOLAM IMPURITY F" or norflurazepam or nor-Flurazepam or Norflutoprazepam or "Ro 5-3367" or "Ro-053367" or "Ro-05-3367").tw,kf,kw. (71)
71 Norflunitrazepam/ or (Norflunitrazepam or Demethylflunitrazepam or Desmethylflunitrazepam or N-Desmethylflunitrazepam or Nor-Flunitrazepam).tw,kf,kw. (170)
72 Olanzapine/ or (Olanzapine or "2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno(2,3-b)(1,5)benzodiazepine" or "LY 170052" or "LY 170053" or LY-170052 or LY170052 or Zolafren or Zyprexa).tw,kf,kw. (57708)
73 Osugacestat/ or (Osugacestat or "BMS 906024" or BMS-906024).tw,kf,kw. (86)
74 Oxazepam/ or (Oxazepam or Abboxapam or Adumbran or Alepam or Ansioxacepam or Anxiolit or Aplakil or Astress or Azutranquil or Drimuel or Droxacepam or Durazepam or Lederpam or Limbial or Nesontil or Noctazepam or Nortemazepam or Nozepam or Ossazepam or Oxanid or Oxa-puren or Oxazepamum or Oxazipam or Oxozepam or Pacienx or Praxiten or Propax or Psicopax or Psiquiwas or

Quilibrex or Sedigoa or Serax or Serenid or Serenid-D or Serepax or Seresta or Serpax or Sigacalm or Sobril or Tacepam or Tarchomin or Tazepam or Uskan or Vaben or Zaxopam).ti,kf,kw. (10273)
75 Pamozirine/ or (Pamozirine or 1343476-98-1 or NF6U5U2UEB or SC-DR002 or SCHEMBL18541706 or UNII-NF6U5U2UEB).tw,kf,kw. (4)
76 Phenazepam/ or (Phenazepam or Fenazepam or PHENZITAT).tw,kf,kw. (993)
77 Pinazepam/ or (Pinazepam or Domar or Duna or Pinazepamum or Z-905).tw,kf,kw. (243)
78 Pirenzepine/ or (Pirenzepine or Gastrotsepin or Gastrozepin or "L-S 519" or "LS 519" or "LS-519" or LS519 or "Piren basan" or Piren-basan or Pirenzepin or PPirenzepin-ratiopharm or Pyrenzepine or Ulcoprotect or Ulgescum).tw,kf,kw. (11718)
79 Prazepam/ or (Prazepam or Centrax or Demetrin or Lysanxia or Reapam).tw,kf,kw. (1794)
80 Quazepam/ or (Quazapam or Doral or Dormalin or Oniria or Prosedar or Quazepamum or Quazium or Sch 16134 or Sch-161 or Sch-16134).tw,kf,kw. (865)
81 Remimazolam/ or (Remimazolam or CNS 7056 or CNS-7056 or ONO 2745 or ONO2745 or ONO-2745).tw,kf,kw. (780)
82 Talampanel/ or (Talampanel or GYKI 53773 or GYKI 537773 or GYKI-53773 or Kinampa or LY 300164 or LY300164 or LY-300164 or "talampanel(ly300164)").tw,kf,kw. (490)
83 Talirine/ or (Talirine or 1Y234W15BL or UNII-1Y234W15BL).tw,kf,kw. (53)
84 Tampramine/ or (Tampramine or UNII-47GSE5RM8N).tw,kf,kw. (2)
85 Tarazepide/ or (Tarazepide or UNII-RK2972YZ2U).tw,kf,kw. (26)
86 Temazepam/ or (Temazepam or "3 Hydroxydiazepam" or 3-Hydroxydiazepam or Dasuen or Euhypnos or Hydroxydiazepam or Levanxol or Methyloxazepam or Nocturne or "Norkotral Tema" or Normison or Normitab or Nortem or Oxydiazepam or Planum or "Pronervon T" or Remestan or Restoril or "Ro 5 5345" or Ro-5-5345 or Ro55345 or "SaH 47 603" or "SaH 47-603" or "SaH 47603" or Signopam or "Tema, Norkotral" or Temaze or "temazep von ct" or Temtabs or "Tenox or Von Ct, Temazep" or "WY 3917" or WY-3917 or WY3917).tw,kf,kw. (11705)
87 Tibezonium iodide/ or (Tibezonium iodide or "Iodure de tibezonium" or "Ioduro de tibezonio" or Maxoral or "REC-15/0691" or Thiabenzazonium or Tibenzonio ioduro or Tibenzonium iodide or Tibezonii iodidum or "Tibezonium (iodide)").tw,kf,kw. (38)
88 Tifluadom/ or (Tifluadom or "KC 5103" or KC-5103 or "KC 5911" or "KC 6128" or KC-5911 or KC-6128 or KC5103 or "Tifluadom/KC-5103" or titfluadom or UNII-TF8X866L0I).tw,kf,kw. (370)
89 Tofisopam/ or (tofisopam or dextofisopam or EGYT-341 or Emandaxin or Grandaxin or levotofisopam or Tofisopamum or tofizopam).tw,kf,kw. (601)
90 Tomaymycin/ or Tomaymycin.tw,kf,kw. (142)
91 Tuclazepam/ or (Tuclazepam or Tuclazepamum or UNII-343211YULR).tw,kf,kw. (0)
92 or/19-91 (459955)
93 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. (687633)
94 Randomized Controlled Trial/ (1376596)
95 exp Randomized Controlled Trials as Topic/ (425306)
96 "Randomized Controlled Trial (topic)"/ (259390)
97 Controlled Clinical Trial/ (564454)
98 exp Controlled Clinical Trials as Topic/ (440705)
99 "Controlled Clinical Trial (topic)"/ (13590)
100 Randomization/ (205993)
101 Random Allocation/ (202124)
102 Double-Blind Method/ (360294)
103 Double Blind Procedure/ (210084)
104 Double-Blind Studies/ (342717)
105 Single-Blind Method/ (82315)
106 Single Blind Procedure/ (51691)
107 Single-Blind Studies/ (84380)
108 Placebos/ (381882)
109 Placebo/ (409141)
110 Control Groups/ (113847)
111 Control Group/ (113847)
112 (random* or sham or placebo*).ti,ab,hw,kf,kw. (4609192)

113 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. (656460)
114 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. (3835)
115 (control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw. (3129595)
116 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw. (130474)
117 allocated.ti,ab,hw. (204700)
118 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw. (136210)
119 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. (31418)
120 (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw. (1648)
121 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw. (17397)
122 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. (38167)
123 (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw. (161686)
124 or/93-123 (6729880)
125 epidemiologic methods/ (251841)
126 epidemiologic studies/ (250817)
127 observational study/ (468139)
128 observational studies as topic/ (335405)
129 clinical studies as topic/ (163734)
130 controlled before-after studies/ (231323)
131 cross-sectional studies/ (897827)
132 historically controlled study/ (241721)
133 interrupted time series analysis/ (224704)
134 exp seroepidemiologic studies/ (33257)
135 national longitudinal study of adolescent health/ (386)
136 cohort studies/ (1220633)
137 cohort analysis/ (1360510)
138 longitudinal studies/ (353451)
139 longitudinal study/ (357743)
140 prospective studies/ (1425891)
141 prospective study/ (1531755)
142 follow-up studies/ (2269062)
143 follow up/ (2043002)
144 followup studies/ (12396)
145 retrospective studies/ (2296579)
146 retrospective study/ (2576538)
147 case-control studies/ (494421)
148 exp case control study/ (1637316)
149 cross-sectional study/ (1026522)
150 observational study/ (468139)
151 quasi experimental methods/ (497)
152 quasi experimental study/ (12300)
153 (observational study or validation studies or clinical study).pt. (146880)
154 (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. (583375)
155 cohort*.ti,ab,kf,kw. (2412677)
156 (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. (1387976)
157 ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. (471355)
158 ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf,kw. (960335)
159 (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf,kw. (1849183)
160 ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf,kw. (385494)
161 (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. (1361)
162 (population adj3 (study or studies or analysis or analyses)).ti,ab,kf,kw. (623885)
163 (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. (306208)

164 ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. (13838)
165 (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf,kw. (1091900)
166 ((natural adj experiment) or (natural adj experiments)).ti,ab,kf,kw. (8402)
167 (quasi adj (experiment or experiments or experimental)).ti,ab,kf,kw. (60900)
168 ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. (7178)
169 (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf,kw. (130944)
170 or/125-169 (11452597)
171 ((case* adj5 control*) or (case adj3 comparison*) or case-comparison or control group*).ti,ab,id. not "Literature Review".md. (1956829)
172 ((cohort or longitudinal or prospective or retrospective).ti,ab,id. or longitudinal study.md. or prospective study.md. or retrospective study.md.) not "Literature Review".md. (5775522)
173 (cross section* or "prevalence study").ti,ab,id. (1384739)
174 or/171-173 (8466229)
175 174 use psyh (527898)
176 170 or 175 (11654224)
177 exp animals/ (57337013)
178 exp animal experimentation/ or exp animal experiment/ (3099654)
179 exp models animal/ (2408371)
180 nonhuman/ (7467066)
181 exp vertebrate/ or exp vertebrates/ (55828134)
182 177 or 178 or 179 or 180 or 181 (59424442)
183 exp humans/ (46668457)
184 exp human experimentation/ or exp human experiment/ (661975)
185 183 or 184 (46671581)
186 182 not 185 (12754791)
187 (12 and 18 and 92 and (124 or 176)) not 186 (1003)
188 remove duplicates from 187 (813)
189 exp Delirium/ use medall or exp *Delirium/ use oemezd or Delirium/ use psyh (32753)
190 Confusion/ use medall or exp *Confusion/ use oemezd or Mental Confusion/ use psyh (10180)
191 Hallucinations/ use medall or exp *Hallucination/ use oemezd or exp Hallucinations/ use psyh (28687)
192 (bewilderment or confusion* or deliria* or delirious* or delirium* or disorientation or hallucinat*).tw,kf,kw,id. (244352)
193 or/189-192 (257673)
194 exp Antipsychotic Agents/ use medall (128177)
195 exp Neuroleptic Agent/ use oemezd (288884)
196 exp Neuroleptic Drugs/ use psyh (33938)
197 (antipsychotic* or anti-psychotic* or ((neuroleptic or neuroleptics) adj (agent or agents or drug or drugs)) or ((butyrophenone or major or phenothiazine) adj (tranquilis* or tranquiliz*)) or neuroleptic*).tw,kf,kw,id. (205028)
198 ("1,2,3,6 tetrahydro 4 phenyl 1 [(3 phenyl 3 cyclohexen 1 yl)methyl]pyridine" or "ci 1007" or ci1007 or "pd 143188" or pd143188 or "150013−70−0").tw,kf,kw. (1903)
199 ("2 [4 [4 (7,9 dioxo 6 thia 8 azaspiro[4.4]nonan 8 yl)butyl] 1 piperazinyl] 3 pyridinecarbonitrile" or "2 [4 [4 (7,9 dioxo 6 thia 8 azaspiro[4.4]nonan 8 yl)butyl] 1 piperazinyl] 3 pyridinecarbonitrile hydrochloride" or "2 [4 [4 (7,9 dioxo 6 thia 8 azaspiro[4.4]nonan 8 yl)butyl] 1 piperazinyl]pyridine 3 carbonitrile" or "bmy 13980" or "bmy 13980 1" or bmy13980 or bmy139801 or "mj 13980 1" or "mj 13980−1" or "mj 139801" or "mj13980 1" or "mj13980−1" or mj139801 or "85581−65−3").tw,kf,kw. (12)
200 ("2 chloro 12 (3 dimethylamino 2 methylpropyl)dibenzo[d,g][1,3,6]dioxazocined" or "2 chloro 12 (2 methyl 3 dimethylaminopropyl) 12h dibenzo[d,g][1,3,6]dioxazocine monohydrochloride" or "2 chloro 12 (3 dimethylamino 2 methylpropyl)dibenzo[d,g][1,3,6]dioxazocine hydrochloride" or "egyt 2509" or egyt2509 or "70133−85−6").tw,kf,kw. (15)
201 ("2 chloro n [alpha (2 piperidinyl)benzyl] 3 trifluoromethylbenzamide" or "2 chloro n [phenyl(piperidin 2 yl)methyl] 3 trifluoromethylbenzamide" or "ssr 504734" or ssr504734).tw,kf,kw. (124)

202 ("2 cyclopropyl 5 [1 (2 fluoro 3 pyridinyl) 5 methyl 1h 1,2,3 triazol 4 yl] 2,3 dihydro 1h isoindol 1 one" or CFMTI or "864864−17−5").tw,kf,kw. (7)
203 "2,3,3a,12b tetrahydro 3 methyl 1h dibenzo[b,f]oxepino[10,11 c]pyrrole".tw,kf,kw. (0)
204 ("3 [3 (methylsulfonyl)phenyl] 1 propylpiperidine" or "3 (3 methylsulfonyl phenyl) 1 propyl piperidine" or "3 (3 methylsulfonyl phenyl) 1 propyl piperidine hydrochloride" or "3 [3 (methylsulfonyl)phenyl] 1 propylpiperidine hydrochloride" or "osu 6162" or osu6162 or "pnu 0096391" or "pnu 96391" or "pnu 96391a" or pnu0096391 or pnu96391 or pnu96391a or "156907−84−5").tw,kf,kw. (226)
205 "6 n (2,2 diphenylethyl)adenosine".tw,kf,kw. (0)
206 "7 hydroxychlorpromazine".tw,kf,kw. (90)
207 "8 ethyl 7,8 dihydro 1,3,5 trimethyl 1h imidazo[1,2 c]pyrazolo[3,4 e]pyrimidine".tw,kf,kw. (7)
208 aceperone/ or (aceperone or Aceperona or Aceperonum or Acetabuton or ACETABUTONE).tw,kf,kw. (142)
209 Acepromazine/ or acepromazine maleate/ or (acepromazine or acetazine or acetopromazine or acetylpromazine or calmivet or plegicil or vetranquil).tw,kf,kw. (4869)
210 aceprometazine/ or (aceprometazine or UNII-984N9YTM4Y).tw,kf,kw. (142)
211 acetophenazine/ or acetophenazine dimaleate/ or (acetophenazine or UNII-8620H6K4QH).tw,kf,kw. (229)
212 adoprazine/ or (adoprazine or "SLV 313" or SLV313 or SLV-313 or UNII-7SNB18Q89D).tw,kf,kw. (101)
213 alimemazine/ or alimemazine tartrate/ or (alimemazine or Isobutrazine or Methylpromazine or Nedeltran or Panectyl or Repeltin or Repetin or Spansule or Temaril or Teralen or Teralene or Theralen or Theralene or Trimeperazine or trimeprazine or Trimeprazine-d6 or UNII-76H78MJJ52 or Vallergan or Vanectyl or Variargil).tw,kf,kw. (2289)
214 "alpha (4 fluorophenyl) 4 (5 fluoro 2 pyrimidinyl) 1 piperazinebutanol"/ or UNII-A5NB5G07JO.tw,kf,kw. (304)
215 "alpha [1 [2 (1,4 benzodioxan 5 yloxy)ethyl] 3 pyrrolidinyl] 4 fluoroacetophenone"/ (31)
216 amitriptyline plus perphenazine/ or ("amitriptyline, perphenazine drug combination" or "Anxipress D" or Deprelio or Elavil Plus or Longopax or Mutabon or "Perphenazine and amitriptyline hydrochloride" or "Perphenazine-amitriptyline combination" or Pertriptyl or "TRIAVIL 2-10" or "TRIAVIL 2-25" or "TRIAVIL 4-10" or "TRIAVIL 4-25" or "TRIAVIL 4-50" or Triptafe).tw,kf,kw. (255)
217 aplindore/ or (aplindore or UNII-Q5O76TA0ML).tw,kf,kw. (27)
218 Amisulpride/ or (amisulpride or barnetil or "dan 2163" or "lin 1418" or solian or sultopride).tw,kf,kw. (9411)
219 Aripiprazole/ or (aripiprazole or "7-(4-(4-(2,3-dichlorophenyl)-1-piperazinyl)butyloxy)-3,4-dihydro-2(1H)-quinolinone" or Abilify or Aripiprazol or "OPC 14597" or OPC-14597).tw,kf,kw. (28365)
220 Azaperone/ or (Azaperone or R-1929 or R1929 or Stresnil).tw,kf,kw. (1154)
221 balipodect/ or (balipodect or "TAK 063" or TAK063 or TAK-063 or UNII-6650W303H0).tw,kf,kw. (101)
222 benperidol/ or (Benperidol or Anquil or Benperidolo or Benperidolum or Benquil or Benzeridol or Benzoperidol or Benzperidol or Frenactil or Frenactyl or Glianimon).tw,kf,kw. (1619)
223 berupipam/ or (berupipam or UNII-420895MAOC).tw,kf,kw. (2)
224 bitopertin/ or (bitopertin or "R 1678" or R-1678 or "RG 1678" or RG1678 or RG-1678 or UNII-Q8L6AN59YY).tw,kf,kw. (309)
225 blonanserin/ or (blonanserin or "AD 5423" or AD5423 or AD-5423 or Lonasen or UNII-AQ316B4F8C).tw,kf,kw. (854)
226 brofoxine/ or (brofoxine or Brofossina or Brofoxina or Brofoxinum or Dimethabrone).tw,kf,kw. (9)
227 bromospiperone/ or (bromospiperone or 4-Bromospiperone or 4-Bromospiroperidol or p-Bromospiperone or p-Bromospiroperidol).tw,kf,kw. (61)
228 bromperidol/ or (bromperidol or Azurene or Bromoperidol or Bromperidolum or Impromen or Tesoprel).tw,kf,kw. (927)
229 Butaclamol/ or (butaclamol or "AY 23,028" or "AY-23,028" or "AY23,028").tw,kf,kw. (2702)
230 butaperazine/ or (butaperazine or Butaperazina or Butaperazinum or Butyrylperazine or Megalectil or Randolectil or Repoise or Tyrylen).tw,kf,kw. (392)
231 carfenazine/ or (carfenazine or Carfenazina or Carfenazinum or Carphenazin or Carphenazine or Procethazine or Proketazine).tw,kf,kw. (111)
232 cariprazine/ or (cariprazine or cis-Cariprazine or Vraylar).tw,kf,kw. (1601)

233 carpipramine/ or (carpipramine or Carbadipimidine or Carpipramina or Carpipraminum or Defekton or Prazinil).tw,kf,kw. (326)
234 carvotroline/ or carvotroline.tw,kf,kw. (6)
235 centbutindole/ or (centbutindole or Biriperona or Biriperone or Biriperonum).tw,kf,kw. (36)
236 chlorphenethazine/ or (chlorphenethazine or Chlorfenethazine or Chlorphenethazine or Ethyl chlorpromazine or Elroquil or Marophen).tw,kf,kw. (60)
237 chlorproethazine/ or (chlorproethazine or Chlorproethazinum or Clorproetazina or Neuriplege).tw,kf,kw. (58)
238 Chlorpromazine/ or (Chlorpromazine or Aminazine or Chlorazine or Chlordelazine or Contomin or Fenactil or Largactil or Propaphenin or Thorazine).tw,kf,kw. (68378)
239 Chlorprothixene/ or (Chlorprothixene or Chlorprotixen or Taractan).tw,kf,kw. (3403)
240 cinuperone/ or (Cinuperone or Cinuperonum).tw,kf,kw. (26)
241 clocapramine/ or (clocapramine or Clocapramina or Clocapraminum).tw,kf,kw. (162)
242 cloflumide mesilate/ or cloflumide.tw,kf,kw. (9)
243 clofluperol/ or (clofluperol or Clofluperidol or Clofluperolum).tw,kf,kw. (33)
244 Clopenthixol/ or (Clopenthixol or alpha-Clopenthixol or Cisordinol or Clopenthixol or Zuclopenthixol).tw,kf,kw. (2203)
245 clopimozide/ or (clopimozide or Clopimozida or Clopimozidum or "R 29,764" or "R 29764" or R-29764).tw,kf,kw. (51)
246 clopipazan/ or clopipazan.tw,kf,kw. (10)
247 clospipramine/ or (clospipramine or Clospipramine or Cremin or Mosapramine dihydrochloride or mosapramine hydrochloride).tw,kf,kw. (142)
248 clotiapine/ or (clotiapine or Clothiapine or Clotiapina or Clotiapinum or Entumin or Entumine or Etumine).tw,kf,kw. (1054)
249 Clozapine/ or (Clozapine or Clorazil or Clozapin or Clozapina or Clozapinum or CLOZARIL or Leponex or Lepotex).tw,kf,kw. (61600)
250 cyamemazine/ or (cyamemazine or Ciamatil or Ciamemazina or Cianatil or Cyamemazin or Cyamemazinum or Cyamepromazine or Kyamepromazin or Kyamepromazine or Tercian).tw,kf,kw. (909)
251 dimetotiazine/ or (dimetotiazine or Banistyl or Dimethiotazine or Dimethodin or Dimethothiazine or Dimetiotazine or Dimetothiazine or Dimetotiazin or Dimetotiazina or Dimetotiazinum or Migristene or Promaquid).tw,kf,kw. (194)
252 dixyrazine/ or (dixyrazine or Dixyrizine or Esocalm or Esucos or Metronal or Roscal).tw,kf,kw. (450)
253 dolasetron mesilate/ or (dolasetron mesilate or Anemet or Anzemet or Dalasetron Mesylate Hydrate or Dolasetron mesilate or Dolasetron methanesulfonate or Dolasetronmesylate).tw,kf,kw. (1506)
254 Droperidol/ or (Dehidrobenzperidol or Dehydrobenzperidol or Droleptan or Droperidol or Inapsine).tw,kf,kw. (12899)
255 duoperone/ or (duoperone or Duoperona or Duoperonum).tw,kf,kw. (6)
256 Etazolate/ or (Etazolate or "SQ 20009" or SQ-20009 or SQ20009).tw,kf,kw. (431)
257 etymemazine/ or (etymemazine or Ethotrimeprazine or Ethyl isobutrazine or Ethylisobutrazine).tw,kf,kw. (9)
258 evenamide/ or (evenamide or Evenamid).tw,kf,kw. (11)
259 farampator/ or (farampator or "CX 691" or CX691 or CX-691 or Org 24448 or Org24448 or Org-24448).tw,kf,kw. (71)
260 fluanisone/ or (fluanisone or Fluanison or Fluanisona or Fluanisonum or Haloanisone).tw,kf,kw. (463)
261 Flupenthixol/ or (alpha-Flupenthixol or cis-Flupenthixol or Emergil or Fluanxol or Flupentixol).tw,kf,kw. (7043)
262 flupentixol decanoate/ or (flupentixol decanoate or Depixol).tw,kf,kw. (949)
263 Fluphenazine/ or (Flufenazin or Fluphenazine or Lyogen or Prolixin).tw,kf,kw. (14632)
264 fluphenazine decanoate/ or (fluphenazine decanoate or Flufenazine decanoate or Fluorophenazine decanoate or Fluphenaline decanoate or Fluphenazine depot or FLUPHENAZINE ENANTHATE IMPURITY C or Fluphenazine O-decanoate or Fluphenazinedecanoate or fluphenazine-decanoate or Fluphenazini decanoas or liogen or Lyogen or Mirenil or Modecate or Moditen depot or Moditen-depo or Prolixin decanoate).tw,kf,kw. (2960)
265 fluphenazine enanthate/ or (Fluphenazine Enanthate or Enanthic acid fluphenazine or Eutimox or Flufenan or Moditen enanthate or Moditen-retard or Prolixin Enanthate).tw,kf,kw. (593)
266 Fluspirilene/ or (Fluspirilene or Fluspirilen or Fluspi or Imap or kivat or Redeptin or

Spirodiflamine).tw,kf,kw. (1870)
267 flutroline/ or (Flutroline or Flutrolino or Flutrolinum or Fluspi or fluspirilen or Fluspirilene or Imap or Kivat or Redeptin or Spirodiflamine).tw,kf,kw. (1354)
268 gevetroline/ or gevetroline.tw,kf,kw. (16)
269 Haloperidol/ or haloperidol decanoate/ or (haloperidol or Aloperidin or Aloperidol or Aloperidon or Aloperidolo or Bioperidolo or Brotopon or Dozic or Duraperidol or Einalon or Eukystol or Fortunan or Galoperiodol or Halidol or Haldol or Halojust or Halol or Halomonth or Halopal or Haloperidolum or Halopidol or Halopoidol or Halosten or Keselan or Linton or Mixidol or Neurodol or Pekuces or Peluces or Pernox or Sernas or Serenace or Serenase or Sigaperidol or Ulcolind or Uliolind).tw,kf,kw. (96967)
270 iclepertin/ or (Iclepertin or "BI 425809" or BI425809 or BI-425809).tw,kf,kw. (65)
271 isofloxythepin/ or isofloxythepin.tw,kf,kw. (100)
272 isomolpan/ or isomolpan.tw,kf,kw. (15)
273 Lamotrigine/ or (lamotrigine or "BW 430C" or BW-430C or BW430C or Crisomet or Labileno or Lamictal or Lamiktal).tw,kf,kw. (38308)
274 landipirdine/ or landipirdine.tw,kf,kw. (16)
275 lenperone/ or (lenperone or AHR 2277 or AHR2277 or AHR-2277 or Lenperona or Lenperonum).tw,kf,kw. (103)
276 Loxapine/ or (loxapine or "CL 71,563" or "CL-71,563" or "CL71,563" or Cloxazepine or Loxapinsuccinate or loxapine succinate or Oxilapine).tw,kf,kw. (3545)
277 Lurasidone Hydrochloride/ or (Lurasidone or latuda).tw,kf,kw. (3462)
278 luvadaxistat/ or luvadexistat.tw,kf,kw. (12)
279 mardepodect/ or mardepodect.tw,kf,kw. (51)
280 maroxepine/ or (Maroxepine or Maroxepin or Maroxepina or Maroxepinum).tw,kf,kw. (18)
281 mazapertine/ or mazapertine.tw,kf,kw. (58)
282 mepiprazole/ or (mepiprazole or Mepiprazol or Mepiprazolum or Quiadon).tw,kf,kw. (73)
283 mesoridazine besylate/ or (Mesoridazine besylate or Lidanar or Lidanil or Mesoridazine benzenesulfonate or mesoridazine monobenzenesulfonate or Serentil).tw,kf,kw. (219)
284 Methiothepin/ or (Methiothepin or Methiothepine or Metitepine).tw,kf,kw. (2878)
285 methopromazine/ or (Methopromazine or Methopromazinum or Methoxypromazine or Metopromazina or Mopazin or Mopazine or Neoproma).tw,kf,kw. (115)
286 Methotrimeprazine/ or (Methotrimeprazine or Levomeprazin or Levomepromazine or Levopromazine or Tisercin or Tizercine or Tizertsin).tw,kf,kw. (7210)
287 metofenazate/ or (metofenazate or Frenolone or Methophenazine or Metofenazato or Metofenazatum or metophenazate or Phrenolon).tw,kf,kw. (117)
288 Molindone/ or (Molindone or Moban).tw,kf,kw. (1638)
289 moperone/ or (Moperone or Luvatren or Luvatrena or Meperon or Methylperidol or Moperona or Moperonum or Mopiperone).tw,kf,kw. (251)
290 neboglamine/ or (neboglamine or CR 2249 or Cr2249 or CR-2249).tw,kf,kw. (16)
291 noctran/ or (Noctran or 78355-48-3 or "FA 522 A").tw,kf,kw. (95)
292 norchlorpromazine/ or (Norchlorpromazine or Demethylchlorpromazine or Demonomethylchlorpromazine or Desmethylchloropromazine or Desmethylchlorpromazine or MONODESMETHYLCHLORPROMAZINE or N-Desmethylchlorpromazine or N-Monodesmethylchlorpromazine or NOR1CHLORPROMAZINE or NOR1-CHLORPROMAZINE).tw,kf,kw. (159)
293 Olanzapine/ or (Olanzapine or "LY 170052" or "LY 170053" or LY-170052 or LY170052 or Zolafren or Zyprexa).tw,kf,kw. (57707)
294 oxiperomide/ or (oxiperomide or Oxiperomida or Oxiperomidum or Oxyperomide or Peromide).tw,kf,kw. (105)
295 oxypertine/ or (oxypertine or Equipertine or Forit or Opertil or Oxipertina or Oxipertine or Oxipertinum or Oxypertin or Oxypertinum).tw,kf,kw. (453)
296 oxyprothepine/ or oxyprothepine decanoate/ or oxyprothepine.tw,kf,kw. (198)
297 Paliperidone Palmitate/ or (paliperidone or "9 Hydroxy risperidone" or "9 Hydroxyrisperidone" or "9 OH risperidone" or 9-hydroxy-risperidone or 9-hydroxyrisperidone or 9-OH-risperidone or Invega).tw,kf,kw. (8793)
298 pecazine/ or (pecazine or Lacumin or mepasin or Mepazin or MEPAZINE or Meprazine or Mesapin or Pacatal or Pacatol or Pakatal or Paxital or Pecatal or Pecazina or Pecazinum).tw,kf,kw. (325)

299 Penfluridol/ or (Penfluridol or Penfluridolum or Semap).tw,kf,kw. (1321)
300 perazine/ or (perazine or Perazin or Pernazine or Taxilan).tw,kf,kw. (1404)
301 periciazine/ or (Periciazine or Aolept or Nelactil or Nemactil or Neulactil or Neuleptil or Periciazin or Periciazina or Periciazinum or PERICYAZINE).tw,kf,kw. (1148)
302 perimetazine/ or (Perimetazine or leptryl or Perimetazin or Perimetazina or Perimetazinum or Perimethazine).tw,kf,kw. (71)
303 Perphenazine/ or perphenazine decanoate/ or (Perphenazine or Chlorperphenazine or Chlorpiprazine or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or Perfenazina or Perfenil or Perphenan or Perphenazin or Perphenazinum or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triphenot).tw,kf,kw. (9979)
304 pf 217830/ or (PF-00217830 or PF-217830).tw,kf,kw. (15)
305 pf 3463275/ or ("PF 03463275" or PF-0346275 or PF-03463275 or PF-3463275).tw,kf,kw. (34)
306 picobenzide/ or (Picobenzide or Picobenzida or Picobenzidum).tw,kf,kw. (32)
307 piflutixol/ or (piflutixol or Piflutixolum or "trans piflutixol-(E)" or trans-Piflutixol).tw,kf,kw. (166)
308 pimavanserin/ or (pimavanserin or Nuplazid).tw,kf,kw. (1220)
309 pimethixene/ or (Pimethixene or Calmixen or Calmixene or Mepithiathene or Pimethixen or Pimethixenum or PIMETIXENE or Pimetixeno).tw,kf,kw. (47)
310 Pimozide/ or (Pimozide or Antalon or Opiran or Orap or "R 623" or "R 6238" or R-623 or R6238 or R-6238).tw,kf,kw. (12156)
311 pipamperone/ or (pipamperone or Dipiperal or Dipiperon or Dipiperone or Floropipamide or Fluoropipamide or Pipamperon or Pipamperona or Pipamperonum or Pipaneperone or Piperonil or Piperonyl or Propitan or "R 3345" or R-3345).tw,kf,kw. (4681)
312 piperacetazine/ or (piperacetazine or Piperacetazina or Piperacetazinum or Piperazetazina or Psymod or Quide).tw,kf,kw. (219)
313 pipotiazine/ or (pipotiazine or Lonseren or Piportil or Pipothiazine or Pipotiazina or Pipotiazinum or RP 19366 or RP-19366).tw,kf,kw. (905)
314 pipotiazine palmitate/ or (Pipotiazine palmitate or Piportil depot or Pipothiazin palmitate or Pipothiazine palmitate or Pipotiazin Retard or Pipotiazine Palmitic Ester or pipotiazine-palmitate).tw,kf,kw. (375)
315 pirenperone/ or (pirenperone or Pirenperona or Pirenperonum or R 47465 or "R-47,465" or R-47465).tw,kf,kw. (454)
316 pomaglumetad methionil/ or (pomaglumetad methionil or LY 2140023 or LY2140023 or LY-2140023).tw,kf,kw. (289)
317 Prochlorperazine/ or prochlorperazine edisylate/ or prochlorperazine maleate/ or (Prochlorperazine or CHLOPERAZINE or Chlormeprazine or Chloropernazine or Chlorperazine or Proazine or Prochloroperazine or Prochlorpemazine or Prochlorperazin or Prochlorperazinum or Prochlorpermazine or Procloperazine or Proclorperazina or Proclorperazine or Tementil or Temetid or Vertigon).tw,kf,kw. (8534)
318 profenamine/ or (profenamine or Ethapropazine or Ethopromazine or ethopropazine or Etopropezina or Fempropazine or Fenpropazina or Isopthazine or Isotazin or Isothazine or Isothiazine or Lysivane or Pardisol or Parfezine or Parkin or Parphezein or Parsidol or Parsitan or Parsotil or Phenopropazine or Phenoprozine).tw,kf,kw. (12817)
319 Promazine/ or (Promazine or Prazin or Prazine or Promazin or Promazina or Promazinum or Promwill or Propazinum or Protactyl or Sinophenin or Sparine).tw,kf,kw. (4184)
320 propiomazine/ or propiomazine maleate/ or (propiomazine or Largon or Phenoctyl or Propavan or Propiomazina or Propiomazinum or Propionylpromethazine).tw,kf,kw. (358)
321 propionylpromazine/ or (propionylpromazine or Combilen or Propionpromazine or Propionylpromazone or Propiopromazine).tw,kf,kw. (146)
322 prothipendyl/ or (prothipendyl or Dominal or Largophren or Phrenotropin or Prothipendylum or Protipendilo or Timoval or Timovan or Tolnate or Tumovan).tw,kf,kw. (621)
323 Quetiapine Fumarate/ or (quetiapine or Seroquel).tw,kf,kw. (38531)
324 Raclopride/ or raclopride tartrate/ or (Raclopride or "FLA 870" or FLA-870 or FLA870 or "FLB 472" or FLB-472 or FLB472).tw,kf,kw. (8728)
325 ralmitaront/ or ralmitaront.tw,kf,kw. (16)
326 Remoxipride/ or Remoxipride.tw,kf,kw. (1610)
327 Reserpine/ or (Reserpine or Raunervil or Raupasil or Rausedil or Rausedyl or Serpasil or Serpivite

or "V Serp" or V-Serp).tw,kf,kw. (41997)
328 rimcazole/ or (rimcazole or BW 234U or BW-234U or Rimcazol or Rimcazolum).tw,kf,kw. (523)
329 Risperidone/ or (Risperidone or Risperdal or "R 64,766" or "R 64766" or "R-64,766" or R-64766 or "R64,766" or R64766 or Risperidone).tw,kf,kw. (61457)
330 Ritanserin/ or (Ritanserin or "6-(2-(4-(Bis(4-fluorophenyl)methylene)-1-piperidinyl)ethyl)-7-methyl-5H-thiazolo(3,2-a)pyrimidin-5-one" or "R 55667" or R-55667 or R55667).tw,kf,kw. (4505)
331 roluperidone/ or (roluperidone or MIN-101 or Roluperidon).tw,kf,kw. (219)
332 romergoline/ or Romergoline.tw,kf,kw. (0)
333 savoxepine/ or (savoxepine or Cipazoxapine or Savoxepin or Savoxepina or Savoxepinum).tw,kf,kw. (59)
334 sb 773812/ or "sb 773812".tw,kf,kw. (9)
335 seridopidine/ or seridopidine.tw,kf,kw. (0)
336 setoperone/ or (setoperone or SEPTOPERONE or Setoperona or Setoperonum).tw,kf,kw. (298)
337 Spiperone/ or (Spiperone or Espiperona or Spiperonum or Spiroperidol or Spiroperidone or Spiropitan).tw,kf,kw. (11094)
338 sulforidazine/ or (sulforidazine or Psychoson or Solforidazina or Sulforidazina or Sulforidazinum or Thioridazine 2-Sulfone Thioridazine sulfone or Thioridazine sulphone or Thioridazine-2-sulfone).tw,kf,kw. (203)
339 suvecaltamide/ or (suvecaltamide or Suvecaltamide).tw,kf,kw. (12)
340 Sulpiride/ or (Sulpiride or Aiglonyl or Arminol or Deponerton or Desisulpid or Digton or Dogmatil or Dolmatil or Eglonyl or Ekilid or Guastil or Lebopride or Meresa or neogama or Pontiride or Psicocen or Sulp or Sulperide or Sulpitil or Sulpivert or Sulpor or Synedil or Tepavil or "Vertigo Meresa" or "vertigo neogama" or Vertigo-Meresa or vertigo-neogama).tw,kf,kw. (21188)
341 Tefludazine/ or (tefludazine or Tefludazina or Tefludazinum).tw,kf,kw. (44)
342 Tetrabenazine/ or deutetrabenazine/ or (tetrabenazine or Nitoman or tetra Benazin or Tetrabenazin or Tetrabenazina or Tetrabenazinum or Tetrabenzaine or Tetrabenzine or Xenazine).tw,kf,kw. (5987)
343 Thiopropazate/ or (thiopropazate or Dartal or Dartalan or Perphenazine acetate or Thiopropazat or Thiopropazatum or Tiopropazato).tw,kf,kw. (192)
344 Thioproperazine/ or (Thioproperazine or Sulfenazin or Thioperazine or Thioproperazin or Thioproperazinum or Thiproperazine or Tioproferazina or Tioproperazin or Tioproperazina or Vontil).tw,kf,kw. (719)
345 thioproperazine methanesulfonate/ or (thioproperazine methanesulfonate or Mageptyl or Majeptil or Thioperazine dimethanesulfonate or Thioperazine mesylate or Thioproperasine dimesylate or Thioproperazine bis-methanesulfonate or Thioproperazine dimesilate or Thioproperazine dimesylate or Thioproperazine dimethanesulfonate or THIOPROPERAZINE DIMETHANESULPHONATE or Thioproperazine mesilate or Thioproperazine mesylate or Thioproperazine methanesulfonate or Thioproperazinum).tw,kf,kw. (224)
346 Thioridazine/ or (Thioridazine or Aldazine or Apo-Thioridazine or ApoThioridazine or Meleril or Mellaril or Melleretten or Melleril or Melleryl or Melzine or Rideril or Sonapax or Thioridazine-neurazpharm or Thioridazineneurazpharm or Thiozine).tw,kf,kw. (16455)
347 Thiothixene/ or (Thiothixene or cis-Thiothixene or Navan or Navane or Navaron or Orbinamon or Tiotixene or Tiotixeno or Tiotixenum).tw,kf,kw. (3333)
348 Tiapride Hydrochloride/ or (Tiapride or Equilium or "FLO 1347" or FLO-1347 or FLO1347 or Tiapridal or Tiapridex or Tiaprizal).tw,kf,kw. (2950)
349 Tilapertin/ or Tilapertin.tw,kf,kw. (0)
350 Timiperone/ or (timiperone or Timiperona or Timiperonum or Tolopelon).tw,kf,kw. (160)
351 Trifluoperazine/ or (Trifluoperazine or Apo-Trifluoperazine or ApoTrifluoperazine or Eskazine or Flupazine or Stelazine or Terfluzine or Trifluoroperazine or Triftazin).tw,kf,kw. (16631)
352 Trifluperidol/ or (Trifluperidol or Trisedil).tw,kf,kw. (751)
353 Triflupromazine/ or (Triflupromazine or Fluopromazine or Siquil or Triflupromazine).tw,kf,kw. (1810)
354 tulrampator/ or tulrampator.tw,kf,kw. (3)
355 ulotaront/ or ulotaront.tw,kf,kw. (75)
356 umespirone/ or umesprione.tw,kf,kw. (18)
357 vabicaserin/ or vabicaserin.tw,kf,kw. (87)
358 zetidoline/ or (zetidoline or Zetidolina or Zetidolinum).tw,kf,kw. (99)
359 zicronapine/ or zicronapine.tw,kf,kw. (18)

360 zoloperone/ or (zoloperone or Zoloperona or Zoloperonum).tw,kf,kw. (12)
361 or/194-360 (599833)
362 (12 and 193 and 361 and 124) not 186 (549)
363 remove duplicates from 362 (400)
364 Early ambulation/ (41912)
365 (joint mobilization/ or mobilization/) use oemezd (40177)
366 exp Exercise therapy/ or exp kinesiotherapy/ (161133)
367 exp Movement/ or exp "movement(physiology)"/ (1162210)
368 exp Musculoskeletal Manipulations/ or exp musculoskeletal manipulation/ (23072)
369 exp Physical Therapy Modalities/ or exp physiotherapy/ (287379)
370 Activities of daily living/ or Daily life activity/ (192369)
371 Rehabilitation/ (138200)
372 Rehabilitation, vocational/ or vocational rehabilitation/ (24850)
373 "Physical and rehabilitation medicine"/ (13108)
374 Exercise/ (507994)
375 Physical therapy modalities/ (138131)
376 Range of motion, articular/ (111446)
377 Recovery of function/ (111255)
378 Muscle strength/ (108054)
379 exp Mobilization/ use oemezd (38668)
380 Joint mobilization/ use oemezd (1576)
381 Physical activity/ use oemezd (212979)
382 Physical Mobility/ use psyh (2931)
383 (Mobili* or physical therapy* or physiotherap* or physical function* or exercis* or activit* of daily living or ADL or rehab* or range of motion or ROM or recovery of function or muscle strength or physical activit* or recovery of function or ambulate or ambulation or mobilise or mobilize or mobilisation or mobilization or mobility or movement).tw,kf,kw. (3365505)
384 or/364-383 (4546139)
385 (12 and 384 and (124 or 176)) not 186 (23459)
386 limit 385 to yr=2022-2024 (3368)
387 remove duplicates from 386 (2452)
388 exp Respiration, Artificial/ or exp artificial ventilation/ (331621)
389 exp Ventilators, Mechanical/ or exp mechanical ventilator/ (16997)
390 ((artificial* or mechanical* or invasive* or high-frequency or positive-pressure or "positive pressure" or negative-pressure or "negative pressure") adj3 (respirat* or ventilat*)).tw,kf,kw. (241370)
391 (artificial airway? or controlled ventilation).tw,kf,kw. (7345)
392 or/388-391 (430709)
393 exp Dexmedetomidine/ or (Dexmedetomidine or "(+)-4-((S)-.ALPHA.,2,3-TRIMETHYLBENZYL)IMIDAZOLE" or "(+)-4-((S)-alpha,2,3-Trimethylbenzyl)imidazole" or "(S)-4-(1-(2,3-dimethylphenyl)ethyl)-1H-imidazole" or "(S)-4-[1-(2,3-Dimethylphenyl)ethyl]-1H-imidazole" or "(S)-5-(1-(2,3-Dimethylphenyl)ethyl)-1H-imidazole" or 108D583 or 113775-47-6 or "1H-Imidazole, 4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-" or "1H-Imidazole, 5-[(1S)-1-(2,3-dimethylphenyl)ethyl]-" or "4-[(1~{S})-1-(2,3-dimethylphenyl)ethyl]-1~{H}-imidazole" or "4-[(1S)-1-(2,3-Dimethylphenyl)ethyl]-1H-imidazol" or "4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole" or "4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-3H-imidazole" or "4-[(s)-1-(2,3-dimethyl-phenyl)-ethyl]-1h-imidazole" or "5-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole" or 67VB76HONO or AB01566872_01 or AB01566872_02 or AKOS025149503 or AKOS026750524 or AS-68685 or "bxcl 501" or bxcl501 BDBM50085683 or C07450 or CCG-266586 or "CHEBI:4466" or CHEMBL778 or CS-0012295 or cepedex or D00514 or DB00633 or "da 9051" or da9051 or delos or Dexdor or Dexmedetomidina or "DexmedetomidineHclC13H16N2.Hcl" or Dexmedetomidinum or dexdomitor or dexdor or DTXSID10873388 or EN300-127736 or GTPL521 or HMS3885M07 or HY-12719 or Igalmi or Medetomidine or MFCD00880557 or "MPV 1440" or MPV-1440 or NCGC00025347-01 or NCGC00371080-02 or NCGC00371080-09 or Precedex or primadex or Q412133 or s3075 or SCHEMBL26433 or sedadex or sileo or SW219607-1 or Tocris-2023 or "TPU 006" or tpu006 or UNII-67VB76HONO or ZINC4632106).tw,kf,kw. (31137)
394 Propofol/ or ("2, 6-Diisopropylphenol" or "2,6 Diisopropylphenol" or "2,6-Bis(1-methylethyl)phenol" or "2,6-bis(Isopropyl)phenol" or "2,6-bis(propan-2-yl)phenol" or "2,6-di isopropyl phenol" or "2,6-di(propan-2-

yl)phenol" or "2,6-Diisopropyl phenol" or "2,6-diisopropyl-phenol" or "2,6-Diisopropylphenol" or "2,6-Di-iso-propylphenol-d18" or "2,6-dipropan-2-ylphenol" or "BIDD:GT0436" or "CHEBI:44915" or "BRN 1866484" or "EINECS 218-206-6" or "ghl.PD_Mitscher_leg0.558" or "HSDB 7123" or "ICI 35,868" or "ICI 35868" or "ICI 35-868" or "ICI35,868" or "MLS-0318084.P017" or "NSC 5105" or "Pharmakon1600-01505022" or "Phenol, 2, 6-bis(1-methylethyl)-" or "Phenol, 2,6-bis(1-methylethyl)" or "Phenol, 2,6-bis(1-methylethyl)-" or "Phenol, 2,6-diisopropyl-" or "Phenol,6-bis(1-methylethyl)-" or "Phenol,6-diisopropyl-" or "SDCCGMLS-0318084.P029" or "SDCCGSBI-0050422.P002" or 2078-54-8 or 3f33 or 3p50 or A814898 or AB00513968 or AB00513968_08 or AB00513968-07 or AC-2038 or AC8633 or AI3-26295 or AKOS009159417 or ALBB-036351 or AM90311 or Ampofol or Anepol or Anesia or Aquafo or Aquafol or AS-13299 or BCP02920 or BCP0726000298 or BDBM50058046 or Biomol-NT_000248 or BPBio1_000950 or BPBio1_000969 or BRD-K82255054-001-03-5 or BRD-K82255054-001-08-4 or BSPBio_000862 or C07523 or CAS-2078-54-8 or CCG-204529 or "CCRIS 9000" or CHEMBL526 or cryotol or CS-W020057 or D00549 or D0617 or D126608 or DB00818 or DDS-04F or diisoprofol or Diisopropylphenol or Dipravan or Diprifusor or Diprivan or Diprofol or Disoprivan or Disoprofol or DTXSID6023523 or EN300-52468 or EU-0100437 or Fresofol or gobbifol or GTPL5464 or hiremon or HMS1570L04 or HMS2089O21 or HMS2094E17 or HMS2097L04 or HMS2231E16 or HMS3259E03 or HMS3261G16 or HMS3369I16 or HMS3714L04 or HY-B0649 or "ici 35 868" or "ici 35868" or ICI-35868 or Ivofol or Lipuro or Lopac0_000437 or Lopac-D126608 or LP00437 or MFCD00008885 or MLS001066348 or MLS001335999 or MLS002454360 or MLS-0318084 or NC00449 or NCGC00015389-01 or NCGC00015389-02 or NCGC00015389-03 or NCGC00015389-04 or NCGC00015389-05 or NCGC00015389-06 or NCGC00015389-07 or NCGC00015389-08 or NCGC00015389-09 or NCGC00015389-10 or NCGC00015389-11 or NCGC00015389-14 or NCGC00015389-17 or NCGC00091538-01 or NCGC00091538-02 or NCGC00091538-03 or NCGC00091538-04 or NCGC00091538-05 or NCGC00091538-06 or NCGC00257228-01 or NCGC00260670-01 or NCGC00261122-01 or NSC5105 or NSC-5105 or NSC758909 or NSC-758909 or plofed or Pofol or Prestwick0_000931 or Prestwick1_000931 or Prestwick2_000931 or Prestwick3_000931 or profast or propocam or "propofol lipuro" or Propofol-Lipuro or Propofolum or propolipid or Propovan or Propoven or provive or rapinovet or Q-201631 or Q422740 or Rapinovet or rapiva or recofol or "recofol n" or ripol or safol or SCHEMBL36245 or SMR000059151 or SPBio_003031 or SPECTRUM1505022 or spifol or spival SR-01000075468 or SR-01000075468-1 or SR-01000075468-4 or SR-01000075468-6 or SY013479 or Tox21_110134 or Tox21_110134_1 or Tox21_201371 or Tox21_303225 or Tox21_500437 or unifol or UNII-YI7VU623SF or YI7VU623SF or ZD-0859 or ZINC968303).tw,kf,kw. (87152)

395 (12 and 392 and 393 and 394 and (124 or 176)) not 186 (632)

396 remove duplicates from 395 (576)

397 Melatonin/ or (melatonin or "5-methoxy n-acetyl-tryptamine" or "BRN 0205542" or "CCRIS 3472" or "EINECS 200-797-7" or "J5.258B" or "NSC 113928" or "3-N-Acetyl-5-methoxyl tryptamine" or "BIDD:ER0618" or "SDCCGMLS-0065812.P001" or "SDCCGMLS-0065812.P002" or "SDCCGSBI-0050765.P003" or 005M655 or 0E2B08C1-B325-45B1-8939-6F9081EFDFA4 or 5-22-12-00042 or 5-methoxy-N-acetyltryptamine or A929721 or AB00053279 or AB00053279_12 or AB00053279-10 or AC-10019 or Acetamide or ACT03490 or adaflex or AKOS000276269 or AMY33320 or "apl 510" or apl510 or aritonin or BA164660 or "bci 049" or bci049 or BCI-049 or BCP28154 or BDBM9019 or BPBio1_000590 or BRD-K97530723-001-07-6 or BRD-K97530723-001-11-8 or BSPBio_000536 or BSPBio_003006 or C01598 or CAS-73-31-4 or CCG-38837 or celton or ceyestaeusom or ceyesto CHEMBL45 or ChemDiv2_003916 or circadin or civasta or CS-1769 or D08170 or DB01065 or DivK1c_000353 or DTXSID1022421 or EN300-6486827 or EU-0100787 or eusom or F1929-1777 or FT-0628191 or FT-0658928 or FT-0670984 or GLXC-25215 or GTPL1357 or GTPL224 or Guna-dermo or HMS1380B22 or HMS1569K18 or HMS1921E04 or HMS2089F09 or HMS2096K18 or HMS2233D23 or HMS3262M16 or HMS3370J20 or HMS3413P14 or HMS3654A22 or HMS3677P14 or HMS3713K18 or HMS3884M05 or HMS501B15 or HSCI1_000400 or HSDB 7509 or HY-B0075 or IDI1_000353 or IDI1_002631 or "jan 13004" or jan13004 or jl5dk93rcl or KBio1_000353 or KBio2_000665 or KBio2_003233 or KBio2_005801 or KBio3_002226 or KBioGR_000591 or KBioSS_000665 or "ki 1001" or ki1001 or KS-1454 or L001261 or lestinora or Lopac0_000787 or Lopac-M-5250 or LP00787 or M 5250 or M1105 or M-1200 or M-1250 or Melapure or Melatobel or mallozen or mecastrin or melabiorytm or melatal or melatan or melatol or melatonina or melatonine or melatonite or mellaras or mellozzan or melovine or MFCD00005655 or MLS000859594 or MLS001055382 or MLS001240204 or mucomel or N-Acetyl-5-methoxytryptamine or N-acetyl-5-methoxy-tryptamine or NCGC00015680-01 or NCGC00015680-02 or NCGC00015680-03 or

NCGC00015680-04 or NCGC00015680-05 or NCGC00015680-06 or NCGC00015680-07 or NCGC00015680-08 or NCGC00015680-09 or NCGC00015680-10 or NCGC00015680-11 or NCGC00015680-12 or NCGC00015680-13 or NCGC00015680-14 or NCGC00015680-15 or NCGC00015680-16 or NCGC00015680-18 or NCGC00015680-35 or NCGC00090727-01 or NCGC00090727-02 or NCGC00090727-03 or NCGC00090727-04 or NCGC00090727-05 or NCGC00090727-06 or NCGC00090727-07 or NCGC00090727-08 or NCGC00090727-09 or NCGC00256404-01 or NCGC00259077-01 or NCGC00261472-01 or NCI60_004378 or NINDS_000353 or noxarem or NSC113928 or NSC-113928 or NSC56423 or NSC-56423 or oniria or Oprea1_104553 or Oprea1_814234 or orlogin or Posidorm or Prestwick_312 or Prestwick0_000458 or Prestwick1_000458 or Prestwick2_000458 or Prestwick3_000458 or Primex or Q180912 or regulin or S1204 or SCHEMBL19018 or sental or slenyto or sloremina or SMP2_000309 or SMR000326666 or "sp 13004" or sp13004 or SPBio_001527 or SPBio_002475 or Spectrum_000185 or SPECTRUM1500690 or Spectrum2_001344 or Spectrum3_001393 or Spectrum4_000066 or Spectrum5_001745 or SR-01000075559 or SR-01000075559-1 or SR-01000075559-6 or SR-01000075559-7 or SR-01000075559-8 or STK386880 or SW196607-4 or SY051401 or syncrodin or TNP00300 or Tox21_110195 or Tox21_110195_1 or Tox21_201527 or Tox21_302926 or Tox21_500787 or UNII-JL5DK93RCL or waferest or Z1191880499 or ZINC57060).tw,kf,kw. (94661)
398 (12 and 397 and (124 or 176)) not 186 (432)
399 remove duplicates from 398 (301)
400 187 or 362 or 387 or 395 or 398 (4819)
401 400 use oemezd (4068)
402 400 use medall (687)
403 400 use psyh (64)

Search Name: PADIS
Date Run: 11/05/2023 19:37:45
Comment: Kim Lewis

ID Search Hits
#1 MeSH descriptor: [Critical Care] explode all trees 2656
#2 MeSH descriptor: [Critical Care Nursing] explode all trees 61
#3 MeSH descriptor: [Critical Illness] explode all trees 3231
#4 MeSH descriptor: [Intensive Care Units] explode all trees 5239
#5 (((acute* or intensive* or critical* or neurointensive* or neuro-intensive* or neurocritical* or neuro-critical*) next (care or therap* or treatment* or unit?)) or healthcare facilit* or health-care facilit*) 144467
#6 (ICU or MICU or CICU or CVICU or CCU or SICU or POCCU or ITU or HDU or ICUs or MICUs or CICUs or CVICUs or CCUs or SICUs or POCCUs or ITUs or HDUs):ti 2420
#7 ((ICU or MICU or CICU or CVICU or CCU or SICU or POCCU or ITU or HDU or ICUs or MICUs or CICUs or CVICUs or CCUs or SICUs or POCCUs or ITUs or HDUs) and ((acute* or intensive* or critical* or neurointensive* or neuro-intensive* or neurocritical* or neuro-critical*) next (care or therap* or treatment* or unit?))) 12419
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7 146358
#9 MeSH descriptor: [Anxiety] explode all trees 13016
#10 MeSH descriptor: [Anxiety Disorders] explode all trees8908
#11 MeSH descriptor: [Adjustment Disorders] explode all trees 271

#12 MeSH descriptor: [Mutism] explode all trees 21
#13 (anxiet* or anxious* or panic* or phobi* or agoraphobi* or GAD or mute or mutism or nervous* or restless* or stress* or PTSD or obsessive compulsive or obsessive-compulsive or OCD or adjustment disorder* or neurotic or neuroses) 176497
#14 #9 or #10 or #11 or #12 or #13 176666
#15 MeSH descriptor: [Benzodiazepines] explode all trees 10549
#16 benzodiazepine or benzodiazepines 6994
#17 #8 and #14 and (#15 or #16) in Trials 392
#18 MeSH descriptor: [Delirium] explode all trees 1386
#19 MeSH descriptor: [Confusion] explode all trees 1635
#20 MeSH descriptor: [Hallucinations] explode all trees 431
#21 bewilderment or confusion* or deliria* or delirious* or delirium* or disorientation or hallucinat* 11836
#22 #18 or #19 or #20 or #21 11836
#23 MeSH descriptor: [Antipsychotic Agents] explode all trees 5633
#24 (antipsychotic* or anti-psychotic* or ((neuroleptic or neuroleptics) next (agent or agents or drug or drugs)) or ((butyrophenone or major or phenothiazine) next (tranquilis* or tranquiliz*)) or neuroleptic*) 12906
#25 #23 or #24 12906
#26 #8 and #22 and #25 in Trials 185
#27 MeSH descriptor: [Early Ambulation] explode all trees 450
#28 MeSH descriptor: [Exercise Therapy] explode all trees 19456
#29 MeSH descriptor: [Movement] explode all trees 47076
#30 MeSH descriptor: [Musculoskeletal Manipulations] explode all trees 4063
#31 MeSH descriptor: [Physical Therapy Modalities] explode all trees 35523
#32 MeSH descriptor: [Activities of Daily Living] explode all trees 12969
#33 MeSH descriptor: [Rehabilitation] explode all trees 50681
#34 MeSH descriptor: [Rehabilitation, Vocational] explode all trees 544
#35 MeSH descriptor: [Physical and Rehabilitation Medicine] explode all trees 5843
#36 MeSH descriptor: [Exercise] explode all trees 38046
#37 MeSH descriptor: [Physical Therapy Modalities] explode all trees 35523
#38 MeSH descriptor: [Range of Motion, Articular] explode all trees 5958
#39 MeSH descriptor: [Recovery of Function] explode all trees 6354
#40 MeSH descriptor: [Muscle Strength] explode all trees 8574
#41 (ambulate or ambulation or mobilise or mobilize or mobilisation or mobilization or mobility or movement) 64179
#42 #27 or #28 or #30 or #31 or #41 93926
#43 #8 and #42 with Publication Year from 2022 to 2023, in Trials 662
#44 MeSH descriptor: [Respiration, Artificial] explode all trees 8219
#45 MeSH descriptor: [Ventilators, Mechanical] explode all trees 366
#46 ((artificial* or mechanical* or invasive* or high-frequency or positive-pressure or "positive pressure" or negative-pressure or "negative pressure") near 3 (respirat* or ventilat*)) 1293
#47 (artificial airway? or controlled ventilation) 35372
#48 #44 or #45 or #46 or #47 37856
#49 MeSH descriptor: [Dexmedetomidine] explode all trees 2498

#50 #49 or dexmedetomidine 7988
#51 MeSH descriptor: [Propofol] explode all trees 5609
#52 #51 or propofol 17439
#53 #8 and #48 and #50 and #52 in Trials 141
#54 MeSH descriptor: [Melatonin] explode all trees 1505
#55 #54 or melatonin 3716
#56 #8 and #55 in Trials 280
#57 #17 or #26 or #43 or #53 or #56 1607

ClinicalTrials.gov
Searches run May 11, 2023

PICO 1
Condition/disease: ("critical care" OR "intensive care" OR "critical illness" OR neurointensive OR neuro-intensive OR neurocritical OR ICU OR CCU OR MICU OR CICU) AND (anxiety OR anxious OR panic OR phobia OR stress OR PTSD OR OCD OR neurotic OR neuroses)
AND
Other terms: (benzodiazepine OR benzodiazepines OR chlordiazepoxide OR clobazam OR clonazepam OR clorazepate OR diazepam OR flumazenil OR flunitrazepam OR flurazepam OR lorazepam OR midazolam OR nitrazepam OR olanzapine OR oxazepam OR pirenzepine OR temazepam)
OR
Afizagabr OR alprazolam OR amitriptyline OR anthramycin OR arfendazam OR camazepam OR carburazepam OR ceclazepide OR cinolazepam OR dealikylflurazepam OR delorazepam OR demoxepam OR devazepide OR soxefazepam OR estazolam OR fludiazepam
OR
flutoprazepam OR fosazepam OR gidazepam OR girisopam OR halazepam OR loflazepate OR loprazolam OR lormetazepam OR lotrafiban OR meclonazepam OR medazepam OR metaclazepam OR nitrosochlordiazepoxide OR nastorazepide OR nerisopam OR nimetazepam
OR
nocrchlordiazepoxide OR norclobazam OR nordazepam OR norfludiazepam OR norflunitrazepam OR osugacestat OR pamozirine OR phenazepam OR pinazepam OR prazepam OR quazepam OR Remimazolam OR talampanel OR Talirine OR Tampramine OR Tarazepide
OR
Tibezonium OR tifluadom OR Tofisopam OR tomaymycin OR tuclazepam

Limited to "adult" or "older adult"
Results: 9 studies

PICO 2
Condition/disease: ("critical care" OR "intensive care" OR "critical illness" OR neurointensive OR neuro-intensive OR neurocritical OR ICU OR CCU OR MICU OR

CICU) AND (delirium OR delirious OR confusion OR confused OR hallucinate OR hallucination OR Hallucinations)
AND
Other terms: antipsychotic OR neuroleptic OR aripiprazole OR Chlorpromazine OR Clozapine OR Fluphenazine OR Haloperidol OR Lamotrigine OR Olanzapine OR Profenamine OR Quetiapine OR Reserpine OR Risperidone OR Sulpiride OR Thioridazine OR Trifluoperazine
OR
Aceperone OR acepromazine OR aceprometazine OR acetophenazine OR adoprazine OR alimemazine OR amitriptyline OR aplindore OR amisulpride OR balipodect OR benperidol OR Berupipam OR bitopertin OR blonanserin OR brofoxine OR bromospiperone
OR
bromperidol OR butaperazine OR carfenazine OR cariprazine OR cariprazine OR carpipramine OR carvotroline OR cenbutindole OR chlorphenethazine OR chlorproethazine OR chlorprothixene OR cinuperone OR clocapramine OR cloflumide OR clofluperol
OR
clopenthixol OR clopimozide OR clopipazan OR clospipramine OR clotiapine OR cyamemazine OR dimetotiazine OR dizyrazine OR dolasetron OR droperidol OR duoperone OR etazolate OR etymemazine OR evenamide OR farampator OR fluanison OR flupenthixol OR flupentixol
OR
fluspirilene OR flutroline OR gevetroline OR iclepertin OR isofloxythepin OR isomolpan OR landipirdine OR lenpoerone OR loxapine OR lurasidone OR luvadaxistat OR mardepodect OR maroxepine OR mazapertine OR mepiprazole or mesoridazine OR methiothepin OR methopromazine
OR
methotrimeprazine OR metofenazate OR molindone OR moperone OR neboglamine OR noctran OR norchlorpromazine OR oxiperomide OR oxypertine OR oxyprothepine OR paliperidone OR pecazine OR penfluridol OR perazine OR periciazine OR perimetazine
OR
perphenazine OR picobenzide OR piflutixol OR pimavanserin OR pimethixene OR pimozide OR pipamperone OR piperacetazine OR piptiazine OR pipotiazine OR pirenperone OR "pomaglumetad methionil" OR prochlorperazine OR promazine OR proplomazine
OR
proplonylpromazine OR prothipendyl OR raclopride OR ralmitaront OR rimcazole OR ritanserin OR roluperidone OR romergoline OR savoxepine OR seridopidine OR setoperone OR spiperone OR sulforidazine OR suvecaltamide OR tefludazine OR Tetrabenazine
OR
thiopropazate OR thioproperazine OR thiothixene OR tiapride OR tilapertin OR timiperone OR tulrampator OR utotaront OR umespirone OR vabicaserin OR zetidoline OR zicronapine

Limited to “adult” or “older adult”
Results: 61 studies

PICO 3
Condition/disease: ("critical care" OR "intensive care" OR "critical illness" OR neurointensive OR neuro-intensive OR neurocritical OR ICU OR CCU OR MICU OR CICU)
Other terms: (ambulate OR ambulation OR mobilise OR mobilize OR mobilization OR mobilization OR mobility OR movement OR physiotherapy OR manipulation OR kinesiotherapy OR "physical therapy" OR rehabilitation OR exercise)
Limited to “adult” or “older adult”
Results: 698 studies

PICO 4
Condition/disease: ("critical care" OR "intensive care" OR "critical illness" OR neurointensive OR neuro-intensive OR neurocritical OR ICU OR CCU OR MICU OR CICU) AND (artificial OR mechanical OR ventilation OR high-frequency OR pressure OR ventilate OR ventilated)
AND
Other terms: (dexmedetomidine OR Dexdor OR precede OR primadex OR sedadex) AND (propofol OR Aquafo OR Aquafol OR Ampofol OR anepol OR anesia OR diprofol OR disoprivan OR disoprofol OR dipravan OR diprifusor OR diprivan OR diprofol OR Disoprivan)
Limited to “adult” or “older adult”
Results: 25 studies

PICO 5
Condition/disease: ("critical care" OR "intensive care" OR "critical illness" OR neurointensive OR neuro-intensive OR neurocritical OR ICU OR CCU OR MICU OR CICU)
AND
Other terms: (melatonin OR mecastrin OR melabiorytm OR melatal OR melatan OR melatol OR melatonia OR melatonine OR meatonite OR mellaras OR mellozzan OR Melovine OR Oriogin Or Posidorm OR Primex OR gegulin OR sental OR slenyto OR sloremina OR waferest)

Limited to “adult” or “older adult”
Results: 38 studies

Embase <1974 to 2024 March 27>
APA PsycInfo <1806 to March Week 4 2024>
Ovid MEDLINE(R) ALL <1946 to March 27, 2024>

1 exp *Critical Care/ use medall 38582
2 *Critical Care Nursing/ use medall 2077
3 exp *Critical Illness/ use medall 20106
4 exp *Intensive Care Units/ use medall 45109
5 exp *Intensive Care/ use oemezd 290846
6 exp *Intensive Care Unit/ use oemezd 63124
7 exp Intensive Care/ use psyh 7505
8 (((acute* or intensive* or critical* or neurointensive* or neuro-intensive* or neurocritical* or neuro-critical*) adj (care or therap* or treatment* or unit?)) or healthcare facilit* or health-care facilit*).ti,kf,kw. 271175
9 (ICU or MICU or CICU or CVICU or CCU or SICU or POCCU or ITU or HDU or ICUs or MICUs or CICUs or CVICUs or CCUs or SICUs or POCCUs or ITUs or HDUs).ti. 42474
10 ((ICU or MICU or CICU or CVICU or CCU or SICU or POCCU or ITU or HDU or ICUs or MICUs or CICUs or CVICUs or CCUs or SICUs or POCCUs or ITUs or HDUs) and ((acute* or intensive* or critical* or neurointensive* or neuro-intensive* or neurocritical* or neuro-critical*) adj (care or therap* or treatment* or unit?))).tw,kf,kw. 177409
11 (intensive care unit? or intensive therapy unit? or burn unit? or coronary care unit? or high dependency unit? or recovery room? or respiratory care unit? or "acute hospital setting" or "acute hospital settings").tw,kf,kw. 440699
12 or/1-11 856840
13 exp Anxiety/ 518985
14 exp Anxiety Disorders/ or exp anxiety disorder/ 470739
15 Adjustment Disorders/ or adjustment disorder/ 10034
16 Mutism/ 5025
17 (anxiet* or anxious* or panic* or phobi* or agoraphobi* or GAD or mute or mutism or nervous* or restless* or stress* or PTSD or obsessive compulsive or obsessive-compulsive or OCD or adjustment disorder* or neurotic or neuroses).tw,kf,kw. 4714367
18 or/13-17 4941113
19 exp Benzodiazepines/ or exp Benzodiazepine derivative/ use oemezd or (Benzodiazepine or "1,2-Benzodiazepine" or 12794-10-4 or "1H-1,2-benzodiazepine" or 264-60-8 or "benzo diazepine" or benzodiazapine or benzodiazepin or benzodiazepines or CHEMBL4297264 or DB12537 or DTXSID90155730 or EN300-26945992 or M0Q7802G2B or Q27283309 or SCHEMBL8137 or UNII-M0Q7802G2B).tw,kf,kw. 417927
20 Afizagabar/ or (afizagabar or s44819 or S-44819).tw,kf,kw. 33
21 Alprazolam/ or (Alprazolam or Alprazolan or Alprox or "Apo Alpraz" or Apo-Alpraz or Cassadan or D-65MT or D65MT or Esparon or Kalma or Novo Alprazol or Novo-Alprazol or "Nu Alpraz" or Nu-Alpraz or Ralozam or Tafil or Trankimazin or "U-31,889" or "U31,889" or Xanax).tw,kf,kw. 27166

22 Amitriptyline plus chlordiazepoxide/ or "amitriptyline plus chlordiazepoxide".tw,kf,kw.25
23 Anthramycin/ or (Anthramycin or Antramicina or Antramycin or Antramycine or Antramycinum).tw,kf,kw. 441
24 Arfendazam/ or (Arfendazam or Arfendazamum).tw,kf,kw. 5
25 Benzodiazepine/ or Benzodiazepine Compounds/ or Benzodiazepines/ or (Benzodiazepine or benzo diazepine or benzodiazapine or benzodiazepin or CHEMBL4297264 or DB12537 or DTXSID90155730 or EN300-26945992 or M0Q7802G2B or Q27283309 or SCHEMBL8137 or UNII-M0Q7802G2B).tw,kf,kw. 144354
26 exp Benzodiazepinones/ or (Benzodiazepinones or Anxyrex or "Apo Bromazepam" or Apo-Bromazepam or Bromazepam or BromaLich or "Bromaz 1A Pharma" or Bromazanil or "bromazep von ct").tw,kf,kw. 338948
27 Bromazepam/ or (Bromazepam or Bromazepam-neuraxpharm or Bromazepam-ratiopharm or durazanil or Gen-Bromazepam or Lexatin or Lexomil or Lexotan or Lexotanil or "Ro 5-3350" or "Ro 53350" or "Von Ct, Bromazep").tw,kf,kw. 4777
28 Camazepam/ or (Camazepam or Albego or "B 5333" or Camazepamum or Limpidon or Nebolan or Panevril or Paxor or "SB 5833" or "S-58-33").tw,kf,kw. 324
29 Carburazepam/ or Uxepam/ or (Carburazepam or Carburazepamum or "Rgh 3331" or "RGH 3331" or RGH-3331 or Uxepam).tw,kf,kw. 17
30 Ceclazepide/ or Ceclazepide.tw,kf,kw. 0
31 Chlordiazepoxide/ or (Chlordiazepoxide or Chlozepid or Elenium or Librium or Methaminodiazepoxide).tw,kf,kw. 18145
32 Cinolazepam/ or (Cinolazepam or Cinolazepamum or Gerodorm or OX 373 or OX-373).tw,kf,kw. 51
33 Clobazam/ or (Clobazam or Frisium or "HR 376" or "LM 2717" or LM-2717 or LM2717 or Onfi or Urbanyl).tw,kf,kw. 11674
34 Clonazepam/ or (Clonazepam or "2H-1,4-Benzodiazepin-2-one, 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-" or Antelepsin or Clonazepam or Klonopin or Rivotril or "Ro 5-4023" or "Ro 54023").tw,kf,kw. 37970
35 Clorazepate/ or Clorazepate Dipotassium/ or Clorazepate potassium/ or (4306-CB or Clorazepate or Chlorazepate or Clorazepic Acid or Tranxene or Tranxilium).tw,kf,kw. 4938
36 Dealkylflurazepam/ or (Dealkylflurazepam or DIDEETHYLFLURAZEPAM or DIDESETHYLFLURAZEPAM).tw,kf,kw. 270
37 Delorazepam/ or (Delorazepam or Chlordemethyldiazepam or Clordesmetildiazepam or Dadumir or Delorazepamum or O-CHLORODESMETHYLDIAZEPAM).tw,kf,kw. 630
38 Demoxepam/ or (Demoxepam or Demossepam or Demoxepamum or "Ro 52092" or "Ro 5-2092" or RO5-2092 or Ro-52092 or RO-5-2092).tw,kf,kw. 294
39 Devazepide/ or (devazepide or je6p7qy7nh or "l 364,718" or "mk 329").tw,kf,kw. 2579
40 exp Diazepam/ or (Diazepam or "7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one" or Apaurin or Diazemuls or Faustan or Relanium or Seduxen or Sibazon or Stesolid or Valium).tw,kf,kw. 114829
41 Doxefazepam/ or (Doxefazepam or "Sas 643" or SAS-643).tw,kf,kw. 48

42 Estazolam/ or (Estazolam or D-40TA or D40TA or Estazolam or Nuctalon or ProSom or Tasedan).tw,kf,kw. 2090
43 Ethyl loflazepate/ or (Ethyl loflazepate or CM 6912 or CM-6912 or "Ethyl fluclozepate" or "ethyl loflazepate" or "Ethylis loflazepas" or "Loflazepate d'ethyle" or "Loflazepato de etilo" or Victan).tw,kf,kw. 382
44 Fludiazepam/ or (fludiazepam or Erispan or Fludiazepamum or "ID 540 OR ID-540").tw,kf,kw. 214
45 Flumazenil/ or (Flumazenil or Anexate or Flumazepil or Lanexat or "Ro 15 1788" or "Ro 15-1788" or "Ro 151788" or Romazicon).tw,kf,kw. 16336
46 Flunitrazepam/ or (Flunitrazepam or "Fluni 1A Pharma" or Flunibeta or Flunimerck or Fluninoc or Flunitrazepam-neuraxpharm or Flunitrazepam-ratiopharm or Flunitrazepam-Teva or flunizep or Fluridrazepam or Narcozep or RO-5-4200 or RO54200 or Rohipnol or Rohypnol).tw,kf,kw. 13268
47 Flurazepam/ or (Flurazepam or Apo-Flurazepam or Dalmadorm or Dalmane or Dormodor or Staurodorm).tw,kf,kw. 6689
48 Flutoprazepam/ or (Flutoprazepam or Flutoprazepamum or KB-509 or Restar or Restas).tw,kf,kw. 89
49 Fosazepam/ or (Fosazepam or Fosazepamum).tw,kf,kw. 40
50 Gidazepam/ or Gidazepam.tw,kf,kw. 83
51 Girisopam/ or (Girisopam or "EGIS 5810" or EGIS-5810 or Girisopamum or GYKI 51189 or GYKI-51189).tw,kf,kw. 48
52 Halazepam/ or (Halazepam or Halazepamum or Halezepam or Pacinone or Paxipam or "Sch 12041" or Sch-12041).tw,kf,kw. 468
53 Loflazepate/ or (loflazepate or CM-6913 or "CM 6913" or Loflazepic acid).tw,kf,kw. 251
54 Loprazolam/ or (loprazolam or "HR 158" or "HR 458" or Loprazolamum or "RU 31158" or "RU-31158" or Triazulenone).tw,kf,kw. 3259
55 Lorazepam/ or (Lorazepam or Apo-Lorazepam or Ativan or Donix or Duralozam or Durazolam or Idalprem or Laubeel or lorazep or Lorazepam or Lorazepam-neuraxpharm or Lorazepam-ratiopharm or Novo-Lorazem or "Nu Loraz" or Nu-Loraz or "Orfidal Wyeth" or Sedicepan or Sinestron or Somagerol or Temesta or "WY 4036" or WY-4036 or WY4036 or "Wyeth, Orfidal").tw,kf,kw. 39413
56 Lormetazepam/ or (Lormetazepam or Dormagen or Ergocalm or Loramet or Loretam or Lormetazepamum or Methyllorazepam or N-Methyllorazepam or Noctamid or Noctamide).tw,kf,kw. 2151
57 Lotrafiban/ or (Lotrafiban or R-Lotrafiban or SB 214857 or SB-214134 or SB-214857 or SB-214857A).tw,kf,kw. 213
58 Meclonazepam/ or (Meclonazepam or "Meclonazepam, (S)-isomer" or Meclonazepamum or "Ro 113128" or "Ro 11-3128" or "Ro 11-3128/002" or Ro-113128 or Ro-11-3128).tw,kf,kw. 191
59 Medazepam/ or (medazepam or Nivelton or Nobraksin or Nobral or Nobrium or Resmit or Rudotel).tw,kf,kw. 1635
60 Metaclazepam/ or (Metaclazepam or "Ka 2547" or Ka2547 or KA-2547 or "KC 2547" or KC-2547 or Metaclazepamum or Metaclazepan or Metuclazepam or Talis).tw,kf,kw. 249

61 Midazolam/ or (Midazolam or Dormicum or "Ro 21 3981" or Ro 21-3981 or "Ro 213981" or Versed).tw,kf,kw. 87100
62 n nitrosochlordiazepoxide/ or (Nitrosochlordizepoxide or 2-N-nitrosochlordiazepoxide or N-Nitrosochlordiazepoxide or N-Nitrosochlorodiazepoxide).tw,kf,kw. 14
63 Nastorazepide/ or (Nastrorazepide or "Z 360" or Z360 or Z-360).tw,kf,kw. 154
64 Nerisopam/ or (Nerisopam or "Gyki 52322" or GYKI-52322).tw,kf,kw. 41
65 Nimetazepam/ or (Nimetazepam or Dormalon or Hypnon or Methylnitrazepam or Nimetazepamum or "S 1530" or S-1530).tw,kf,kw. 254
66 Nitrazepam/ or (Nitrazepam or Alodorm or Dormalon or Dormo-Puren or Eatan or Imadorm or imeson or Mogadon or Nitrazadon or Nitrazep or Nitrodiazepam or Novanox or Radedorm or Remnos or Serenade or Somnite).tw,kf,kw. 8948
67 Norchlordiazepoxide/ or (Norchlordiazepoxide or Calsamin or Calsmin or "Dormicum (anticonvulsant)" or Dormin-5 or Dormo-Puren or Dumolid or Eatan or Epibenzalin or Epinelbon or Eunoctin or Eunoktin or Gerson or Hipnax or Hipsal or Ibrovek or Imeson or Imesont or Ipersed or Magadon or Megadon or Mitidin or Mogadan or Mogadon or Mogadone or N-Desmethylnimetazepam or Nelbon or Nelmat or Neozepam or Neuchlonic or Nitrados or Nitravet or Nitrazepamum or Nitrempax or Nitrenpax or Noctesed or Pacisyn or Paxisyn or Pelson or Persopit or Radedorm or Relact or Remnos or Somitran or Somnased or Somnibel or Somnite or Sonebon or Sonnolin or Trazenin or Unisomnia).tw,kf,kw. 1834
68 Norclobazam/ or (Norclobazam or "CLOBAZAM IMPURITY A" or "CLOBAZAM METABOLITE M9" or "Clobazam-M nor" or Clofazin or Demethylclobazam or N-Demethylclobazam or N-Desmethyl Clobazam-d5 or NOR-CLOBAZAM).tw,kf,kw. 335
69 Nordazepam/ or (Nordezepam or Calmday or Dealkylprazepam or Demethyldiazepam or Deoxydemoxepam or Desmethyldiazepam or Desalkylhalazepam or "Descyclopropylmethyl Prazepam" or Descyclopropylmethylprazepam or Destrifluoroethylhalazepam or N-Desalkylhalazepam or N-Descyclopropylmethyl-Prazepam or N-Descyclopropylmethylprazepam or N-Destrifluoroethylhalazepam or Nordaz or Nordazepam or Nordiazepam or Norprazepam or "Ro 5 2180" or "Ro 5-2180" or "Ro 52180" or Tranxilium or Vegesan).tw,kf,kw. 3959
70 Norfludiazepam/ or (Norfludiazepam or "CM 7116" or CM-7116 or Descarbethoxyloflazepate or "MIDAZOLAM IMPURITY F" or norflurazepam or nor-Flurazepam or Norflutoprazepam or "Ro 5-3367" or "Ro-053367" or "Ro-05-3367").tw,kf,kw. 72
71 Norflunitrazepam/ or (Norflunitrazepam or Demethylflunitrazepam or Desmethylflunitrazepam or N-Desmethylflunitrazepam or Nor-Flunitrazepam).tw,kf,kw. 172
72 Olanzapine/ or (Olanzapine or "2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno(2,3-b)(1,5)benzodiazepine" or "LY 170052" or "LY 170053" or LY-170052 or LY170052 or Zolafren or Zyprexa).tw,kf,kw. 60128
73 Osugacestat/ or (Osugacestat or "BMS 906024" or BMS-906024).tw,kf,kw. 102
74 Oxazepam/ or (Oxazepam or Abboxapam or Adumbran or Alepam or Ansioxacepam or Anxiolit or Aplakil or Astress or Azutranquil or Drimuel or Droxacepam or Durazepam or Lederpam or Limbial or Nesontil or Noctazepam or Nortemazepam or Nozepam or Ossazepam or Oxanid or Oxa-puren or Oxazepamum or Oxazipam or

Oxozepam or Pacienx or Praxiten or Propax or Psicopax or Psiquiwas or Quilibrex or Sedigoa or Serax or Serenid or Serenid-D or Serepax or Seresta or Serpax or Sigacalm or Sobril or Tacepam or Tarchomin or Tazepam or Uskan or Vaben or Zaxopam).ti,kf,kw. 10479
75 Pamozirine/ or (Pamozirine or 1343476-98-1 or NF6U5U2UEB or SC-DR002 or SCHEMBL18541706 or UNII-NF6U5U2UEB).tw,kf,kw. 4
76 Phenazepam/ or (Phenazepam or Fenazepam or PHENZITAT).tw,kf,kw. 1012
77 Pinazepam/ or (Pinazepam or Domar or Duna or Pinazepamum or Z-905).tw,kf,kw. 266
78 Pirenzepine/ or (Pirenzepine or Gastrotsepin or Gastrozepin or "L-S 519" or "LS 519" or "LS-519" or LS519 or "Piren basan" or Piren-basan or Pirenzepin or PPirenzepin-ratiopharm or Pyrenzepine or Ulcoprotect or Ulgescum).tw,kf,kw. 11762
79 Prazepam/ or (Prazepam or Centrax or Demetrin or Lysanxia or Reapam).tw,kf,kw. 1820
80 Quazepam/ or (Quazapam or Doral or Dormalin or Oniria or Prosedar or Quazepamum or Quazium or Sch 16134 or Sch-161 or Sch-16134).tw,kf,kw. 922
81 Remimazolam/ or (Remimazolam or CNS 7056 or CNS-7056 or ONO 2745 or ONO2745 or ONO-2745).tw,kf,kw. 1166
82 Talampanel/ or (Talampanel or GYKI 53773 or GYKI 537773 or GYKI-53773 or Kinampa or LY 300164 or LY300164 or LY-300164 or "talampanel(ly300164)").tw,kf,kw. 497
83 Talirine/ or (Talirine or 1Y234W15BL or UNII-1Y234W15BL).tw,kf,kw. 54
84 Tampramine/ or (Tampramine or UNII-47GSE5RM8N).tw,kf,kw. 2
85 Tarazepide/ or (Tarazepide or UNII-RK2972YZ2U).tw,kf,kw. 31
86 Temazepam/ or (Temazepam or "3 Hydroxydiazepam" or 3-Hydroxydiazepam or Dasuen or Euhypnos or Hydroxydiazepam or Levanxol or Methyloxazepam or Nocturne or "Norkotral Tema" or Normison or Normitab or Nortem or Oxydiazepam or Planum or "Pronervon T" or Remestan or Restoril or "Ro 5 5345" or Ro-5-5345 or Ro55345 or "SaH 47 603" or "SaH 47-603" or "SaH 47603" or Signopam or "Tema, Norkotral" or Temaze or "temazep von ct" or Temtabs or "Tenox or Von Ct, Temazep" or "WY 3917" or WY-3917 or WY3917).tw,kf,kw. 11969
87 Tibezonium iodide/ or (Tibezonium iodide or "Iodure de tibezonium" or "Ioduro de tibezonio" or Maxoral or "REC-15/0691" or Thiabenzazonium or Tibenzonio ioduro or Tibenzonium iodide or Tibezonii iodidum or "Tibezonium (iodide)").tw,kf,kw. 38
88 Tifluadom/ or (Tifluadom or "KC 5103" or KC-5103 or "KC 5911" or "KC 6128" or KC-5911 or KC-6128 or KC5103 or "Tifluadom/KC-5103" or titfluadom or UNII-TF8X866L0I).tw,kf,kw. 370
89 Tofisopam/ or (tofisopam or dextofisopam or EGYT-341 or Emandaxin or Grandaxin or levotofisopam or Tofisopamum or tofizopam).tw,kf,kw.615
90 Tomaymycin/ or Tomaymycin.tw,kf,kw. 144
91 Tuclazepam/ or (Tuclazepam or Tuclazepamum or UNII-343211YULR).tw,kf,kw. 0
92 or/19-91 476460
93 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. 705872
94 Randomized Controlled Trial/ 1426071

95 exp Randomized Controlled Trials as Topic/ 443312
96 "Randomized Controlled Trial (topic)"/ 270997
97 Controlled Clinical Trial/ 568221
98 exp Controlled Clinical Trials as Topic/ 458477
99 "Controlled Clinical Trial (topic)"/ 13458
100 Randomization/ 206168
101 Random Allocation/ 200968
102 Double-Blind Method/ 370293
103 Double Blind Procedure/ 217397
104 Double-Blind Studies/ 352718
105 Single-Blind Method/ 85402
106 Single Blind Procedure/ 54139
107 Single-Blind Studies/ 87468
108 Placebos/ 389973
109 Placebo/ 417555
110 Control Groups/ 113840
111 Control Group/ 113840
112 (random* or sham or placebo*).ti,ab,hw,kf,kw. 4824615
113 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. 676775
114 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. 4252
115 (control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw. 3282772
116 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw. 137421
117 allocated.ti,ab,hw. 215590
118 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw. 144004
119 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. 34017
120 (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw. 1794
121 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw. 18801
122 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. 42131
123 (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw. 171943
124 or/93-123 7034300
125 epidemiologic methods/ 269193
126 epidemiologic studies/ 268371
127 observational study/ 519397
128 observational studies as topic/ 375326
129 clinical studies as topic/ 167010
130 controlled before-after studies/ 248695
131 cross-sectional studies/ 991608
132 historically controlled study/ 259088
133 interrupted time series analysis/ 242234
134 exp seroepidemiologic studies/ 34231
135 national longitudinal study of adolescent health/ 387
136 cohort studies/ 1339996

137 cohort analysis/ 1480482
138 longitudinal studies/ 375779
139 longitudinal study/ 380071
140 prospective studies/ 1488215
141 prospective study/ 1594180
142 follow-up studies/ 2395111
143 follow up/ 2165358
144 followup studies/ 12402
145 retrospective studies/ 2501493
146 retrospective study/ 2782737
147 case-control studies/ 509070
148 exp case control study/ 1725945
149 cross-sectional study/ 1120631
150 observational study/ 519397
151 quasi experimental methods/ 540
152 quasi experimental study/ 13405
153 (observational study or validation studies or clinical study).pt. 159522
154 (observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. 633927
155 cohort*.ti,ab,kf,kw. 2595723
156 (prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. 1459057
157 ((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. 494005
158 ((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf,kw. 1016013
159 (retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf,kw. 1989566
160 ((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf,kw. 401857
161 (case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. 1370
162 (population adj3 (study or studies or analysis or analyses)).ti,ab,kf,kw. 659036
163 (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. 333460
164 ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. 14650
165 (cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf,kw. 1191463
166 ((natural adj experiment) or (natural adj experiments)).ti,ab,kf,kw. 9180
167 (quasi adj (experiment or experiments or experimental)).ti,ab,kf,kw. 66248
168 ((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw. 7603
169 (prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf,kw. 139012

170 or/125-169 12136250
171 ((case* adj5 control*) or (case adj3 comparison*) or case-comparison or control group*).ti,ab,id. not "Literature Review".md. 2050991
172 ((cohort or longitudinal or prospective or retrospective).ti,ab,id. or longitudinal study.md. or prospective study.md. or retrospective study.md.) not "Literature Review".md. 6136971
173 (cross section* or "prevalence study").ti,ab,id. 1498044
174 or/171-173 8988888
175 174 use psyh559259
176 170 or 175 12347197
177 exp animals/ 59021313
178 exp animal experimentation/ or exp animal experiment/ 3174482
179 exp models animal/ 2475868
180 nonhuman/ 7669635
181 exp vertebrate/ or exp vertebrates/ 57436824
182 177 or 178 or 179 or 180 or 181 61195746
183 exp humans/ 48201882
184 exp human experimentation/ or exp human experiment/ 670239
185 183 or 184 48205205
186 182 not 185 12992634
187 (12 and 18 and 92 and (124 or 176)) not 186 1080
188 remove duplicates from 187 880
189 exp Delirium/ use medall or exp *Delirium/ use oemezd or Delirium/ use psyh 34662
190 Confusion/ use medall or exp *Confusion/ use oemezd or Mental Confusion/ use psyh 10440
191 Hallucinations/ use medall or exp *Hallucination/ use oemezd or exp Hallucinations/ use psyh 29332
192 (bewilderment or confusion* or deliria* or delirious* or delirium* or disorientation or hallucinat*).tw,kf,kw,id. 256247
193 or/189-192 269797
194 exp Antipsychotic Agents/ use medall 129824
195 exp Neuroleptic Agent/ use oemezd 298078
196 exp Neuroleptic Drugs/ use psyh 34892
197 (antipsychotic* or anti-psychotic* or ((neuroleptic or neuroleptics) adj (agent or agents or drug or drugs)) or ((butyrophenone or major or phenothiazine) adj (tranquilis* or tranquiliz*)) or neuroleptic*).tw,kf,kw,id. 210912
198 ("1,2,3,6 tetrahydro 4 phenyl 1 [(3 phenyl 3 cyclohexen 1 yl)methyl]pyridine" or "ci 1007" or ci1007 or "pd 143188" or pd143188 or "150013−70−0").tw,kf,kw. 2123
199 ("2 [4 [4 (7,9 dioxo 6 thia 8 azaspiro[4.4]nonan 8 yl)butyl] 1 piperazinyl] 3 pyridinecarbonitrile" or "2 [4 [4 (7,9 dioxo 6 thia 8 azaspiro[4.4]nonan 8 yl)butyl] 1 piperazinyl] 3 pyridinecarbonitrile hydrochloride" or "2 [4 [4 (7,9 dioxo 6 thia 8 azaspiro[4.4]nonan 8 yl)butyl] 1 piperazinyl]pyridine 3 carbonitrile" or "bmy 13980" or "bmy 13980 1" or bmy13980 or bmy139801 or "mj 13980 1" or "mj 13980−1" or "mj 139801" or "mj13980 1" or "mj13980−1" or mj139801 or "85581−65−3").tw,kf,kw. 12

200 ("2 chloro 12 (3 dimethylamino 2 methylpropyl)dibenzo[d,g][1,3,6]dioxazocined" or "2 chloro 12 (2 methyl 3 dimethylaminopropyl) 12h dibenzo[d,g][1,3,6]dioxazocine monohydrochloride" or "2 chloro 12 (3 dimethylamino 2 methylpropyl)dibenzo[d,g][1,3,6]dioxazocine hydrochloride" or "egyt 2509" or egyt2509 or "70133−85−6").tw,kf,kw. 15
201 ("2 chloro n [alpha (2 piperidinyl)benzyl] 3 trifluoromethylbenzamide" or "2 chloro n [phenyl(piperidin 2 yl)methyl] 3 trifluoromethylbenzamide" or "ssr 504734" or ssr504734).tw,kf,kw. 126
202 ("2 cyclopropyl 5 [1 (2 fluoro 3 pyridinyl) 5 methyl 1h 1,2,3 triazol 4 yl] 2,3 dihydro 1h isoindol 1 one" or CFMTI or "864864−17−5").tw,kf,kw. 7
203 "2,3,3a,12b tetrahydro 3 methyl 1h dibenzo[b,f]oxepino[10,11 c]pyrrole".tw,kf,kw. 0
204 ("3 [3 (methylsulfonyl)phenyl] 1 propylpiperidine" or "3 (3 methylsulfonyl phenyl) 1 propyl piperidine" or "3 (3 methylsulfonyl phenyl) 1 propyl piperidine hydrochloride" or "3 [3 (methylsulfonyl)phenyl] 1 propylpiperidine hydrochloride" or "osu 6162" or osu6162 or "pnu 0096391" or "pnu 96391" or "pnu 96391a" or pnu0096391 or pnu96391 or pnu96391a or "156907−84−5").tw,kf,kw. 224
205 "6 n (2,2 diphenylethyl)adenosine".tw,kf,kw. 0
206 "7 hydroxychlorpromazine".tw,kf,kw. 92
207 "8 ethyl 7,8 dihydro 1,3,5 trimethyl 1h imidazo[1,2 c]pyrazolo[3,4 e]pyrimidine".tw,kf,kw. 7
208 aceperone/ or (aceperone or Aceperona or Aceperonum or Acetabuton or ACETABUTONE).tw,kf,kw. 142
209 Acepromazine/ or acepromazine maleate/ or (acepromazine or acetazine or acetopromazine or acetylpromazine or calmivet or plegicil or vetranquil).tw,kf,kw. 5183
210 aceprometazine/ or (aceprometazine or UNII-984N9YTM4Y).tw,kf,kw. 144
211 acetophenazine/ or acetophenazine dimaleate/ or (acetophenazine or UNII-8620H6K4QH).tw,kf,kw. 231
212 adoprazine/ or (adoprazine or "SLV 313" or SLV313 or SLV-313 or UNII-7SNB18Q89D).tw,kf,kw. 102
213 alimemazine/ or alimemazine tartrate/ or (alimemazine or Isobutrazine or Methylpromazine or Nedeltran or Panectyl or Repeltin or Repetin or Spansule or Temaril or Teralen or Teralene or Theralen or Theralene or Trimeperazine or trimeprazine or Trimeprazine-d6 or UNII-76H78MJJ52 or Vallergan or Vanectyl or Variargil).tw,kf,kw. 2325
214 "alpha (4 fluorophenyl) 4 (5 fluoro 2 pyrimidinyl) 1 piperazinebutanol"/ or UNII-A5NB5G07JO.tw,kf,kw. 305
215 "alpha [1 [2 (1,4 benzodioxan 5 yloxy)ethyl] 3 pyrrolidinyl] 4 fluoroacetophenone"/ 31
216 amitriptyline plus perphenazine/ or ("amitriptyline, perphenazine drug combination" or "Anxipress D" or Deprelio or Elavil Plus or Longopax or Mutabon or "Perphenazine and amitriptyline hydrochloride" or "Perphenazine-amitriptyline combination" or Pertriptyl or "TRIAVIL 2-10" or "TRIAVIL 2-25" or "TRIAVIL 4-10" or "TRIAVIL 4-25" or "TRIAVIL 4-50" or Triptafe).tw,kf,kw. 259
217 aplindore/ or (aplindore or UNII-Q5O76TA0ML).tw,kf,kw. 27

218 Amisulpride/ or (amisulpride or barnetil or "dan 2163" or "lin 1418" or solian or sultopride).tw,kf,kw. 9789
219 Aripiprazole/ or (aripiprazole or "7-(4-(4-(2,3-dichlorophenyl)-1-piperazinyl)butyloxy)-3,4-dihydro-2(1H)-quinolinone" or Abilify or Aripiprazol or "OPC 14597" or OPC-14597).tw,kf,kw. 30116
220 Azaperone/ or (Azaperone or R-1929 or R1929 or Stresnil).tw,kf,kw. 1233
221 balipodect/ or (balipodect or "TAK 063" or TAK063 or TAK-063 or UNII-6650W303H0).tw,kf,kw. 101
222 benperidol/ or (Benperidol or Anquil or Benperidolo or Benperidolum or Benquil or Benzeridol or Benzoperidol or Benzperidol or Frenactil or Frenactyl or Glianimon).tw,kf,kw.1632
223 berupipam/ or (berupipam or UNII-420895MAOC).tw,kf,kw. 2
224 bitopertin/ or (bitopertin or "R 1678" or R-1678 or "RG 1678" or RG1678 or RG-1678 or UNII-Q8L6AN59YY).tw,kf,kw. 327
225 blonanserin/ or (blonanserin or "AD 5423" or AD5423 or AD-5423 or Lonasen or UNII-AQ316B4F8C).tw,kf,kw. 884
226 brofoxine/ or (brofoxine or Brofossina or Brofoxina or Brofoxinum or Dimethabrone).tw,kf,kw. 9
227 bromospiperone/ or (bromospiperone or 4-Bromospiperone or 4-Bromospiroperidol or p-Bromospiperone or p-Bromospiroperidol).tw,kf,kw. 61
228 bromperidol/ or (bromperidol or Azurene or Bromoperidol or Bromperidolum or Impromen or Tesoprel).tw,kf,kw. 938
229 Butaclamol/ or (butaclamol or "AY 23,028" or "AY-23,028" or "AY23,028").tw,kf,kw. 2710
230 butaperazine/ or (butaperazine or Butaperazina or Butaperazinum or Butyrylperazine or Megalectil or Randolectil or Repoise or Tyrylen).tw,kf,kw. 393
231 carfenazine/ or (carfenazine or Carfenazina or Carfenazinum or Carphenazin or Carphenazine or Procethazine or Proketazine).tw,kf,kw. 111
232 cariprazine/ or (cariprazine or cis-Cariprazine or Vraylar).tw,kf,kw. 1826
233 carpipramine/ or (carpipramine or Carbadipimidine or Carpipramina or Carpipraminum or Defekton or Prazinil).tw,kf,kw. 330
234 carvotroline/ or carvotroline.tw,kf,kw. 6
235 centbutindole/ or (centbutindole or Biriperona or Biriperone or Biriperonum).tw,kf,kw. 36
236 chlorphenethazine/ or (chlorphenethazine or Chlorfenethazine or Chlorphenethazine or Ethyl chlorpromazine or Elroquil or Marophen).tw,kf,kw. 60
237 chlorproethazine/ or (chlorproethazine or Chlorproethazinum or Clorproetazina or Neuriplege).tw,kf,kw. 58
238 Chlorpromazine/ or (Chlorpromazine or Aminazine or Chlorazine or Chlordelazine or Contomin or Fenactil or Largactil or Propaphenin or Thorazine).tw,kf,kw.69463
239 Chlorprothixene/ or (Chlorprothixene or Chlorprotixen or Taractan).tw,kf,kw. 3457
240 cinuperone/ or (Cinuperone or Cinuperonum).tw,kf,kw. 26
241 clocapramine/ or (clocapramine or Clocapramina or Clocapraminum).tw,kf,kw. 166

242 cloflumide mesilate/ or cloflumide.tw,kf,kw. 9
243 clofluperol/ or (clofluperol or Clofluperidol or Clofluperolum).tw,kf,kw. 33
244 Clopenthixol/ or (Clopenthixol or alpha-Clopenthixol or Cisordinol or Clopenthixol or Zuclopenthixol).tw,kf,kw. 2241
245 clopimozide/ or (clopimozide or Clopimozida or Clopimozidum or "R 29,764" or "R 29764" or R-29764).tw,kf,kw. 51
246 clopipazan/ or clopipazan.tw,kf,kw. 10
247 clospipramine/ or (clospipramine or Clospipramine or Cremin or Mosapramine dihydrochloride or mosapramine hydrochloride).tw,kf,kw. 150
248 clotiapine/ or (clotiapine or Clothiapine or Clotiapina or Clotiapinum or Entumin or Entumine or Etumine).tw,kf,kw. 1072
249 Clozapine/ or (Clozapine or Clorazil or Clozapin or Clozapina or Clozapinum or CLOZARIL or Leponex or Lepotex).tw,kf,kw. 63691
250 cyamemazine/ or (cyamemazine or Ciamatil or Ciamemazina or Cianatil or Cyamemazin or Cyamemazinum or Cyamepromazine or Kyamepromazin or Kyamepromazine or Tercian).tw,kf,kw. 944
251 dimetotiazine/ or (dimetotiazine or Banistyl or Dimethiotazine or Dimethodin or Dimethothiazine or Dimetiotazine or Dimetothiazine or Dimetotiazin or Dimetotiazina or Dimetotiazinum or Migristene or Promaquid).tw,kf,kw. 197
252 dixyrazine/ or (dixyrazine or Dixyrizine or Esocalm or Esucos or Metronal or Roscal).tw,kf,kw. 451
253 dolasetron mesilate/ or (dolasetron mesilate or Anemet or Anzemet or Dalasetron Mesylate Hydrate or Dolasetron mesilate or Dolasetron methanesulfonate or Dolasetronmesylate).tw,kf,kw. 1531
254 Droperidol/ or (Dehidrobenzperidol or Dehydrobenzperidol or Droleptan or Droperidol or Inapsine).tw,kf,kw. 13110
255 duoperone/ or (duoperone or Duoperona or Duoperonum).tw,kf,kw. 6
256 Etazolate/ or (Etazolate or "SQ 20009" or SQ-20009 or SQ20009).tw,kf,kw. 434
257 etymemazine/ or (etymemazine or Ethotrimeprazine or Ethyl isobutrazine or Ethylisobutrazine).tw,kf,kw. 9
258 evenamide/ or (evenamide or Evenamid).tw,kf,kw. 18
259 farampator/ or (farampator or "CX 691" or CX691 or CX-691 or Org 24448 or Org24448 or Org-24448).tw,kf,kw. 73
260 fluanisone/ or (fluanisone or Fluanison or Fluanisona or Fluanisonum or Haloanisone).tw,kf,kw. 469
261 Flupenthixol/ or (alpha-Flupenthixol or cis-Flupenthixol or Emergil or Fluanxol or Flupentixol).tw,kf,kw. 7190
262 flupentixol decanoate/ or (flupentixol decanoate or Depixol).tw,kf,kw. 961
263 Fluphenazine/ or (Flufenazin or Fluphenazine or Lyogen or Prolixin).tw,kf,kw. 14873
264 fluphenazine decanoate/ or (fluphenazine decanoate or Flufenazine decanoate or Fluorophenazine decanoate or Fluphenaline decanoate or Fluphenazine depot or FLUPHENAZINE ENANTHATE IMPURITY C or Fluphenazine O-decanoate or Fluphenazinedecanoate or fluphenazine-decanoate or Fluphenazini decanoas or liogen

or Lyogen or Mirenil or Modecate or Moditen depot or Moditen-depo or Prolixin decanoate).tw,kf,kw. 3007
265 fluphenazine enanthate/ or (Fluphenazine Enanthate or Enanthic acid fluphenazine or Eutimox or Flufenan or Moditen enanthate or Moditen-retard or Prolixin Enanthate).tw,kf,kw. 598
266 Fluspirilene/ or (Fluspirilene or Fluspirilen or Fluspi or Imap or kivat or Redeptin or Spirodiflamine).tw,kf,kw.1911
267 flutroline/ or (Flutroline or Flutrolino or Flutrolinum or Fluspi or fluspirilen or Fluspirilene or Imap or Kivat or Redeptin or Spirodiflamine).tw,kf,kw. 1383
268 gevetroline/ or gevetroline.tw,kf,kw. 17
269 Haloperidol/ or haloperidol decanoate/ or (haloperidol or Aloperidin or Aloperidol or Aloperidon or Aloperidolo or Bioperidolo or Brotopon or Dozic or Duraperidol or Einalon or Eukystol or Fortunan or Galoperiodol or Halidol or Haldol or Halojust or Halol or Halomonth or Halopal or Haloperidolum or Halopidol or Halopoidol or Halosten or Keselan or Linton or Mixidol or Neurodol or Pekuces or Peluces or Pernox or Sernas or Serenace or Serenase or Sigaperidol or Ulcolind or Uliolind).tw,kf,kw. 98830
270 iclepertin/ or (Iclepertin or "BI 425809" or BI425809 or BI-425809).tw,kf,kw. 83
271 isofloxythepin/ or isofloxythepin.tw,kf,kw.100
272 isomolpan/ or isomolpan.tw,kf,kw.15
273 Lamotrigine/ or (lamotrigine or "BW 430C" or BW-430C or BW430C or Crisomet or Labileno or Lamictal or Lamiktal).tw,kf,kw. 40105
274 landipirdine/ or landipirdine.tw,kf,kw. 20
275 lenperone/ or (lenperone or AHR 2277 or AHR2277 or AHR-2277 or Lenperona or Lenperonum).tw,kf,kw. 109
276 Loxapine/ or (loxapine or "CL 71,563" or "CL-71,563" or "CL71,563" or Cloxazepine or Loxapinsuccinate or loxapine succinate or Oxilapine).tw,kf,kw. 3631
277 Lurasidone Hydrochloride/ or (Lurasidone or latuda).tw,kf,kw. 3763
278 luvadaxistat/ or luvadexistat.tw,kf,kw. 19
279 mardepodect/ or mardepodect.tw,kf,kw. 55
280 maroxepine/ or (Maroxepine or Maroxepin or Maroxepina or Maroxepinum).tw,kf,kw. 18
281 mazapertine/ or mazapertine.tw,kf,kw. 58
282 mepiprazole/ or (mepiprazole or Mepiprazol or Mepiprazolum or Quiadon).tw,kf,kw. 73
283 mesoridazine besylate/ or (Mesoridazine besylate or Lidanar or Lidanil or Mesoridazine benzenesulfonate or mesoridazine monobenzenesulfonate or Serentil).tw,kf,kw. 223
284 Methiothepin/ or (Methiothepin or Methiothepine or Metitepine).tw,kf,kw. 2891
285 methopromazine/ or (Methopromazine or Methopromazinum or Methoxypromazine or Metopromazina or Mopazin or Mopazine or Neoproma).tw,kf,kw. 115
286 Methotrimeprazine/ or (Methotrimeprazine or Levomeprazin or Levomepromazine or Levopromazine or Tisercin or Tizercine or Tizertsin).tw,kf,kw. 7378

287 metofenazate/ or (metofenazate or Frenolone or Methophenazine or Metofenazato or Metofenazatum or metophenazate or Phrenolon).tw,kf,kw. 116
288 Molindone/ or (Molindone or Moban).tw,kf,kw. 1661
289 moperone/ or (Moperone or Luvatren or Luvatrena or Meperon or Methylperidol or Moperona or Moperonum or Mopiperone).tw,kf,kw. 253
290 neboglamine/ or (neboglamine or CR 2249 or Cr2249 or CR-2249).tw,kf,kw. 16
291 noctran/ or (Noctran or 78355-48-3 or "FA 522 A").tw,kf,kw. 97
292 norchlorpromazine/ or (Norchlorpromazine or Demethylchlorpromazine or Demonomethylchlorpromazine or Desmethylchloropromazine or Desmethylchlorpromazine or MONODESMETHYLCHLORPROMAZINE or N-Desmethylchlorpromazine or N-Monodesmethylchlorpromazine or NOR1CHLORPROMAZINE or NOR1-CHLORPROMAZINE).tw,kf,kw. 162
293 Olanzapine/ or (Olanzapine or "LY 170052" or "LY 170053" or LY-170052 or LY170052 or Zolafren or Zyprexa).tw,kf,kw. 60127
294 oxiperomide/ or (oxiperomide or Oxiperomida or Oxiperomidum or Oxyperomide or Peromide).tw,kf,kw. 105
295 oxypertine/ or (oxypertine or Equipertine or Forit or Opertil or Oxipertina or Oxipertine or Oxipertinum or Oxypertin or Oxypertinum).tw,kf,kw. 456
296 oxyprothepine/ or oxyprothepine decanoate/ or oxyprothepine.tw,kf,kw. 198
297 Paliperidone Palmitate/ or (paliperidone or "9 Hydroxy risperidone" or "9 Hydroxyrisperidone" or "9 OH risperidone" or 9-hydroxy-risperidone or 9-hydroxyrisperidone or 9-OH-risperidone or Invega).tw,kf,kw. 9387
298 pecazine/ or (pecazine or Lacumin or mepasin or Mepazin or MEPAZINE or Meprazine or Mesapin or Pacatal or Pacatol or Pakatal or Paxital or Pecatal or Pecazina or Pecazinum).tw,kf,kw.330
299 Penfluridol/ or (Penfluridol or Penfluridolum or Semap).tw,kf,kw. 1348
300 perazine/ or (perazine or Perazin or Pernazine or Taxilan).tw,kf,kw. 1417
301 periciazine/ or (Periciazine or Aolept or Nelactil or Nemactil or Neulactil or Neuleptil or Periciazin or Periciazina or Periciazinum or PERICYAZINE).tw,kf,kw. 1178
302 perimetazine/ or (Perimetazine or leptryl or Perimetazin or Perimetazina or Perimetazinum or Perimethazine).tw,kf,kw. 71
303 Perphenazine/ or perphenazine decanoate/ or (Perphenazine or Chlorperphenazine or Chlorpiprazine or Emesinal or Etaperazin or Etaperazine or Ethaperazine or Etrafon or Perfenazina or Perfenil or Perphenan or Perphenazin or Perphenazinum or Thilatazin or Tranquisan or Trifaron or Trilafon or Trilifan or Triphenot).tw,kf,kw. 10148
304 pf 217830/ or (PF-00217830 or PF-217830).tw,kf,kw. 15
305 pf 3463275/ or ("PF 03463275" or PF-0346275 or PF-03463275 or PF-3463275).tw,kf,kw. 37
306 picobenzide/ or (Picobenzide or Picobenzida or Picobenzidum).tw,kf,kw. 32
307 piflutixol/ or (piflutixol or Piflutixolum or "trans piflutixol-(E)" or trans-Piflutixol).tw,kf,kw. 166
308 pimavanserin/ or (pimavanserin or Nuplazid).tw,kf,kw. 1332
309 pimethixene/ or (Pimethixene or Calmixen or Calmixene or Mepithiathene or Pimethixen or Pimethixenum or PIMETIXENE or Pimetixeno).tw,kf,kw. 47

310 Pimozide/ or (Pimozide or Antalon or Opiran or Orap or "R 623" or "R 6238" or R-623 or R6238 or R-6238).tw,kf,kw. 12341
311 pipamperone/ or (pipamperone or Dipiperal or Dipiperon or Dipiperone or Floropipamide or Fluoropipamide or Pipamperon or Pipamperona or Pipamperonum or Pipaneperone or Piperonil or Piperonyl or Propitan or "R 3345" or R-3345).tw,kf,kw. 4836
312 piperacetazine/ or (piperacetazine or Piperacetazina or Piperacetazinum or Piperazetazina or Psymod or Quide).tw,kf,kw. 223
313 pipotiazine/ or (pipotiazine or Lonseren or Piportil or Pipothiazine or Pipotiazina or Pipotiazinum or RP 19366 or RP-19366).tw,kf,kw. 914
314 pipotiazine palmitate/ or (Pipotiazine palmitate or Piportil depot or Pipothiazin palmitate or Pipothiazine palmitate or Pipotiazin Retard or Pipotiazine Palmitic Ester or pipotiazine-palmitate).tw,kf,kw. 380
315 pirenperone/ or (pirenperone or Pirenperona or Pirenperonum or R 47465 or "R-47,465" or R-47465).tw,kf,kw. 457
316 pomaglumetad methionil/ or (pomaglumetad methionil or LY 2140023 or LY2140023 or LY-2140023).tw,kf,kw. 293
317 Prochlorperazine/ or prochlorperazine edisylate/ or prochlorperazine maleate/ or (Prochlorperazine or CHLOPERAZINE or Chlormeprazine or Chloropernazine or Chlorperazine or Proazine or Prochloroperazine or Prochlorpemazine or Prochlorperazin or Prochlorperazinum or Prochlorpermazine or Procloperazine or Proclorperazina or Proclorperazine or Tementil or Temetid or Vertigon).tw,kf,kw. 8767
318 profenamine/ or (profenamine or Ethapropazine or Ethopromazine or ethopropazine or Etopropezina or Fempropazine or Fenpropazina or Isopthazine or Isotazin or Isothazine or Isothiazine or Lysivane or Pardisol or Parfezine or Parkin or Parphezein or Parsidol or Parsitan or Parsotil or Phenopropazine or Phenoprozine).tw,kf,kw. 13755
319 Promazine/ or (Promazine or Prazin or Prazine or Promazin or Promazina or Promazinum or Promwill or Propazinum or Protactyl or Sinophenin or Sparine).tw,kf,kw. 4234
320 propiomazine/ or propiomazine maleate/ or (propiomazine or Largon or Phenoctyl or Propavan or Propiomazina or Propiomazinum or Propionylpromethazine).tw,kf,kw. 372
321 propionylpromazine/ or (propionylpromazine or Combilen or Propionpromazine or Propionylpromazone or Propiopromazine).tw,kf,kw. 147
322 prothipendyl/ or (prothipendyl or Dominal or Largophren or Phrenotropin or Prothipendylum or Protipendilo or Timoval or Timovan or Tolnate or Tumovan).tw,kf,kw. 639
323 Quetiapine Fumarate/ or (quetiapine or Seroquel).tw,kf,kw. 40402
324 Raclopride/ or raclopride tartrate/ or (Raclopride or "FLA 870" or FLA-870 or FLA870 or "FLB 472" or FLB-472 or FLB472).tw,kf,kw. 8793
325 ralmitaront/ or ralmitaront.tw,kf,kw. 26
326 Remoxipride/ or Remoxipride.tw,kf,kw. 1612
327 Reserpine/ or (Reserpine or Raunervil or Raupasil or Rausedil or Rausedyl or Serpasil or Serpivite or "V Serp" or V-Serp).tw,kf,kw. 42327

328 rimcazole/ or (rimcazole or BW 234U or BW-234U or Rimcazol or Rimcazolum).tw,kf,kw. 528
329 Risperidone/ or (Risperidone or Risperdal or "R 64,766" or "R 64766" or "R-64,766" or R-64766 or "R64,766" or R64766 or Risperidone).tw,kf,kw. 63706
330 Ritanserin/ or (Ritanserin or "6-(2-(4-(Bis(4-fluorophenyl)methylene)-1-piperidinyl)ethyl)-7-methyl-5H-thiazolo(3,2-a)pyrimidin-5-one" or "R 55667" or R-55667 or R55667).tw,kf,kw. 4520
331 roluperidone/ or (roluperidone or MIN-101 or Roluperidon).tw,kf,kw. 226
332 romergoline/ or Romergoline.tw,kf,kw. 0
333 savoxepine/ or (savoxepine or Cipazoxapine or Savoxepin or Savoxepina or Savoxepinum).tw,kf,kw. 59
334 sb 773812/ or "sb 773812".tw,kf,kw. 10
335 seridopidine/ or seridopidine.tw,kf,kw. 0
336 setoperone/ or (setoperone or SEPTOPERONE or Setoperona or Setoperonum).tw,kf,kw. 299
337 Spiperone/ or (Spiperone or Espiperona or Spiperonum or Spiroperidol or Spiroperidone or Spiropitan).tw,kf,kw. 11129
338 sulforidazine/ or (sulforidazine or Psychoson or Solforidazina or Sulforidazina or Sulforidazinum or Thioridazine 2-Sulfone Thioridazine sulfone or Thioridazine sulphone or Thioridazine-2-sulfone).tw,kf,kw. 204
339 suvecaltamide/ or (suvecaltamide or Suvecaltamide).tw,kf,kw. 14
340 Sulpiride/ or (Sulpiride or Aiglonyl or Arminol or Deponerton or Desisulpid or Digton or Dogmatil or Dolmatil or Eglonyl or Ekilid or Guastil or Lebopride or Meresa or neogama or Pontiride or Psicocen or Sulp or Sulperide or Sulpitil or Sulpivert or Sulpor or Synedil or Tepavil or "Vertigo Meresa" or "vertigo neogama" or Vertigo-Meresa or vertigo-neogama).tw,kf,kw.21468
341 Tefludazine/ or (tefludazine or Tefludazina or Tefludazinum).tw,kf,kw. 44
342 Tetrabenazine/ or deutetrabenazine/ or (tetrabenazine or Nitoman or tetra Benazin or Tetrabenazin or Tetrabenazina or Tetrabenazinum or Tetrabenzaine or Tetrabenzine or Xenazine).tw,kf,kw. 6207
343 Thiopropazate/ or (thiopropazate or Dartal or Dartalan or Perphenazine acetate or Thiopropazat or Thiopropazatum or Tiopropazato).tw,kf,kw. 194
344 Thioproperazine/ or (Thioproperazine or Sulfenazin or Thioperazine or Thioproperazin or Thioproperazinum or Thiproperazine or Tioproferazina or Tioproperazin or Tioproperazina or Vontil).tw,kf,kw. 722
345 thioproperazine methanesulfonate/ or (thioproperazine methanesulfonate or Mageptyl or Majeptil or Thioperazine dimethanesulfonate or Thioperazine mesylate or Thioproperasine dimesylate or Thioproperazine bis-methanesulfonate or Thioproperazine dimesilate or Thioproperazine dimesylate or Thioproperazine dimethanesulfonate or THIOPROPERAZINE DIMETHANESULPHONATE or Thioproperazine mesilate or Thioproperazine mesylate or Thioproperazine methanesulfonate or Thioproperazinum).tw,kf,kw. 224
346 Thioridazine/ or (Thioridazine or Aldazine or Apo-Thioridazine or ApoThioridazine or Meleril or Mellaril or Melleretten or Melleril or Melleryl or Melzine or Rideril or Sonapax or Thioridazine-neurazpharm or Thioridazineneurazpharm or Thiozine).tw,kf,kw. 16668

347 Thiothixene/ or (Thiothixene or cis-Thiothixene or Navan or Navane or Navaron or Orbinamon or Tiotixene or Tiotixeno or Tiotixenum).tw,kf,kw. 3405
348 Tiapride Hydrochloride/ or (Tiapride or Equilium or "FLO 1347" or FLO-1347 or FLO1347 or Tiapridal or Tiapridex or Tiaprizal).tw,kf,kw. 3043
349 Tilapertin/ or Tilapertin.tw,kf,kw. 1
350 Timiperone/ or (timiperone or Timiperona or Timiperonum or Tolopelon).tw,kf,kw. 165
351 Trifluoperazine/ or (Trifluoperazine or Apo-Trifluoperazine or ApoTrifluoperazine or Eskazine or Flupazine or Stelazine or Terfluzine or Trifluoroperazine or Triftazin).tw,kf,kw. 16804
352 Trifluperidol/ or (Trifluperidol or Trisedil).tw,kf,kw. 750
353 Triflupromazine/ or (Triflupromazine or Fluopromazine or Siquil or Triflupromazine).tw,kf,kw. 1822
354 tulrampator/ or tulrampator.tw,kf,kw. 3
355 ulotaront/ or ulotaront.tw,kf,kw. 140
356 umespirone/ or umesprione.tw,kf,kw. 18
357 vabicaserin/ or vabicaserin.tw,kf,kw. 86
358 zetidoline/ or (zetidoline or Zetidolina or Zetidolinum).tw,kf,kw. 99
359 zicronapine/ or zicronapine.tw,kf,kw. 19
360 zoloperone/ or (zoloperone or Zoloperona or Zoloperonum).tw,kf,kw. 13
361 or/194-360 617002
362 (12 and 193 and 361 and 124) not 186 599
363 remove duplicates from 362 440
364 Early ambulation/ 44386
365 (joint mobilization/ or mobilization/) use oemezd 42662
366 exp Exercise therapy/ or exp kinesiotherapy/ 169781
367 exp Movement/ or exp "movement(physiology)"/ 1198443
368 exp Musculoskeletal Manipulations/ or exp musculoskeletal manipulation/ 23790
369 exp Physical Therapy Modalities/ or exp physiotherapy/ 299655
370 Activities of daily living/ or Daily life activity/ 201188
371 Rehabilitation/ 139800
372 Rehabilitation, vocational/ or vocational rehabilitation/ 25186
373 "Physical and rehabilitation medicine"/ 13322
374 Exercise/ 533518
375 Physical therapy modalities/ 144735
376 Range of motion, articular/ 118806
377 Recovery of function/ 113557
378 Muscle strength/ 115145
379 exp Mobilization/ use oemezd 41060
380 Joint mobilization/ use oemezd 1674
381 Physical activity/ use oemezd 228632
382 Physical Mobility/ use psyh3079
383 (Mobili* or physical therapy* or physiotherap* or physical function* or exercis* or activit* of daily living or ADL or rehab* or range of motion or ROM or recovery of function or muscle strength or physical activit* or recovery of function or ambulate or

ambulation or mobilise or mobilize or mobilisation or mobilization or mobility or movement).tw,kf,kw. 3522532
384 or/364-383 4740992
385 (12 and 384 and (124 or 176)) not 186 25236
386 limit 385 to yr=2022-2024 5386
387 remove duplicates from 386 4018
388 exp Respiration, Artificial/ or exp artificial ventilation/ 349237
389 exp Ventilators, Mechanical/ or exp mechanical ventilator/ 18028
390 ((artificial* or mechanical* or invasive* or high-frequency or positive-pressure or "positive pressure" or negative-pressure or "negative pressure") adj3 (respirat* or ventilat*)).tw,kf,kw. 252899
391 (artificial airway? or controlled ventilation).tw,kf,kw. 7569
392 or/388-391 453931
393 exp Dexmedetomidine/ or (Dexmedetomidine or "(+)-4-((S)-.ALPHA.,2,3-TRIMETHYLBENZYL)IMIDAZOLE" or "(+)-4-((S)-alpha,2,3-Trimethylbenzyl)imidazole" or "(S)-4-(1-(2,3-dimethylphenyl)ethyl)-1H-imidazole" or "(S)-4-[1-(2,3-Dimethylphenyl)ethyl]-1H-imidazole" or "(S)-5-(1-(2,3-Dimethylphenyl)ethyl)-1H-imidazole" or 108D583 or 113775-47-6 or "1H-Imidazole, 4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-" or "1H-Imidazole, 5-[(1S)-1-(2,3-dimethylphenyl)ethyl]-" or "4-[(1~{S})-1-(2,3-dimethylphenyl)ethyl]-1~{H}-imidazole" or "4-[(1S)-1-(2,3-Dimethylphenyl)ethyl]-1H-imidazol" or "4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole" or "4-[(1S)-1-(2,3-dimethylphenyl)ethyl]-3H-imidazole" or "4-[(s)-1-(2,3-dimethyl-phenyl)-ethyl]-1h-imidazole" or "5-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole" or 67VB76HONO or AB01566872_01 or AB01566872_02 or AKOS025149503 or AKOS026750524 or AS-68685 or "bxcl 501" or bxcl501 BDBM50085683 or C07450 or CCG-266586 or "CHEBI:4466" or CHEMBL778 or CS-0012295 or cepedex or D00514 or DB00633 or "da 9051" or da9051 or delos or Dexdor or Dexmedetomidina or "DexmedetomidineHclC13H16N2.Hcl" or Dexmedetomidinum or dexdomitor or dexdor or DTXSID10873388 or EN300-127736 or GTPL521 or HMS3885M07 or HY-12719 or Igalmi or Medetomidine or MFCD00880557 or "MPV 1440" or MPV-1440 or NCGC00025347-01 or NCGC00371080-02 or NCGC00371080-09 or Precedex or primadex or Q412133 or s3075 or SCHEMBL26433 or sedadex or sileo or SW219607-1 or Tocris-2023 or "TPU 006" or tpu006 or UNII-67VB76HONO or ZINC4632106).tw,kf,kw. 34178
394 Propofol/ or ("2, 6-Diisopropylphenol" or "2,6 Diisopropylphenol" or "2,6-Bis(1-methylethyl)phenol" or "2,6-bis(Isopropyl)phenol" or "2,6-bis(propan-2-yl)phenol" or "2,6-di isopropyl phenol" or "2,6-di(propan-2-yl)phenol" or "2,6-Diisopropyl phenol" or "2,6-diisopropyl-phenol" or "2,6-Diisopropylphenol" or "2,6-Di-iso-propylphenol-d18" or "2,6-dipropan-2-ylphenol" or "BIDD:GT0436" or "CHEBI:44915" or "BRN 1866484" or "EINECS 218-206-6" or "ghl.PD_Mitscher_leg0.558" or "HSDB 7123" or "ICI 35,868" or "ICI 35868" or "ICI 35-868" or "ICI35,868" or "MLS-0318084.P017" or "NSC 5105" or "Pharmakon1600-01505022" or "Phenol, 2, 6-bis(1-methylethyl)-" or "Phenol, 2,6-bis(1-methylethyl)" or "Phenol, 2,6-bis(1-methylethyl)-" or "Phenol, 2,6-diisopropyl-" or "Phenol,6-bis(1-methylethyl)-" or "Phenol,6-diisopropyl-" or "SDCCGMLS-0318084.P029" or "SDCCGSBI-0050422.P002" or 2078-54-8 or 3f33 or 3p50 or A814898 or AB00513968 or AB00513968_08 or AB00513968-07 or AC-2038 or

AC8633 or AI3-26295 or AKOS009159417 or ALBB-036351 or AM90311 or Ampofol or Anepol or Anesia or Aquafo or Aquafol or AS-13299 or BCP02920 or BCP0726000298 or BDBM50058046 or Biomol-NT_000248 or BPBio1_000950 or BPBio1_000969 or BRD-K82255054-001-03-5 or BRD-K82255054-001-08-4 or BSPBio_000862 or C07523 or CAS-2078-54-8 or CCG-204529 or "CCRIS 9000" or CHEMBL526 or cryotol or CS-W020057 or D00549 or D0617 or D126608 or DB00818 or DDS-04F or diisoprofol or Diisopropylphenol or Dipravan or Diprifusor or Diprivan or Diprofol or Disoprivan or Disoprofol or DTXSID6023523 or EN300-52468 or EU-0100437 or Fresofol or gobbifol or GTPL5464 or hiremon or HMS1570L04 or HMS2089O21 or HMS2094E17 or HMS2097L04 or HMS2231E16 or HMS3259E03 or HMS3261G16 or HMS3369I16 or HMS3714L04 or HY-B0649 or "ici 35 868" or "ici 35868" or ICI-35868 or Ivofol or Lipuro or Lopac0_000437 or Lopac-D126608 or LP00437 or MFCD00008885 or MLS001066348 or MLS001335999 or MLS002454360 or MLS-0318084 or NC00449 or NCGC00015389-01 or NCGC00015389-02 or NCGC00015389-03 or NCGC00015389-04 or NCGC00015389-05 or NCGC00015389-06 or NCGC00015389-07 or NCGC00015389-08 or NCGC00015389-09 or NCGC00015389-10 or NCGC00015389-11 or NCGC00015389-14 or NCGC00015389-17 or NCGC00091538-01 or NCGC00091538-02 or NCGC00091538-03 or NCGC00091538-04 or NCGC00091538-05 or NCGC00091538-06 or NCGC00257228-01 or NCGC00260670-01 or NCGC00261122-01 or NSC5105 or NSC-5105 or NSC758909 or NSC-758909 or plofed or Pofol or Prestwick0_000931 or Prestwick1_000931 or Prestwick2_000931 or Prestwick3_000931 or profast or propocam or "propofol lipuro" or Propofol-Lipuro or Propofolum or propolipid or Propovan or Propoven or provive or rapinovet or Q-201631 or Q422740 or Rapinovet or rapiva or recofol or "recofol n" or ripol or safol or SCHEMBL36245 or SMR000059151 or SPBio_003031 or SPECTRUM1505022 or spifol or spival SR-01000075468 or SR-01000075468-1 or SR-01000075468-4 or SR-01000075468-6 or SY013479 or Tox21_110134 or Tox21_110134_1 or Tox21_201371 or Tox21_303225 or Tox21_500437 or unifol or UNII-YI7VU623SF or YI7VU623SF or ZD-0859 or ZINC968303).tw,kf,kw. 92659

395 (12 and 392 and 393 and 394 and (124 or 176)) not 186 712

396 remove duplicates from 395 658

397 Melatonin/ or (melatonin or "5-methoxy n-acetyl-tryptamine" or "BRN 0205542" or "CCRIS 3472" or "EINECS 200-797-7" or "J5.258B" or "NSC 113928" or "3-N-Acetyl-5-methoxyl tryptamine" or "BIDD:ER0618" or "SDCCGMLS-0065812.P001" or "SDCCGMLS-0065812.P002" or "SDCCGSBI-0050765.P003" or 005M655 or 0E2B08C1-B325-45B1-8939-6F9081EFDFA4 or 5-22-12-00042 or 5-methoxy-N-acetyltryptamine or A929721 or AB00053279 or AB00053279_12 or AB00053279-10 or AC-10019 or Acetamide or ACT03490 or adaflex or AKOS000276269 or AMY33320 or "apl 510" or apl510 or aritonin or BA164660 or "bci 049" or bci049 or BCI-049 or BCP28154 or BDBM9019 or BPBio1_000590 or BRD-K97530723-001-07-6 or BRD-K97530723-001-11-8 or BSPBio_000536 or BSPBio_003006 or C01598 or CAS-73-31-4 or CCG-38837 or celton or ceyestaeusom or ceyesto CHEMBL45 or ChemDiv2_003916 or circadin or civasta or CS-1769 or D08170 or DB01065 or DivK1c_000353 or DTXSID1022421 or EN300-6486827 or EU-0100787 or eusom or F1929-1777 or FT-0628191 or FT-0658928 or FT-0670984 or GLXC-25215 or GTPL1357 or GTPL224 or Guna-dermo or HMS1380B22 or HMS1569K18 or

HMS1921E04 or HMS2089F09 or HMS2096K18 or HMS2233D23 or HMS3262M16 or HMS3370J20 or HMS3413P14 or HMS3654A22 or HMS3677P14 or HMS3713K18 or HMS3884M05 or HMS501B15 or HSCI1_000400 or HSDB 7509 or HY-B0075 or IDI1_000353 or IDI1_002631 or "jan 13004" or jan13004 or jl5dk93rcl or KBio1_000353 or KBio2_000665 or KBio2_003233 or KBio2_005801 or KBio3_002226 or KBioGR_000591 or KBioSS_000665 or "ki 1001" or ki1001 or KS-1454 or L001261 or lestinora or Lopac0_000787 or Lopac-M-5250 or LP00787 or M 5250 or M1105 or M-1200 or M-1250 or Melapure or Melatobel or mallozen or mecastrin or melabiorytm or melatal or melatan or melatol or melatonina or melatonine or melatonite or mellaras or mellozzan or melovine or MFCD00005655 or MLS000859594 or MLS001055382 or MLS001240204 or mucomel or N-Acetyl-5-methoxytryptamine or N-acetyl-5-methoxy-tryptamine or NCGC00015680-01 or NCGC00015680-02 or NCGC00015680-03 or NCGC00015680-04 or NCGC00015680-05 or NCGC00015680-06 or NCGC00015680-07 or NCGC00015680-08 or NCGC00015680-09 or NCGC00015680-10 or NCGC00015680-11 or NCGC00015680-12 or NCGC00015680-13 or NCGC00015680-14 or NCGC00015680-15 or NCGC00015680-16 or NCGC00015680-18 or NCGC00015680-35 or NCGC00090727-01 or NCGC00090727-02 or NCGC00090727-03 or NCGC00090727-04 or NCGC00090727-05 or NCGC00090727-06 or NCGC00090727-07 or NCGC00090727-08 or NCGC00090727-09 or NCGC00256404-01 or NCGC00259077-01 or NCGC00261472-01 or NCI60_004378 or NINDS_000353 or noxarem or NSC113928 or NSC-113928 or NSC56423 or NSC-56423 or oniria or Oprea1_104553 or Oprea1_814234 or orlogin or Posidorm or Prestwick_312 or Prestwick0_000458 or Prestwick1_000458 or Prestwick2_000458 or Prestwick3_000458 or Primex or Q180912 or regulin or S1204 or SCHEMBL19018 or sental or slenyto or sloremina or SMP2_000309 or SMR000326666 or "sp 13004" or sp13004 or SPBio_001527 or SPBio_002475 or Spectrum_000185 or SPECTRUM1500690 or Spectrum2_001344 or Spectrum3_001393 or Spectrum4_000066 or Spectrum5_001745 or SR-01000075559 or SR-01000075559-1 or SR-01000075559-6 or SR-01000075559-7 or SR-01000075559-8 or STK386880 or SW196607-4 or SY051401 or syncrodin or TNP00300 or Tox21_110195 or Tox21_110195_1 or Tox21_201527 or Tox21_302926 or Tox21_500787 or UNII-JL5DK93RCL or waferest or Z1191880499 or ZINC57060).tw,kf,kw.98689
398 (12 and 397 and (124 or 176)) not 186 482
399 remove duplicates from 398 334
400 187 or 362 or 387 or 395 or 398 6594
401 400 use oemezd 5701
402 400 use medall 815
403 400 use psyh78
404 limit 401 to dd=20230511-20240327 615
405 limit 402 to (ed=20230511-20240327 or ez=20230511-20240327) 154
406 limit 403 to up=20230511-20240327 15
407 404 or 405 or 406 784
408 187 and 407 26
409 362 and 407 29
410 387 and 407 710
411 395 and 407 7

412 398 and 407 22

EBM Reviews - Cochrane Central Register of Controlled Trials <February 2024>

1 exp critical care/ 3044
2 exp critical care nursing/ 72
3 exp critical illness/ 3605
4 exp intensive care units/ 5916
5 (((acute* or intensive* or critical* or neurointensive* or neuro-intensive* or neurocritical* or neuro-critical*) adj (care or therap* or treatment* or unit?)) or healthcare facilit* or health-care facilit*).mp. 48684
6 (ICU or MICU or CICU or CVICU or CCU or SICU or POCCU or ITU or HDU or ICUs or MICUs or CICUs or CVICUs or CCUs or SICUs or POCCUs or ITUs or HDUs).ti. 2607
7 ((ICU or MICU or CICU or CVICU or CCU or SICU or POCCU or ITU or HDU or ICUs or MICUs or CICUs or CVICUs or CCUs or SICUs or POCCUs or ITUs or HDUs) and ((acute* or intensive* or critical* or neurointensive* or neuro-intensive* or neurocritical* or neuro-critical*) adj (care or therap* or treatment* or unit?))).mp. 11368
8 or/1-7 50838
9 exp anxiety/ 12316
10 exp anxiety disorders/ 9973
11 exp adjustment disorders/ 292
12 exp mutism/ 28
13 (anxiet* or anxious* or panic* or phobi* or agoraphobi* or GAD or mute or mutism or nervous* or restless* or stress* or PTSD or obsessive compulsive or obsessive-compulsive or OCD or adjustment disorder* or neurotic or neuroses).mp. 180623
14 or/9-13 180818
15 exp benzodiazepines/ 11572
16 (benzodiazepine or bensodiazepines).mp. 3358
17 8 and 14 and (15 or 16) 157
18 exp delirium/ 1528
19 exp confusion/ 1687
20 exp hallucinations/ 473
21 (bewilderment or confusion* or deliria* or delirious* or delirium* or disorientation or hallucinat*).mp. 11174
22 or/18-21 11174
23 exp antipsychotic agents/ 12808
24 (antipsychotic* or anti-psychotic* or ((neuroleptic or neuroleptics) adj (agent or agents or drug or drugs)) or ((butyrophenone or major or phenothiazine) adj (tranquilis* or tranquiliz*)) or neuroleptic*).mp. 12813
25 or/23-24 18678
26 8 and 22 and 25 177
27 exp early ambulation/ 495
28 exp exercise therapy/ 21333
29 exp movement/ 47804
30 exp musculoskeletal manipulations/ 4211

31 exp physical therapy modalities/ 38797
32 exp activities of daily living/ 12946
33 exp rehabilitation/ 53348
34 exp rehabilitation, vocational/ 621
35 exp exercise/ 38172
36 exp physical therapy modalities/ 38797
37 exp range of motion, articular/ 6701
38 exp recovery of function/ 7192
39 exp muscle strength/ 8839
40 (ambulate or ambulation or mobilise or mobilize or mobilisation or mobilization or mobility or movement).mp. 62465
41 or/27-40 146328
42 8 and 41 3137
43 exp respiration, artificial/ 9184
44 exp ventilators, mechanical/ 424
45 ((artificial* or mechanical* or invasive* or high-frequency or positive-pressure or "positive pressure" or negative-pressure or "negative pressure") adj3 (respirat* or ventilat*)).mp. 25709
46 (artificial airway? or controlled ventilation).mp. 1316
47 or/43-46 27895
48 exp dexmedetomidine/ 2874
49 48 or dexmedetomidine.mp. 9134
50 exp propofol/ or propofol.mp. 18426
51 8 and 47 and 49 and 50 135
52 exp melatonin/ or melatonin.mp. 3880
53 8 and 52 221
54 17 or 26 or 42 or 51 or 53 3768
55 ("2023" or "2024").dl. 157672
56 54 and 55 314
57 17 and 56 1
58 26 and 56 16
59 42 and 56 258
60 51 and 56 15
61 53 and 56 30

6. Systematic Review and Data Synthesis

Study Selection
We screened all citations independently and in duplicate (K.L, K.L.C, V.A, S.C, R.S, J.M, U.A) in two stages. First, we screened titles and abstracts, and then for any citation selected in this first stage, we screened the full texts. We included published full articles or abstracts with any randomized control trials (RCTs) that presented original data that addressed the Population, Intervention, and Comparison for each PICO. We captured reasons for exclusion during full text review. A third reviewer (K.L, K.L.C) adjudicated disagreements, when necessary. We also contacted experts in the field and reviewed references of included studies to ensure we did not miss any additional studies.

Data Collection Process and Data Items
Reviewers (K.L, K.L.C, D.C, B.T, S.R, J.M, R.S, P.S, E.K, J.S, S.K, A.K, S.D) abstracted data independently and in triplicate using a pre-specified standardized data abstraction form. Senior methodologists (K.L and K.L.C) adjudicated disagreements. We collected data on trial characteristics, demographic data, intervention and control procedures, and outcomes of interest. In the case of missing data, we contacted the study authors.

Risk of Bias Assessment in Individual Studies
We assessed risk of bias independently and in duplicate using the Cochrane Modified Risk of Bias tool for RCTs. We used the tool to assess for risk of bias (ROB) in the following domains: randomized sequence generation, allocation concealment, blinding of treatment team, blinding of outcome assessors, incomplete data, selective reporting, and other. We rated each domain as "low", "possibly low", "some concerns", "possibly high", or "high". We determined overall ROB for each trial based on the highest risk attributed to any one domain. We assessed certainty of evidence for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. In keeping with GRADE methods, we use terminology consistent with the overall certainty of evidence. This includes stronger language for high certainty evidence, and less certain language ('probably' or 'may') for moderate or low certainty evidence, respectively.

Summary Measures and Synthesis of Results
We used the DerSimonnian-Laird random effects model with inverse-variance weighting to generate pooled treatment effects across studies. We assessed heterogeneity between trials using a combination of the Chi^2 test, the I^2 statistic, and visual inspection of the forest plots. We present results of dichotomous outcomes using relative risk (RR) and continuous outcomes as mean difference (MD), both with 95% confidence intervals (CIs). We have also provided absolute differences with 95% CIs which we used for GRADE ratings. If medians and interquartile ranges (IQR) were reported instead of mean and standard deviation (SD), we used the Cochrane method to convert the median into a mean.

7. GRADE Methodology

1. Certainty in the evidence. We used well-established GRADE approaches to determine overall certainty in the evidence separately for each outcome. One of the clinician-methodologists then generated an Evidence Profile using the GDT software (www.GRADEPRO.com). In the GRADE approach, randomized controlled trials are initially considered to yield 'high' certainty evidence, which may then be downgraded if there are concerns around one or more of the following domains: (1) risk of bias, (2) inconsistency, (3) indirectness of the evidence, (4) imprecision, and (5) 'other' factors, which includes publication bias. The certainty of the evidence for each outcome was then categorized as 'high', 'moderate', 'low', or 'very low':

Certainty Level	Description
⨁⨁⨁⨁ High	We are very confident that the true effect lies close to that of the estimate of the effect.
⨁⨁⨁◯ Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of that effect, but there is a possibility that it is substantially different.
⨁⨁◯◯ Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⨁◯◯◯ Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

2. Evidence-to-Decision Framework
For each PICO question, panel members held one or more web-based meetings via Zoom video conferencing platform, to review the Evidence Profile, discuss the evidence and various factors that may influence decision-making, and to generate a recommendation. The GRADE Evidence-to-Decision (EtD) framework was used to help organize panel discussions during deliberation meetings. The EtD incorporates panel judgment across 12 domains:

Domain	Question
Priority of the Problem	Is the problem a priority?
Desirable effects	How substantial are the desirable effects?
Undesirable effects	How substantial are the undesirable effects?
Certainty of evidence	What is the overall certainty of the evidence of effects?
Values	Is there important uncertainty or variability in how much people value the main outcome?
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison?
Resources required	How large are the resource requirements (costs)?
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)?
Cost effectiveness	Does cost-effectiveness of the intervention favor the intervention or the comparison?

Equity	What would be the impact on health equity?
Acceptability	Is the intervention acceptable to key stakeholders?
Feasibility	Is the intervention feasible to implement?

3. Recommendation Generation

After reviewing the Evidence Profile and discussing each consideration in the EtD for a PICO question, the panel deliberated and decided on a recommendation direction (for, against, neutral) and strength (strong vs. conditional). By convention, strong recommendations are phrased as "We recommend…" and conditional recommendations as "We suggest…". The description of recommendation strengths and their implications for patients, clinicians, and policy makers are shown in **Table 2**.

8. Final Voting Process

After all draft recommendations were generated, all panel members, except the clinician-methodologists, were electronically polled to indicate their agreement with each recommendation. The poll for each recommendation consisted of the PICO question, the draft recommendation statement, and a Rationale drafted by guideline leadership. Panelists were asked to select from three options: 'Agree', or 'Disagree'. An opportunity was provided to provide comments to explain their selection for each recommendation and these were reviewed and where appropriate, addressed by panel leadership. Panel members with conflicts of interest for a particular question were asked to Abstain from voting on the associated recommendation. Based on SCCM requirements, consensus was defined as 80% agreement among at least 75% of panel members, excluding those who abstained.

Voting Results

Recommendations	Recommendation Strength, Direction, and Certainty of Evidence	Response Rate (%)	Yes (%)	No (%)	Abstain (%)
There is insufficient evidence to make a recommendation on the use of benzodiazepines to treat anxiety in adult patients admitted to the ICU.	No recommendation, no evidence available	100%	95%	5%	0%
We suggest using dexmedetomidine over propofol for sedation in mechanically ventilated adults admitted to intensive care units where light sedation and reduction in delirium are of highest priorities	Conditional recommendation; For intervention; Moderate certainty	100%	100%	0%	0%
The panel is unable to issue a recommendation for or against the use of antipsychotics over usual care for the treatment of delirium in adult patient admitted to intensive care units	Conditional recommendation, For Intervention or Comparison; Low certainty	100%	95%	5%	0%
We suggest providing enhanced mobilization over usual care rehabilitation/mobilization to patients admitted to intensive care units	Conditional recommendation; For intervention; Moderate certainty	100%	100%	0%	0%
We suggest administering melatonin over no melatonin in adults admitted to intensive care units to improve patient outcomes	Conditional recommendation, For intervention; Low certainty	100%	95%	5%	0%

Voting panel members n=20

9. Evidence Summaries, Forest Plots, and Evidence-to-Decision Framework

1-Anxiety
2-Sedation
3-Delirium
4-Immobilization
5-Sleep

9.1 PICO 1-Benzodiazepines to treat anxiety.

PICO 1-In adults admitted to the ICU, do benzodiazepines administered for anxiety vs no benzodiazepines, impact patient outcomes?

P: Adults admitted to the ICU who are anxious
I: A benzodiazepine of any dose, route, duration, or frequency
C: No benzodiazepine
O: 1. Incidence of anxiety; 2. Incidence of agitation; 3. Incidence of delirium; 4. Duration of mechanical ventilation; 5. Incidence of post-ICU PTSD; 6. Incidence of post-ICU anxiety; 7. Mortality; 8. QoL post-ICU/functional/cognitive abilities

1. Characteristics Of Included Trials

Author Year	Patient characteristics	Inclusion/Exclusion Criteria	Intervention	Comparison	Outcomes
Bidwell 2012 Retrospective cohort study-Before and after United States Burn Centre Single center N=36 patients	Age: 40.9 yo (9.6) Men: 63.9% ICU: Burn 100% Psychiatric history: 19.4%	**Inclusion:** Burn patients with uncontrolled pain or anxiety associated with dressing changes	Midazolam 1mg IV then additional doses of 0.5mg IV up to 3mg/h N=14	No midazolam N=22	1)Oral morphine equivalents 2)Mean pain scores 3)Opioids required on discharge 4)Adverse events

Outcomes from Bidwell

1. Adverse events- "only one patient experienced an adverse event of oxygen desaturation to 88% intraprocedural, but quickly recovered to an appropriate oxygen saturation levels". No mention of AE on control group
2. No patient who received midazolam required flumazenil

3. Forest Plots-N/A

2. Evidence-To-Decision Framework

Should benzodiazepines vs. no benzodiazepines be used for adults admitted to the ICU with anxiety?	
POPULATION:	adults admitted to the ICU with anxiety
INTERVENTION:	benzodiazepines
COMPARISON:	no benzodiazepines

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Anxiety is a common and a long-lasting event post ICU. Forty percent of ICU survivors describe having anxiety at 1 and 5 years after their critical illness (1). Despite the wide acceptance that hospitalized patients likely experience anxiety, there is little data. A recent retrospective study in the United states performed a cohort study and concluded that 45% of patients (confidence interval 35-55%) had documented anxiety, with similar prevalence regardless of if the patient was admitted to the medical or trauma/surgical ICU (2). This paper also found that of those that were anxious, 87% were prescribed a benzo compared to 58% of those that were not anxious (p=0.02). Therefore, this is likely a very important problem and a common strategy of treatment.	1. Bienvenu OJ, Friedman LA, Colantuoni E, et al. Psychiatric symptoms after acute respiratory distress syndrome: a 5-year longitudinal study. *Intensive Care Med*. 2018;44(1):38–47. 2. May AD, Parker AM, Caldwell ES, et al. Provider-Documented Anxiety in the ICU: Prevalence, Risk Factors, and Associated Patient Outcomes. *Journal of Intensive Care Medicine*. 2021;36(12):1424-1430.

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	No trials were identified that examined the use of benzodiazepines.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	Direct: Bidwell et al performed a before and after study where burn patients who had uncontrolled pain and anxiety associated with dressing changes were given either midazolam (1mg IV then 0.5mg IV up to 3mg/h) compared to those that did not receive midazolam. Of the 36 patients, only one patient in the benzo group had an adverse event where their oxygen desaturated to 88% intra-procedurally, but recovered quickly. Indirectly-Increased delirium (3-6). They are used ubiquitously, there are likely adverse side effects regardless of indication, but it is unknown. Benzodiazepines may worsen underlying cause of behavioural symptoms (e.g. delirium). There is diversity of the population and diversity of indications, making it difficult to comment on the undesirable effects.	3. Stelfox T, Fiest K. Sedation strategy and ICU delirium: a multicentre, population-based propensity score-matched cohort study. BMJ Open. 2021 Jul 20;11(7):e045087. doi: 10.1136/bmjopen-2020-045087. PMID: 34285003; PMCID: PMC8292822. 4. Pandharipande P, Cotton BA, Shintani A, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma* 2008;65(01):34–416. Pisani MA, 5.Murphy TE, Araujo KL, Slattum P, Van Ness PH, Inouye SK. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. *Crit Care Med* 2009;37(01):177–1836. 6.McPherson JA, Wagner CE, Boehm LM, et al. Delirium in the cardiovascular ICU: exploring modifiable risk factors. *Crit Care Med* 2013;41(02):405–413

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	There are no studies, so cannot comment on certainty of evidence	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Our PICO was as follows: **P:** Adults admitted to the ICU who are anxious **I:** A benzodiazepine of any dose, route, duration, or frequency **C:** No benzodiazepine **O:** 1. Incidence of anxiety; 2. Incidence of agitation; 3. Incidence of delirium; 4. Duration of mechanical ventilation; 5. Incidence of post-ICU PTSD; 6. Incidence of post-ICU anxiety; 7. Mortality; 8. QoL post-ICU/functional/cognitive abilities -Some of the ultimate goals and clinical importance of the outcomes may not be reflected here-issues such as pain and suffering are not recognized and of lower priority to clinicians inadvertently but will likely be very important to patients. There is also currently a lack of conceptual clarity as to what anxiety is in the ICU. Clinicians likely are most concerned about anxiety causing agitation that will result in other more tangible issues (ventilator asynchrony, self extubation, tachyarrhythmias, for example), versus the actual patient experience is a lower priority. -Most clinicians may also not think about the long-term sequela of anxiety -We do not know anxiety as an independent construct in the ICU and it is hard to separate anxiety from other behavioural symptoms. Therefore, we don't know how problematic it can be, we may be missing some important values and outcomes. We simply need more research in this area.	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	No identified direct studies so inability to provide a balance of desirable vs undesirable effects	
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	Benzodiazepines are a cheap medication and likely broadly available. It would likely be a cheap resource, but no evidence was identified. -While we don't know the potential efficacy, there are potential side effects (e.g., delirium) and the cost of delirium can be quite substantial. -No cost benefit analyses performed so we are not sure	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ○ Low ○ Moderate ○ High ● No included studies	No included studies	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	Benzodiazepines are a cheap medication and likely broadly available. It would likely be a cheap resource, but no evidence was identified -While we don't know the potential efficacy, there are potential side effects (e.g., delirium). The cost of delirium can be quite substantial. -No cost benefit analyses performed so we are not sure	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased	-There may be inequity in how the behaviours are perceived or managed	

○ Increased ○ Varies ● Don't know	-Behaviour symptoms may be treated much more aggressively for persons of colour compared to Caucasians as well as those that are older compared to younger patients -There is known health equity surrounding sedation -Despite all of this, we are unsure about equity	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	-Likely acceptable -Benzodiazepines are ubiquitously used (e.g., 87% of those in the retrospective study in 2021 received a benzo for anxiety) (2)	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	-IV or oral options -This is a feasible and easy medication to administer	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	**Don't know**
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention

○	○	●	○	○

CONCLUSIONS

Recommendation
Recommendation: There is insufficient evidence to make a recommendation on the use of benzodiazepines to treat anxiety in adult patients admitted to the intensive care unit.

9.2 PICO 2-Dexmedetomidine for sedation

PICO 2: In mechanically ventilated adults admitted to the ICU, should dexmedetomidine, when compared with propofol, be used for sedation?
Population: Adults admitted to the ICU who are mechanically ventilated and require sedation
Intervention: Dexmedetomidine of any dose, route, duration, frequency
Comparison: Propofol of any dose, duration, frequency
Outcomes: 1. % of RASS measurements inside target range; 2. Incidence of delirium; 3. Duration of delirium; 4. Duration of mechanical ventilation; 5. ICU LOS; 6. Use of additional rescue medications while in ICU; 7. Mortality; 8. Quality of life post-ICU/Functional status post-ICU/Cognitive abilities post-ICU

1.Characteristics of Included Trials

Source	Patient characteristics	Inclusion criteria	Initiation of dex infusion	Duration of dex infusion (h)	Treatment Group(s)	Control Group(s)	Primary Outcome
Chang *et al* 2018 RCT Taiwan Single center n=60	Mean age: 70.5 % Female: 41.7% Mean APACHE II: 13 % Surgical: 100% % CV surgical: 0%	**Inclusion:** Age 20-99, major abdominal surgery **Exclusion:** 1)HR<60 bpm, high degree AV block 2)Refractory shock despite resuscitation (MAP <60 mmHg) 3)New MI 4)New York Heart Association Class IV heart failure 5)Acute physiology and chronic health evaluation II score >30 6)Severe liver cirrhosis (Child Pugh class B or C) 7)Organ transplantation within 1year 8)Pregnancy 9)Allergy to dex or propofol 10)Enrolled in other clinical trial of dexmedetomidine or propofol within 1month 11)Do not resuscitate	When arousable and RASS >0	Up to 24h	Dex 0.1–0.7 µg/kg/h -Titrated to RASS of 0 to -2	Propofol 0.3-1.6 mg/kg/h -Titrated to RASS of 0 to -2	Cardiac index
Conti *et al* 2016 RCT Italy	Mean age: 68.8 % Female: NR Mean APACHE II: NR	**Inclusion:** Adults, intubated and mechanically ventilated for >24h, received propofol as sole agent for sedation, with RASS	After one failed weaning trial and been	Up to extubation or 14d maximum	Dex 0.2-1.4 µg/kg/h -Titrated to RASS of -2 to +1	Propofol 0.3-4 mg/kg/h -Titrated to RASS of -2 to +1	Asynchrony index

Multi-center n=20	% Surgical: 35% % CV surgical: NR	target of +1 to -2, and failed one weaning trial **Exclusion:** 1)Patients who had failed more than 1 weaning trial 2)Acute intracranial or spinal neurologic disorder 3)Uncompensated acute circulatory failure 4)Severe bradycardia	mechanically ventilated in the ICU for >24h				
Corbett *et al* 2005 RCT United States Single center n=89	Mean age: 63.0 % Female: 18% Mean APACHE II: NR % Surgical: 100% % CV surgical: 100%	**Inclusion:** Age ≥18, non-emergent CABG surgery, expected duration IMV<24h **Exclusion:** 1)Inability to obtain informed consent 2)Documented hypersensitivity to either drug or any component of the drugs 3)Severe hypotension, defined as SBP< 90 mm Hg immediately before initiation of study drug 4)HR <40 beats/min immediately before initiation of the study drug 5)Renal insufficiency 6)Hepatic dysfunction 7)Requirement for continued neuromuscular blocking agents postoperatively 8)Requirement for epidural or spinal anesthesia 9)Gross obesity defined as >100% over ideal body weight 10)Known history of alcohol or drug abuse 11)Neurologic impairment or recent severe central nervous system trauma	After bypass initiated	Up to 1h post extubation	Dex 1 µg/kg bolus then 0.2-0.7 µg/kg/h -Titrated to a RSS of 5 for the first 2h post op, followed by a score of 3-4 for the remaining time	Propofol 5-75 µg/kg/min -Titrated to a RSS of 5 for the first 2h post op, followed by a score of 3-4 for the remaining time	Patient-perceived satisfaction
Djaiani *et al* 2016 RCT Canada	Mean age: 72.6 % Female: 24.6%	**Inclusion:** Age ≥60, complex CV surgery, or 70+ and CABG for single-valve or isolated coronary revascularization surgery	ICU arrival	Up to 24h	Dex 0.4 µg/kg bolus if stable then 0.2-0.7 µg/kg/h	Propofol 25-50 µg/kg/min	Delirium

Single center n=183	Mean APACHE II: NR % Surgical: 100% % CV surgical: 100%	**Exclusion:** 1)Serious mental illness 2)Delirium 3)Severe dementia 4)Undergoing an emergency procedure			-Titrated to light sedation defined as a SAS of 4	-Titrated to light sedation defined as a SAS of 4	
Elbaradie *et al* 2004 RCT Egypt Single center n=60	Mean age: 66 % Female: NR Mean APACHE II: NR % Surgical: 100% % CV surgical: 0%	**Inclusion:** Adults from major thoracic, abdominal or pelvis cancer surgeries expected to require a minimum 6h of sedation and IMV post-op **Exclusion:** 1)Neurosurgical procedures, 2)Known allergy to propofol or dex 3)Known or suspected pregnancy 4)Gross obesity (over 50% above ideal body weight) 5)Severe hepatic or renal disease where the neurologic condition was difficult to evaluate, 6)Spinal or epidural anesthesia, 7)History of steroid therapy within the last 3 months, 8)Uncontrolled diabetes	When could open eyes on command in ICU	At extubation	Dex 2.5 µg/kg/h bolus then 0.2-0.5 µg/kg/h -Titrated to RSS of 2-5	Propofol 1mg/kg bolus then 0.5-1 mg/kg/h -Titrated to RSS of 2-5	NR
Elgebaly *et al* 2018 RCT Egypt Single center n=50	Mean age: 53.1 % Female: 54% Mean APACHE II: NR % Surgical: 100% % CV surgical: 100%	**Inclusion:** Age ≥18, cardiovascular surgery and IMV post-op **Exclusion:** 1)Acute severe neurological disorder 2) MAP <55 mmHg despite appropriate intravenous volume replacement and vasopressors 3)HR <50/min, atrioventricular-conduction block Grade II or III (unless pacemaker installed) 4)Patients using alpha-2 agonists or antagonists within 24h 5)Patient on both dex and propofol concomitantly for the primary sedation or an alternative agent as the primary sedation 6)Had a prior solid organ transplant	ICU arrival	At extubation	Dex starting rate of 0.8 µg/kg/h (range not provided) -Titrated to RASS -2 to +1	Propofol starting rate of 1.5 mg/kg/h (range not provided) -Titrated to RASS -2 to +1	Efficacy and safety

		7)Pregnant or lactating					
Eremenko *et al* 2014 RCT Russia n=55	Mean age: 57.8 % Female: 34.5% Mean APACHE II: NR % Surgical: 100% % CV surgical: 100%	**Inclusion:** Age ≥18, cardiac or thoracic aorta surgery and need >24h of sedation **Exclusion:** 1)Post op MI 2)CVA 3)>200ml of blood loss in 1h 4)Complications causing a likely increase in duration of IMV>24h	ICU arrival	After Aldrete score of 9 achieved	Dex 0.2-0.7 µg/kg/h -Targeted sedation not indicated	Propofol 0.3-2 mg/kg/h -Targeted sedation not indicated	NR
Fang *et al* 2014 RCT China Single center n=108	Mean age: 74.0 % Female: 42.6% Mean APACHE II: 12.6 % Surgical: 100% % CV surgical: 0%	**Inclusion:** Age 65-80, post-surgical patients (abdominal, thoracic, lower extremity, spine) **Exclusion:** 1)Patients with craniocerebral or cardiac surgery 2)Severe liver or kidney damage 3)Bradycardia and hypotension	ICU arrival	At extubation	Dex 0.2-0.7 µg/kg/h -Titrated to a RSS 3-4	Propofol 0.3-4mg/kg/h -Titrated to a RSS 3-4	NR
Herr *et al* 2003 RCT United States Multi-center n=295	Mean age: 62.2 % Female: 10.0% Mean APACHE II: NR % Surgical: 100% % CV surgical: 100%	**Inclusion:** Adults scheduled for CABG surgery **Exclusion:** 1)Patients that were pregnant or lactating 2)Patients with neurologic conditions where a response would be difficult to evaluate 3)Uncontrolled diabetes 4)Grossly obese 5)EF<30% 6)Hospitalized with an overdose 7)Patient receiving a neuromuscular blocker 8)Epidural or spinal analgesia during the ICU stay 9)Patient has an increased risk 10)Hemodynamic instability	Intraoperat-ively at sternal closure	Up to 6h post-extubation, or a maximum of 24h	Dex 1 µg/kg bolus then 0.2-0.7 µg/kg/h -Titrated to RSS≥3 before extubation and ≥2 after extubation	Propofol (dose not specified) -Titrated to RSS ≥3 before extubation and ≥2 after extubation	Sedation efficacy

Hughes *et al* 2021 RCT USA Multi-center n=422	Mean age: 59.5* % Female: 42.9% Mean APACHE II: 27* % Surgical: 35% % CV surgical: 0% % with sepsis: 100%	**Inclusion:** Adults with suspected/known infection, IMV for < 96h, expected neuromuscular blockade <48h **Exclusion:** 1)Patients with pre-existing cognitive disease 2)Rapidly resolving organ failure 3)Moribund 4)Alcohol or benzo dependency 5)Seizure requiring benzos 6)2nd or 3rd degree heart block 7)Neuromuscular blocker >48h	Within 96 hours of meeting all inclusion criteria	Up to 14 days, extubation or ICU discharge	Dex 0.15-1.5 µg/kg/h -Target to light sedation defined as a RASS 0 to -2	Propofol 5-50 µg/kg/min -Target to light sedation defined as a RASS 0 to -2	Days alive without delirium or coma
Jakob *et al* 2012 RCT Europe Multi-centere n=498	Mean age: 65.0 % Female: 34.5% Mean APACHE II: NR % Surgical: 33.9% % CV surgical: NR	**Inclusion:** Age ≥18 and expected IMV/sedation >24h, needing light to moderate sedation **Exclusion:** 1)Acute severe neurological disorder 2)MAP less than 55mmHg despite appropriate intravenous volume replacement and vasopressors 3)HR< 50/min atrioventricular-conduction grade II or III (unless pacemaker installed) 4)Use of alpha2 agonists or antagonists within 24 hours prior	Within 72h of ICU admission and within 48h of starting continuous sedation	Up to 14d, or at time of extubation	Dex 0.2-1.4 µg/kg/h -Titration to RASS 0 to -3 (moderate to light sedation)	Propofol 0.3-4.0 mg/kg/h -Titration to RASS 0 to -3 (moderate to light sedation)	Proportion of time at target sedation
Karaman *et al* 2015 RCT Turkey Wingle center n=64	Mean age: 63.2 % Female: 14.1% Mean APACHE II: NR % Surgical: 100% % CV surgical: 100%	**Inclusion:** Age 40-75, elective CABG, ASA score <IV **Exclusion:** 1)Chronic renal failure liver failure, congestive heart failure, valvular heart disease, or respiratory system disorder, 2)Allergy towards propofol or dex 3)Dementia or Alzheimer's disease 4)A left ventricle ejection fraction of ≤40 % 5)BMI of ≥30 6)Anticonvulsive, antidepressant and psychoactive drug use	ICU arrival	Until extubation	Dex 0.2-1.0 µg/kg/h -Titrate to keep BIS values between 60 and 90 and RSS values between 3 to 4	Propofol 1-3 mg/kg/h -Titrate to keep BIS values between 60 and 90 and RSS values between 3 to 4	Duration of IMV

		7)A cardiopulmonary bypass time of ≥120 min 8)Re-operated and emergency patients, 9)The postoperative stage exclusion criteria were bleeding (chest tube drainage >100 mL/h), renal insufficiency (urine output <0.5 mL/kg/h in first 6 h), increase in serum creatinine level (>50 % of initial level), prolonged support of inotropic and vasodilating drugs due to cardiac problems and patients who cannot be extubated within the first 6 h because of pulmonary problems that prohibit weaning.					
Kress *et al* 2018 RCT United States Single center n=41	Mean age: 63.8 % Female: 48.8% Mean APACHE II: NR % Surgical: 0% % CV surgical: 0%	**Inclusion:** Age >18, anticipated IMV >48h **Exclusion:** 1)IMV for >36h 2)Primary neurologic disease 3)Post-cardiac arrest 4)Does not speak English 5)Pregnancy or lactation 6)Active MI 7)2nd or 3rd degree heart block 8)Pancreatitis 9)Triglyceride>400mg/dl	Within 96h of starting IMV	At extubation or up to 7 days	Dex 0.2-1.5 µg/kg/h -Titrated to target RASS	Propofol 5-50 µg/kg/min -Titrated to target RASS	Proportion of days with delirium
Liu *et al* 2016 RCT China Single center n=88	Mean age: 54.8 % Female: 60.2% Mean APACHE II: NR % Surgical: 100% % CV surgical: 100%	Age ≥18, elective on-pump cardiac surgery, lack of pre-op atrial fibrillation **Exclusion:** 1)acute severe neurologic disorder 2)MAP< 55 mmHg (despite administration of appropriate intravenous volume replacement and vasopressors) 3)HR< 50 bpm grade II or III atrioventricular conduction block (unless pacemaker installed) 4)Propofol or dex allergy 5)Insulin-dependent diabetes, 6)BMI> 30 7)Patients who underwent reoperation	ICU arrival	Before extubation at physician discretion	Dex 0-1.5 µg/kg/h -Titrated to keep RASS 0 to -3	Propofol 0.3-3 mg/k/h -Titrated to keep RASS 0 to -3	Incidence of postop atrial fibrillation within 96h of surgery

		8)Patients who received 2 or more sedatives after randomization 9)Had a sedation time <4 hours or >24 hours					
Liu *et al* 2020 RCT China Single center n=200	Mean age: 55.5 % Female: 42.5% Mean APACHE II: 29 % Surgical: NR % CV surgical: 0%	**Inclusion:** Age ≥18, septic shock, requiring IMV **Exclusion:** 1)History of nephropathy 2)Severe valvular heart diseases 3)Brady arrhythmia 4)Severe pulmonary diseases 5)Malignant tumors 6)Pregnancy 7)Immunodeficiency	ICU arrival, after initiation of septic shock management	5 days	Dex 1 µg /kg bolus then 0.2-0.3 µg/kg/h -Titrated to RASS -2 to 0	Propofol 1mg/kg bolus then 1-3mg/kg/h -Titrated to RASS -2 to 0	Incidence of AKI
Maldonado *et al* 2009 RCT USA n=118	Mean age: 57.7 % Female: 36.4% Mean APACHE II: NR % Surgical: 100% % CV surgical: 100%	**Inclusion:** Age 18-90, elective cardiac valve operations on CABG without a history of dementia **Exclusion:** 1)Pre-existing diagnosis of dementia, schizophrenia, need for psychotropic meds 2)active or recent substance abuse 3)Stoke within the last 6 months 4)Evidence of heart block 5)Pregnancy 6)Anticipated intraoperative deep hypothermic circulatory arrest	After weaning from CABG	Up to 24h	Dex 0.4 µg/kg bolus then 0.2-0.7 µg/kg/h -Titrated to RSS of 3 before extubation and 2 after extubation	1) Propofol 25-50 µg/kg/min or 2) Midazolam 0.5-2 mg/h -Titrated to RSS of 3 before extubation and 2 after extubation	Delirium
Memis *et al* 2009 RCT Turkey Single center n=40	Mean age: 57.0 % Female: 32.5% Mean APACHE II: 21 % Surgical: NR % CV surgical: 0%	**Inclusion:** >18yo IMV patients with early septic shock **Exclusion:** 1)Allergy to propofol or dex 2)Known or suspected brain death 3)Unstable hemoglobin levels 4)Significant arrhythmias 5)Acute MI 6)Continuous renal replacement therapy 7)Pregnancy	In early septic shock	24h	Dex 1 µg/kg bolus then 0.2-2.5 µg/kg/h -Titrated to RSS below 2	Propofol 1 mg/kg bolus then 1-3 mg/kg/h -Titrated to RSS below 2	Hepatic blood flow (indocyanine green elimination)
Moeen *et al* 2021 RCT	Mean age: 54 % Female: 42.5%	**Inclusion:** Patients >18yo who were diagnosed with intraabdominal sepsis and required	Upon arrival to the ICU	24h	Dex 1 µg/kg bolus then 0.2-1.5 µg/kg/h -Titrated to RSS 2 to 4	Propofol 1 mg/kg bolus then 20-80 µg/kg/min	Serum IL-6 levels

Egypt Single center n=60	Mean APACHE II: NR % Surgical: 100% %CV surgical: 0%	urgent surgery for source control and post-operative sedation and mechanical ventilation **Exclusion:** 1)Known allergy to the studied drugs: propofol, dexmedetomidine, or midazolam 2)Confirmed pregnancy and 3)Known or suspected brain death				-Titrated to RSS 2 to 4	
Myatra *et al* 2010 RCT India Unclear single vs multi n=100	Mean age: NR % Female: NR Mean APACHE II: NR % Surgical: 100% % CV surgical: NR	**Inclusion:** Postoperative patients requiring short-term ventilation (6-24h) **Exclusion:** NR (an abstract)	NR	NR	Dex 1 µg/kg bolus then 0.2-1 µg/kg/h -Titrated to RSS 2 to 4	Propofol 1 mg/kg bolus then 1-2 mg/kg/h -Titrated to RSS 2 to 4	NR
Paliwal 2015 RCT India Single center n=60	Mean age: 46.2yo % Female: NR Mean APACHE II: NR % Surgical: "mix medical and surgical patients" %CV surgical: NR	**Inclusion:** Adults 18-80yo requiring sedation and IMV for 12hours **Exclusion:** 1)Pregnant 2)Excessive obesity (body weight over 50% above ideal body weight) 3)Severe hepatic, renal, or CNS involvement 4)Significant arrhythmias or high degree of atrioventricular nodal block 5)Allergies to dex or propofol	Upon arrival to the ICU	NR	Dex 1 µg/kg bolus then 0.2-0.7 µg/kg/h -Titrated to RSS 4 to 5	Propofol 1 mg/kg bolus then 1-3mg/kg/h -Titrated to RSS 4 to 5	NR
Pestilci *et al* 2015 RCT Turkey Single center n=42	Mean age: 63.0 % Female: 11.9% Mean APACHE II: NR % Surgical: 100% % CV surgical: 100%	**Inclusion:** Age 40-75 undergoing cardiac surgery and no need for cardiac support or vasopressors **Exclusion:** 1)Chronic renal failure 2)Chronic liver failure 3)Psychiatric disorder 4)Hematologic disorder 5)Respiratory disorder 6)Allergy to propofol and/or dex	Sternal closure	Until extubation	Dex 0.2-0.7 µg/kg/h -Unclear titration goals	Propofol 0.2-0.7 mg/kg/h -Unclear titration goals	NR

Rashid *et al* 2017 RCT India Single center N=60	Mean age: 27.1 % Female: 100% Mean APACHE II: NR % Surgical: 100% % CV surgical: 0%	**Inclusion:** Patients who delivered through cesarian section following GA within 24h of a seizure for eclampsia, and required postoperative ventilatory support **Exclusion:** 1)Prior history of chronic hypertension, cardiac, hepatic, renal, or endocrinal disease 2)Chronic headache, seizure Disorder, or any neurological disorder 3)Allergy to any medicines used during the treatment 4)Hemolysis, elevated liver enzymes, and low platelet syndrome	Immediately upon ICU admission	NR	Dex in a loading dose of 1 µg/kg, followed by a continuous infusion at 0.2–1.2 µg/kg/h -Titration to RSS 2–3	Propofol in a loading dose of 1 mg/kg, followed by maintenance infusion dose of 2–8 mg/kg/h -Titration to RSS 2–3	ICU length of stay and adverse events
Ruokonen *et al* 2009 RCT Finland/ Switzerland Multi-center n=85	Mean age: 66.0* % Female: 17.6% Mean APACHE II: NR % Surgical: 47.1% % CV surgical: NR	**Inclusion:** Age ≥18, required sedation/MV for >24h, anticipated ICU stay >48h **Exclusion:** 1)Acute severe neurological disorder, 2)MAP 55 mmHg despite volume and vasopressors 3)HR<50 beats/min, AV-conduction block II–III (unless pacemaker installed) 4)Sequential Organ Failure Assessment score >2 5)Bilirubin >101µmol/L 6)Lactation or positive pregnancy test 7)Muscle relaxation 8)Loss of hearing or vision, 9)Any other condition interfering with RASS assessment 10)Use of a2-agonists or antagonists at the time of randomization	Within 72h of ICU admission	Up to 14d	Dex 0.25-1.4 µg/kg/h -Titration to RASS as per treating team	Propofol 0.8-4 mg/kg/h -Titration to RASS as per treating team	Sedation efficacy and ICU LOS
Srivastava *et al* 2014 RCT India Single center n=86	Mean age: 51.3 % Female: 22.2% Mean APACHE II: NR % Surgical: 100%	**Inclusion:** Age 20-65, undergoing neurosurgical procedure with post-operative IMV **Exclusion:** 1)Significant hepatic, renal, or neurologic impairment	ICU arrival	At extubation	Dex 1 µg/kg bolus then 0.4-0.7 µg/kg/h -Targeted to RSS 2-4	Propofol 1 mg/kg bolus then 1-3 mg/kg/h -Targeted to RSS 2-4	Sedation efficacy

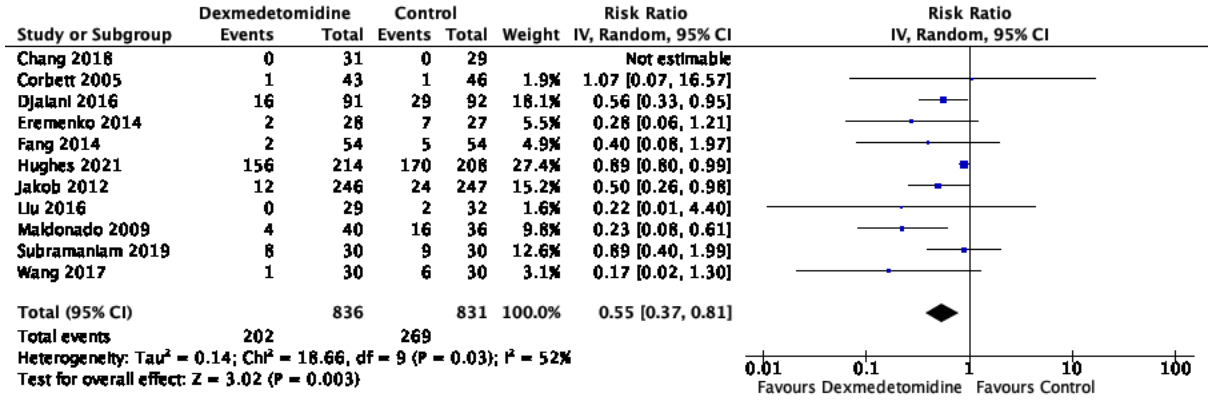
	% CV surgical: 0%	2)Second or third degree heart block, 3)History of use of long-term benzodiazepine, opioids 4)Known allergy to any of the study drug 5)Gross obesity (over 50% above ideal body weight) 6)Known or suspected pregnancy					
Subramanian *et al* 2019 RCT United States Single center n=60	Mean age: 70.0* % Female: 15% Mean APACHE II: NR % Surgical: 100% % CV surgical: 100%	**Inclusion:** Age ≥60, undergoing coronary artery bypass graft surgery with or without aortic and/or mitral valve replacement requiring cardiopulmonary bypass **Exclusion:** 1)Patients with a preoperative left ventricular ejection fraction of less than 30%, 2)Preexisting cognitive impairment, Alzheimer disease, Parkinson disease, medications for cognitive decline, seizures 3)Creatinine levels above 5mg/dL, 4)Liver dysfunction, 5)Recent history of alcohol misuse, 6)English-language limitations 7)Hypersensitivity to study medications 8)Patients undergoing emergent surgery	Sternum closure	6 hours postop or until extubate-ion. whichever came first	Dex 0.5-1 µg/kg bolus then 0.1-1.4 µg/kg/h -Unclear titration goals	Propofol 20-100 µg/kg/min -Unclear titration goals	Delirium
Tasdogan *et al* 2009 RCT Turkey Single center n=40	Mean age: 54.0* % Female: 37.5% Mean APACHE II: 18.5 % Surgical: 100% % CV surgical: 0%	**Inclusion:** Severe sepsis after abdominal surgery **Exclusion:** 1)Known allergy to propofol or dexmedetomidine, 2)Possible or confirmed pregnancy, 3)Hemodynamic instability 3)Heart failure (class III or IV of the New York Heart Association), 4)Renal failure, liver failure 5)Known or suspected brain death.	ICU arrival	24h	Dex 1 µg/kg bolus then 0.2-2.5 µg/kg/h -Titrated to RSS <2	Propofol 1 mg/kg bolus then 1-3 mg/kg/h -Titrated to RSS <2	Effects on serum cytokine levels
Venn *et al* 2001 RCT	Mean age: 67.1 % Female: NR Mean APACHE II: 15.9	**Inclusion:** Age ≥18, major abdominal or pelvic surgery requiring ≥8 hours of postop IMV	ICU arrival	Up to 24h	Dex 2.5 µg/kg bolus then 0.2-2.5 µg/kg/h -Titrated to RSS >2	Propofol bolus 1mg/kg then 1-3 mg/kg/h -Titrated to RSS >2	Effect on adrenocortical function

United Kingdom Single center n=20	% Surgical: 100% % CV surgical: 0%	**Exclusion:** Exclusion criteria not discussed					
Wang *et al* 2017 RCT China Single center n=60	Mean age: 53.7 % Female: 53.3% Mean APACHE II: NR % Surgical: 100% % CV surgical: 100%	**Inclusion criteria:** Age 18-85, post-cardiac valve surgery and anticipated to require >12h of IMV **Exclusion criteria:** 1)Intracranial disease 2)Mental health 3)Severe sleep disorder 4)Alcohol abuse 5)Prolonged surgery 6)Complications with surgery such as cardiac arrest or need for thoracotomy	NR	NR	Dex 0.2-0.7 µg/kg/h -Titration to BIS of 70-85 and RASS -2 to 3	Propofol 1.2-3.0 mg/kg/h -Titration to BIS of 70-85 and RASS-2 to 3	NR
Wang *et al* 2019 RCT China Single center n=323	Mean age: 82.3 % Female: 52.6% Mean APACHE II: NR % Surgical: 57.9% % CV surgical: NR	**Inclusion criteria:** Age ≥70 requiring sedation in the ICU Exclusion criteria: 1) Chronic drug abuse 2)Terminally ill patient 3)Other	NR	NR	Dex bolus 0.5-1 µg/kg then 0.1-1 µg/kg/h -Titration to appropriate RSS as determined by treating physician	Propofol bolus 0.5-1 mg/kg then 25-75 µg/kg/min -Titration to appropriate RSS as determined by treating physician	NR

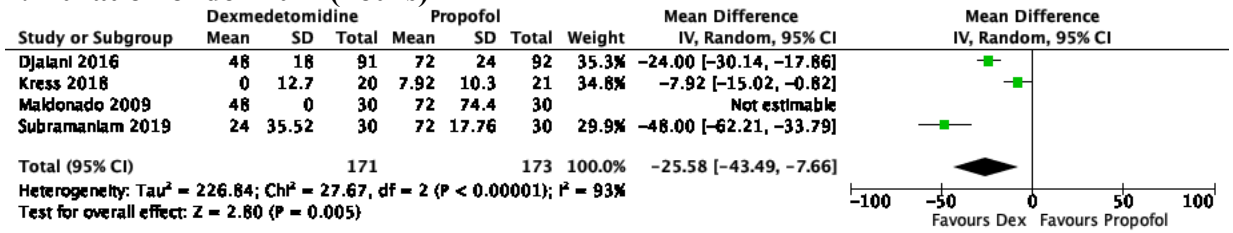
AKI-Acute kidney injury; ASA=American society of Anesthesiologists score; APACHE=Acute Physiology and Chronic Health Evaluation; AV=Atrioventricular; BIS=Bispectral index score; BMI=Body mass index; BPM=Beats per minute; CABG=Coronary artery bypass graft; CV=Cardiovascular; CVA=Cerebrovascular accident; Dex=Dexmedetomidine; HR=Heart rate; ICU=Intensive care unit; IMV=Invasive mechanical ventilation; MAP=Mean arterial pressure; MI=Myocardial infarction; NR=Not recorded; RASS=Richmond Agitation-Sedation Scale; RCT=Randomized clinical exam; RSS=Ramsay Sedation Scale; SAS= Riker Sedation-Agitation Scale; SBP=Systolic blood pressure

2. Forest Plots

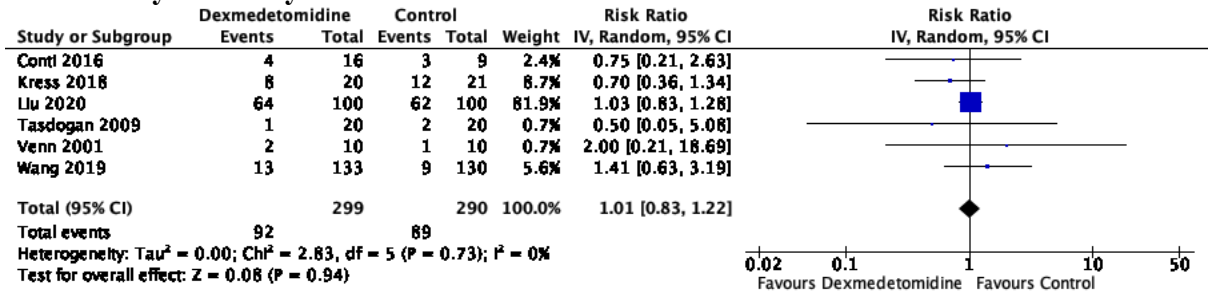
1. Delirium



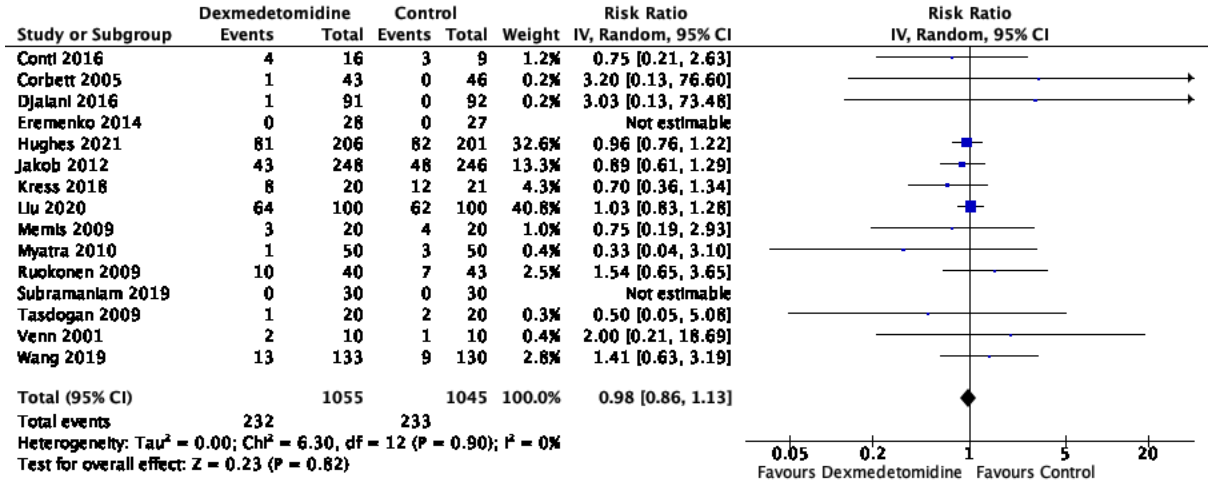
2. Duration of delirium (hours)



3. Mortality at 28 days



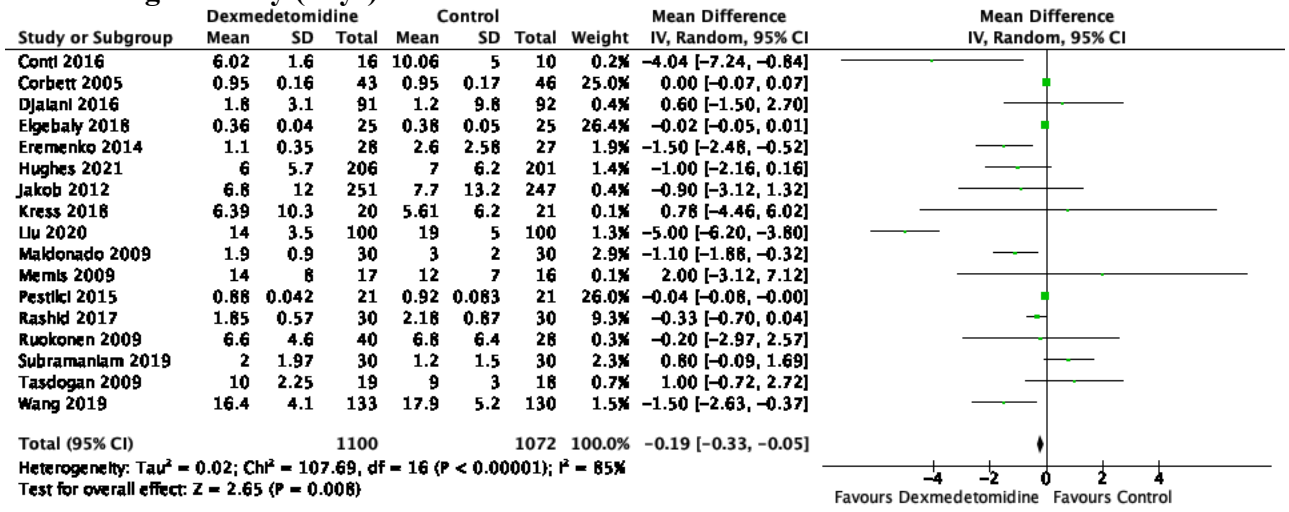
4. Mortality at longest follow-up



Study or Subgroup	Dexmedetomidine Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Conti 2016	4	16	3	9	1.2%	0.75 [0.21, 2.63]
Corbett 2005	1	43	0	46	0.2%	3.20 [0.13, 76.60]
Djalani 2016	1	91	0	92	0.2%	3.03 [0.13, 73.48]
Eremenko 2014	0	28	0	27		Not estimable
Hughes 2021	81	206	82	201	32.6%	0.96 [0.76, 1.22]
Jakob 2012	43	248	48	246	13.3%	0.89 [0.61, 1.29]
Kress 2018	8	20	12	21	4.3%	0.70 [0.36, 1.34]
Liu 2020	64	100	62	100	40.8%	1.03 [0.83, 1.28]
Memis 2009	3	20	4	20	1.0%	0.75 [0.19, 2.93]
Myatra 2010	1	50	3	50	0.4%	0.33 [0.04, 3.10]
Ruokonen 2009	10	40	7	43	2.5%	1.54 [0.65, 3.65]
Subramaniam 2019	0	30	0	30		Not estimable
Tasdogan 2009	1	20	2	20	0.3%	0.50 [0.05, 5.08]
Venn 2001	2	10	1	10	0.4%	2.00 [0.21, 18.69]
Wang 2019	13	133	9	130	2.8%	1.41 [0.63, 3.19]
Total (95% CI)		1055		1045	100.0%	0.98 [0.86, 1.13]
Total events	232		233			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.30$, $df = 12$ ($P = 0.90$); $I^2 = 0\%$
Test for overall effect: $Z = 0.23$ ($P = 0.82$)

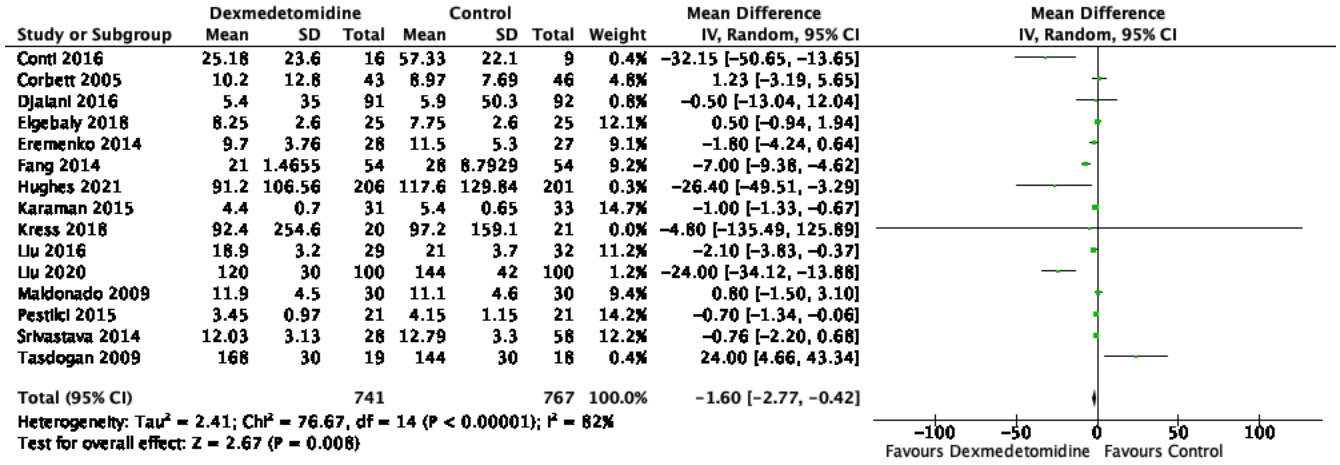
5. ICU length of stay (days)



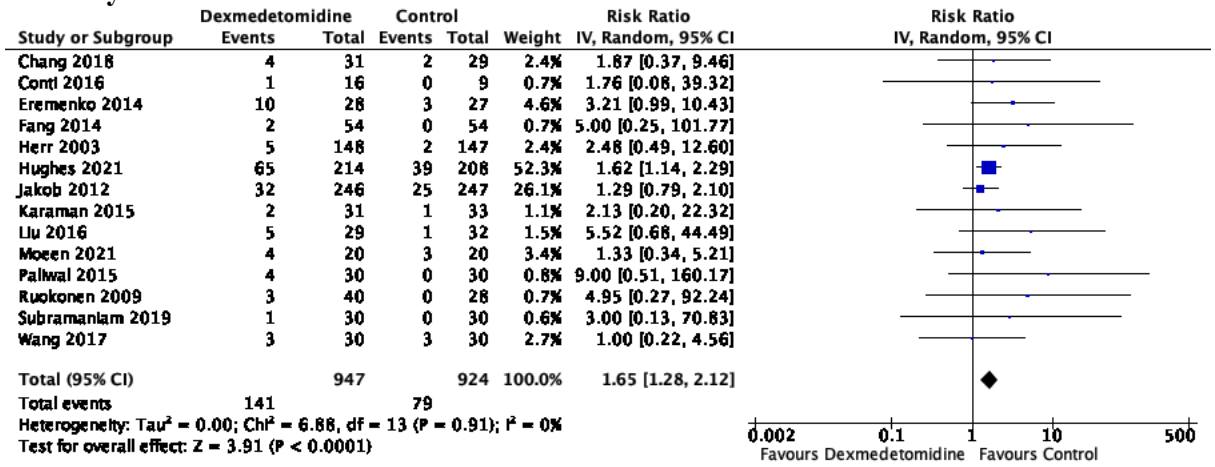
Study or Subgroup	Dexmedetomidine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Conti 2016	6.02	1.6	16	10.06	5	10	0.2%	−4.04 [−7.24, −0.84]
Corbett 2005	0.95	0.16	43	0.95	0.17	46	25.0%	0.00 [−0.07, 0.07]
Djalani 2016	1.8	3.1	91	1.2	9.8	92	0.4%	0.60 [−1.50, 2.70]
Elgebaly 2018	0.36	0.04	25	0.38	0.05	25	26.4%	−0.02 [−0.05, 0.01]
Eremenko 2014	1.1	0.35	28	2.6	2.58	27	1.9%	−1.50 [−2.48, −0.52]
Hughes 2021	6	5.7	206	7	6.2	201	1.4%	−1.00 [−2.16, 0.16]
Jakob 2012	6.8	12	251	7.7	13.2	247	0.4%	−0.90 [−3.12, 1.32]
Kress 2018	6.39	10.3	20	5.61	6.2	21	0.1%	0.78 [−4.46, 6.02]
Liu 2020	14	3.5	100	19	5	100	1.3%	−5.00 [−6.20, −3.80]
Maldonado 2009	1.9	0.9	30	3	2	30	2.9%	−1.10 [−1.88, −0.32]
Memis 2009	14	8	17	12	7	16	0.1%	2.00 [−3.12, 7.12]
Pestiki 2015	0.88	0.042	21	0.92	0.083	21	26.0%	−0.04 [−0.08, −0.00]
Rashid 2017	1.85	0.57	30	2.18	0.87	30	9.3%	−0.33 [−0.70, 0.04]
Ruokonen 2009	6.6	4.6	40	6.8	6.4	28	0.3%	−0.20 [−2.97, 2.57]
Subramaniam 2019	2	1.97	30	1.2	1.5	30	2.3%	0.80 [−0.09, 1.69]
Tasdogan 2009	10	2.25	19	9	3	18	0.7%	1.00 [−0.72, 2.72]
Wang 2019	16.4	4.1	133	17.9	5.2	130	1.5%	−1.50 [−2.63, −0.37]
Total (95% CI)			1100			1072	100.0%	−0.19 [−0.33, −0.05]

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 107.69$, $df = 16$ ($P < 0.00001$); $I^2 = 85\%$
Test for overall effect: $Z = 2.65$ ($P = 0.008$)

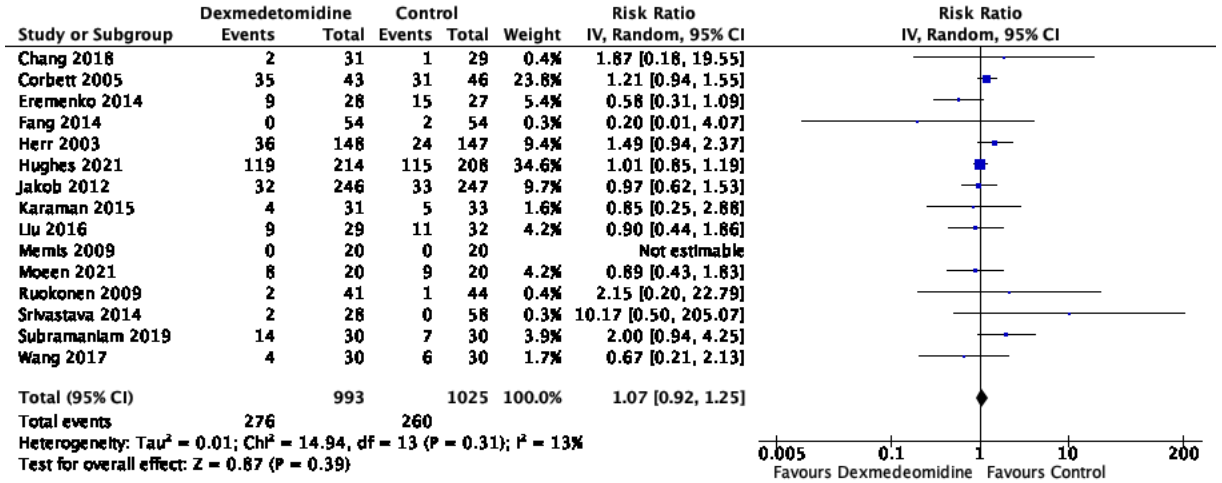
6. Duration invasive mechanical ventilation (hours)



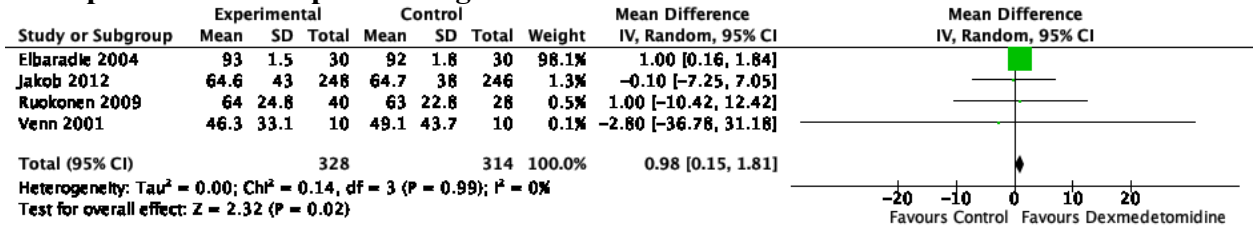
7. Bradycardia



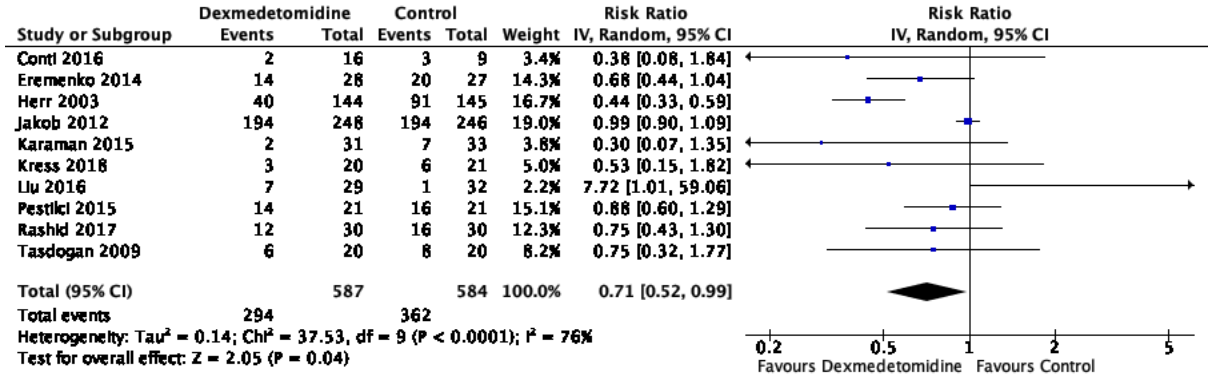
8. Hypotension



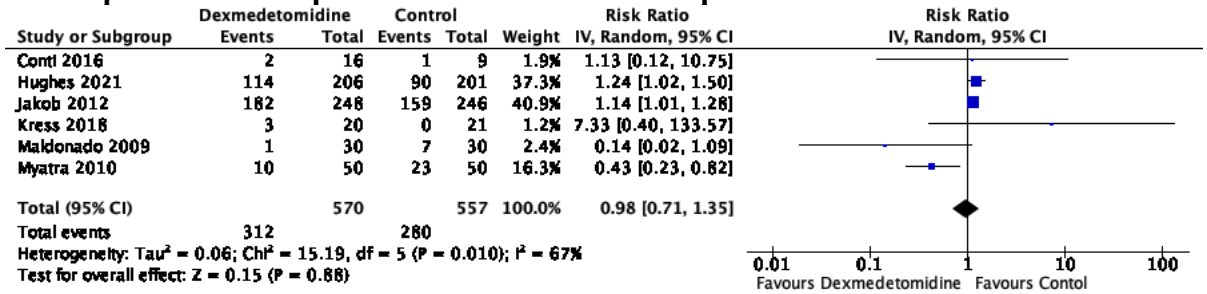
9. Proportion of time spent at target sedation



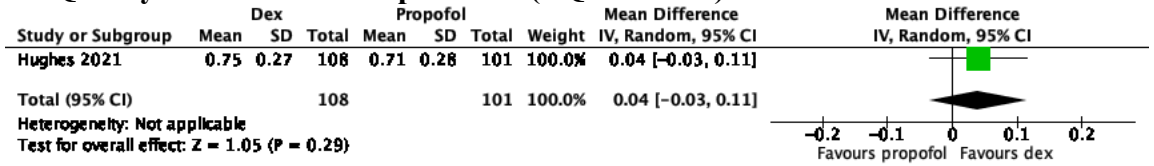
10. Proportion that required supplemental opioids



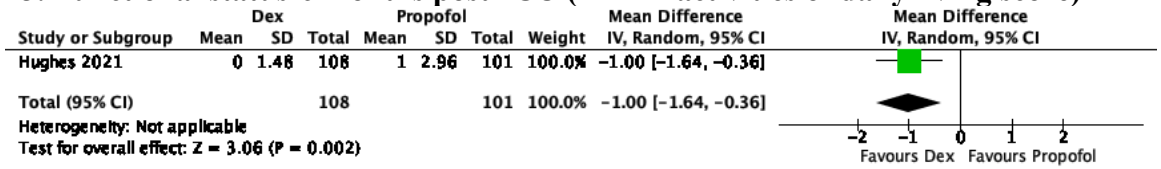
11. Proportion that required additional benzodiazepines



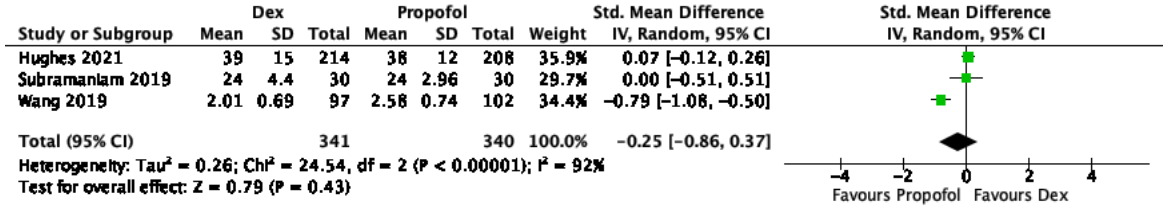
12. Quality of Life-6 months post ICU (EQ-5D score)



13. Functional status-6 months post-ICU (KATZ activities of daily living score)



14. Cognitive abilities post-ICU (SEM)



3. Risk of bias

Trial	Random Sequence Generation	Randomized Concealment	Blinding-Clinical Team/Patient	Blinding-Outcome Assessors	Incomplete Data	Selection bias	Other	Overall
Chang *et al* 2018	Low	Possibly high	Low	Low	Low	High	Possibly low	High
Conti *et al* 2016	Possibly low	Possibly low	Low	Low	Low	Low	Possibly high	High
Corbett *et al* 2005	Low	Possibly low	High	High	Low	Low	Possibly low	High
Djaiani *et al* 2016	Low	Possibly low	Low	Low	Low	Low	Possibly high	High
Elbaradie *et al* 2004	Possibly low	Possibly low	High	High	Possibly low	Low	Possibly low	High
Elgebaly *et al* 2018	Possibly low	Possibly low	Low	Low	Low	Low	Low	Low
Eremenko *et al* 2014	Low	Possibly low	Possibly low	Possibly low	Low	Low	Possibly low	Low
Fang *et al* 2014	Possibly low	Possibly high	Possibly high	Possibly high	Possibly low	Possibly low	Possibly low	High
Herr *et al* 2003	Low	High	High	High	Low	Low	Low	High
Hughes *et al* 2021	Low	Low	Low	Low	Low	Low	Low	Low
Jakob *et al* 2012	Low	Low	Low	Low	Low	Low	Possibly high	High
Karaman *et al* 2015	Possibly low	High	Low	Low	Low	Low	Possibly low	High
Kress *et al* 2018	Possibly low	Possibly low	Low	Low	High	Low	Possibly low	High
Liu *et al* 2016	Low	Possibly low	Low	Low	Low	Low	Low	Low
Liu *et al* 2020	Possibly low	Possibly low	Possibly low	Possibly low	Possibly high	Low	Low	High
Maldonado *et al* 2009	Low	Possibly low	High	High	High	Low	Possibly low	High
Memis *et al* 2009	Low	High	Low	Low	Possibly low	Low	Low	High
Moeen *et al*	Low	Possibly high	Possibly low	Possibly low	Low	Low	Low	High

2021								
Myatra *et al* 2010	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Potentially high	High
Paliwal *et al* 2015	Possibly low	Possibly low	Possibly low	Unclear	Low	Unclear	Possibly low	Unclear
Pestilci *et al* 2015	Low	Low	Possibly high	Possibly high	Possibly low	Possibly low	Possibly low	High
Rashid *et al* 2017	Low	Possibly low	Low	Low	Low	Possibly low	Low	Low
Ruokonen *et al* 2009	Possibly low	Possibly low	Low	Low	High	Low	Possibly high	High
Srivastava *et al* 2014	Low	Possibly low	High	High	Low	Low	Low	High
Subramanian *et al* 2019	Low	Possibly Low	Low	Low	Low	Low	Low	Low
Tasdogan *et al* 2009	Low	High	Low	Low	Low	Low	Low	High
Venn *et al* 2001	Possibly low	High	Low	Low	Low	Low	Possibly high	High
Wang *et al* 2017	Low	Possibly low	Possibly low	Possibly low	Low	Possibly low	Possibly low	Low
Wang *et al* 2019	Possibly low	Possibly low	Possibly low	Possibly low	High	Possibly low	Low	High

4. Summary Of Findings Table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomidine	propofol	Relative (95% CI)	Absolute (95% CI)		
Delirium												
11	randomised trials	not serious[a]	serious[b]	not serious	not serious[c]	none	202/836 (24.2%)	269/831 (32.4%)	**RR 0.55** (0.37 to 0.81)	**15 fewer per 100** (from 20 fewer to 6 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Duration of delirium (hours)												
4	randomised trials	not serious[d]	serious[e]	not serious	serious[f]	none	171	173	-	MD **25.58 lower** (43.49 lower to 7.66 lower)	⨁⨁◯◯ Low	CRITICAL
28d mortality												
6	randomised trials	serious[g]	not serious	not serious	very serious[h]	none	92/299 (30.8%)	89/290 (30.7%)	**RR 1.01** (0.83 to 1.22)	**0 fewer per 100** (from 5 fewer to 7 more)	⨁◯◯◯ Very low	IMPORTANT
Mortality at longest follow-up												
15	randomised trials	not serious[d]	not serious	not serious	very serious[i]	none	232/1055 (22.0%)	233/1045 (22.3%)	**RR 0.98** (0.86 to 1.13)	**0 fewer per 100** (from 3 fewer to 3 more)	⨁⨁◯◯ Low	IMPORTANT
ICU Length of Stay (days)												
17	randomised trials	serious[j]	serious[e]	not serious	not serious	none	1100	1072	-	MD **0.19 lower** (0.33 lower to 0.05 lower)	⨁⨁◯◯ Low	CRITICAL
Duration IMV (hours)												
15	randomised trials	serious[j]	serious[e]	not serious	not serious	none	741	767	-	MD **1.6 lower** (2.77 lower to 0.42 lower)	⨁⨁◯◯ Low	CRITICAL
Bradycardia												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomidine	propofol	Relative (95% CI)	Absolute (95% CI)		
14	randomised trials	not serious[d]	not serious	not serious	serious[k]	none	141/947 (14.9%)	79/924 (8.5%)	**RR 1.65** (1.28 to 2.12)	**6 more per 100** (from 2 more to 10 more)	⨁⨁⨁◯ Moderate	CRITICAL
Hypotension												
15	randomised trials	serious[l]	not serious	not serious	serious[m]	none	276/993 (27.8%)	260/1025 (25.4%)	**RR 1.07** (0.92 to 1.25)	**2 more per 100** (from 2 fewer to 6 more)	⨁⨁◯◯ Low	CRITICAL
% of time at target sedation												
4	randomised trials	serious[g]	not serious	not serious	serious[n]	none	328	314	-	MD **0.98 higher** (0.15 higher to 1.81 higher)	⨁⨁◯◯ Low	CRITICAL
% that required supplemental analgesics												
10	randomised trials	not serious[d]	serious[e]	not serious	not serious	none	294/587 (50.1%)	362/584 (62.0%)	**RR 0.71** (0.52 to 0.99)	**18 fewer per 100** (from 30 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Quality of Life (EQ-5D)												
1	randomised trials	not serious	not serious	not serious	very serious[o]	none	108	101	-	MD **0.04 higher** (0.03 lower to 0.11 higher)	⨁⨁◯◯ Low	IMPORTANT
Functional Status Post-ICU												
1	randomised trials	not serious	not serious	not serious	very serious[o]	none	108	101	-	MD **1 lower** (1.64 lower to 0.36 lower)	⨁⨁◯◯ Low	IMPORTANT
Cognitive abilities post-ICU												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexmedetomidine	propofol	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[p]	serious[a]	not serious	serious[q]	none	341	340	-	SMD **0.25 lower** (0.86 lower to 0.37 higher)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference

Explanations

a. When high ROB trials are removed, the point estimate still demonstrates benefit
b. I^2 is 52% and P=0.03, point estimates and confidence intervals roughly overlap. This may be explained by an effect modification of target of light sedation, however, there were no studies the exclusively enrolled deep sedation to provide a test for subgroup difference
c. MID set at 5/100
d. Although most studies have ROB, when the high ROB studies are removed, the point estimate is preserved
e. I^2 is well over 50%, and confidence intervals and point estimates are not overlapping
f. Although the confidence intervals are precise, the optimal information size is not met
g. Most of the publications have ROB
h. The confidence interval crosses the line of both harm and benefit. If the minimally important clinical difference is 1 per 100, the upper end of the confidence interval is crossed, as is the threshold for important harm
i. Estimate of effect demonstrates both benefit and harm. With a minimally important clinical difference of 1 patient per 100, the upper end of the confidence interval crosses the line of no effect, as is the threshold for harm (1 per 100 patients)
j. Most trials have ROB, when the high ROB trials are removed the confidence interval crosses the line of no effect
k. Low number of events (less than optimal information size)
l. When the high ROB trials are removed, the point estimate changes to reduction in risk of hypotension
m. With a minimally important clinical difference of 5 per 100, the upper end of the confidence interval crosses the line for important harm
n. OIS is not met
o. Only 1 trial, the confidence interval cross line of both benefit and harm
p. When high ROB trials are removed, the point estimate changes from favoring propofol to favoring dexmedetomidine
q. The confidence intervals cross the line of both harm and benefit

5. Evidence-To-Decision Framework

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes	In 2018, the Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in critically ill adults were published. A	[1] Hughes, C et al. Dexmedetomidine or Propofol for Sedation in Mechanically Ventilated Adults with Sepsis. N Engl J Med 2021; 384:1424-1436

● Yes ○ Varies ○ Don't know	weak recommendation (low certainty evidence) was issued to use propofol or dexmedetomidine over benzodiazepines for sedation in mechanically ventilated adults. Given that the large RCT MENDS2 [1] was recently published, it warranted an updated search to identify if a recommendation could be made.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**<u>Important effect of:</u>** **1. Reduction in delirium,** RR 0.55, 95% CI 0.37 to 0.81 (moderate certainty) **2. Duration of delirium** (hours), MD -25.58h, 95% CI -43.49h to -7.66h (low certainty) **3. ICU length of stay** (days), MD -0.19d, 95% CI -0.33d to -0.05d (low certainty) **4. % of time at target sedation,** MD 098%, 95% CI 0.15 to 1.81%) (low certainty) **5. % that require additional analgesics**, RR 0.71, 95% CI 0.52 to 0.99 (moderate certainty) **6. Functional status 6 months post-ICU**, MD -1, 95% CI-1.64 to -0.36 (low certainty) **<u>Little to no effect</u>** **1.Duration IMV** (hours), -1.6h, 95% CI -2.77h to -0.42h (low certainty) **2.Mortality at longest follow up** (low certainty) **<u>Uncertainty</u>** **1.28d mortality** (very low certainty) **2.Quality of life** (low certainty) **3.Cognitive abilities post-ICU** (very low certainty)	
Undesirable Effects		

How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**<u>Adverse events</u>** **1. Bradycardia,** RR 1.65, 95% CI 1.28 to 2.12, ARR 6 more per 100 patients, 95% CI from 2 more to 10 more (moderate certainty) **2. Hypotension,** RR 1.07, 95% CI 0.92 to 1.25, ARR from 2 more per 100, 95% CI from 2 fewer to 6 more (low certainty)	Small because most of the time resolution simply requires a dose reduction

Certainty of evidence

What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	**<u>Important effect of:</u>** **1. Reduction in delirium,** RR 0.55, 95% CI 0.37 to 0.81 (moderate certainty) **2. Duration of delirium** (hours), MD -25.58h, 95% CI -43.49h to -7.66h (low certainty) **3. ICU length of stay** (days), MD -0.19d, 95% CI -0.33d to -0.05d (low certainty) **4. % of time at target sedation,** MD 098%, 95% CI 0.15 to 1.81%) (low certainty) **5. % that require additional analgesics**, RR 0.71, 95% CI 0.52 to 0.99 (moderate certainty) **6. Functional status 6 months post-ICU**, MD -1, 95% CI-1.64 to -0.36 (low certainty) **<u>Little to no effect</u>** **1.Duration IMV** (hours), -1.6h, 95% CI -2.77h to -0.42h (low certainty) **2.Mortality at longest follow up** (low certainty)	

	<u>Uncertainty</u> **1.28d mortality** (very low certainty) **2.Quality of life** (low certainty) **3.Cognitive abilities post-ICU** (very low certainty) **<u>Adverse events</u>** **1. Bradycardia,** RR 1.65, 95% CI 1.28 to 2.12, ARR 6 more per 100 patients, 95% CI from 2 more to 10 more (moderate certainty) **2. Hypotension,** RR 1.07, 95% CI 0.92 to 1.25, ARR from 2 more per 100, 95% CI from 2 fewer to 6 more (low certainty)	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	-Included long term outcomes that was noted as a gap in the 2018 guidelines -Also had 3 patient partners	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**Important effect of:** **1. Reduction in delirium,** RR 0.55, 95% CI 0.37 to 0.81 (moderate certainty) **2. Duration of delirium** (hours), MD -25.58h, 95% CI -43.49h to -7.66h (low certainty) **3. ICU length of stay** (days), MD -0.19d, 95% CI -0.33d to -0.05d (low certainty) **4. % of time at target sedation,** MD 098%, 95% CI 0.15 to 1.81%) (low certainty) **5. % that require additional analgesics**, RR 0.71, 95% CI 0.52 to 0.99 (moderate certainty) **6. Functional status 6 months post-ICU**, MD -1, 95% CI-1.64 to -0.36 (low certainty) **Little to no effect** **1.Duration IMV** (hours), -1.6h, 95% CI -2.77h to -0.42h (low certainty) **2.Mortality at longest follow up** (low certainty) **Uncertainty** **1.28d mortality** (very low certainty) **2.Quality of life** (low certainty) **3.Cognitive abilities post-ICU** (very low certainty) **Adverse events** **1. Bradycardia,** RR 1.65, 95% CI 1.28 to 2.12, ARR 6 more per 100 patients, 95% CI from 2 more to 10 more (moderate certainty) **2. Hypotension,** RR 1.07, 95% CI 0.92 to 1.25, ARR from 2 more per 100, 95% CI from 2 fewer to 6 more (low certainty)	
Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	-The cost of dex varies upon the region of practice - A recent economic analysis of the use of DEX vs propofol in the US, found that DEX-based sedation compared to PRO was associated with similar ICU and hospital costs (US$ 67,561 vs. 78,429, p = 0.39; US$ 71,923 vs. 71,084, p = 0.1). -However, there is varying costs throughout the world, even within countries as the cost of generics varies greatly	1. Turunen H, Jakob SM, Ruokonen E et al (2015) Dexmedetomidine versus standard care sedation with propofol or midazolam in intensive care: an economic evaluation. Crit Care 19:67. https:// doi. org/ 10. 1186/ s13054-015-0787-y 2. CADTH (2017) Dexmedetomidine for sedation in the critical 3. Mo Y, Shcherbakova N, Zeibeq, Muzykovsky K, Li W, Gasperino J. Clinical and economic impact of the use of dexmedetomidine for sedation in the intensive care unit compared to propofol

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	There is a lot of variation depending upon location	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	Depends upon your location	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	-The cost will vary drastically depending upon what area you are in. -In addition, smaller rural communities or countries may not carry dexmedetomidine	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	A ubiquitous medication used in ICU from higher income countries -Likely standard of care	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No concerns	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

We suggest using dexmedetomidine over propofol for sedation in mechanically ventilated adult patients admitted to the intensive care unit where light sedation and/or a reduction in delirium are of highest priorities (Conditional recommendation; For intervention; Moderate certainty of evidence)

9.3 PICO 3-Antipsychotics for Delirium

PICO 3- In adults admitted to the ICU, do antipsychotics administered for delirium vs no antipsychotics, impact patient outcomes?

P- Adults with delirium who are admitted to the ICU
I- Any antipsychotic medication, of any dose, route, duration, or frequency
C- No antipsychotics
O-1.Mortality-28d and at longest follow-up; 2.Duration of mechanical ventilation; 3.Incidence/Duration of delirium ; 4. ICU LOS; 5. Hospital LOS; 6. Patient's function/cognition/QoL post-ICU; 7.Incidence of post-ICU anxiety/PTSD; 8.Adverse events

1. Characteristics of Included Trials

Author, year	Patients included	Inclusion/Exclusion criteria	Intervention	Control	Primary outcome
Andersen-Ranberg 2022 RCT Europe Multi-center General ICU n=987	Mean age: 70.5±10.0 % Females: 34.2% Mean APACHE II: NR Hypoactive delirium at randomization: 54.7% Hyperactive delirium at randomization: 45.3%	**Inclusion criteria:** 1) Age ≥ 18 years old 2) Admitted to the ICU 3) Positive delirium using CAM-ICU or ICDSC **Exclusion criteria:** 1) Contraindications for haloperidol/intolerance to haloperidol or additives 2) Habitual treatment with antipsychotic medication 3) Permanently incompetent patient 4)Delirium assessment non-applicable 5) Withdrawal from active therapy or brain death 6) Alcohol-induced delirium 7) Treatment with antipsychotics in the 8) Fertile woman 9)Patient under coercive measured by regulation authorities 10)Consent non-attainable	Haloperidol 2.5mg IV, three times daily -May administer additional doses of haloperidol up to a daily total of 20mg -Rescue medication of propofol, benzodiazepines, or alpha 2 agonists were permitted at discretion of the clinical team for uncontrollable delirium N=501 -Up until discharge or death, to a maximum of 90days after randomization n=501	Placebo IV three times daily n=486	Days alive and out of hospital from randomization to day 90
Atalan 2013 RCT Turkey Single center Post CV-surgery ICU n=53	Mean Age: 65.87 ±9.03 % Females: 26.4% Mean APACHE II: 6.01±1.86 Hypoactive delirium at enrollment: 0% Hyperactive delirium at enrollment: 100%	**Inclusion criteria:** 1)Post cardiac surgery patients (with or without bypass) with hyperactive delirium (diagnosed by CAM-ICU, and if positive, a RASS>2). **Exclusion criteria:** 1)Hypoactive delirium 2)History of Dementia 3)Decreased level of consciousness 4)Parkinson's disease and	Haloperidol 5mg IM q1h to RASS -1 to +1 -May received lorazepam 2.5mg BID PRN for ongoing agitation -n=26	Morphine 5mg IM q1h to RASS -1 to +1 -n=27	1)Duration time of delirious behavior 2)Daily total medication doses 3)Need for additional sedative drug 4)RASS scores, the percentage of patients who maintained a

		5)Recent seizures prior to surgery.			RASS score within the target scores 5)Reintubation 6)Redo-surgery 7)Length of ICU and hospital stay 8)Readmission to the ICU 9)Hospital mortality rate (no primary identified)
Devlin 2010 RCT United States Single center Medical and surgical ICU n=36	Mean Age: 63±14.7 % Females: 44% Mean APACHE II: 20.6±7.3 Hypoactive delirium at enrollment: NR Hyperactive delirium at enrollment: NR	**Inclusion Criteria:** 1)Admitted to the ICU with a diagnosis of Delirium (diagnosed by ICDSC ≥4), 2)Had a PRN order of haloperidol, and 3)Were tolerating enteral nutrition (≥20ml/hx12h) **Exclusion criteria:** 1)Recent antipsychotic use 2)Inability to tolerate enteral nutrition 3)Primary neurologic condition 4)Advanced liver disease 5)Active alcohol withdrawal.	Quetiapine 50 mg PO q12h -Allowed to titrate the Quetiapine up by 50mg to a maximum dose of 200mg q12h -Allowed to have PRN Haloperidol breakthrough -n=18	Placebo -Allowed to have PRN Haloperidol breakthrough -n=18	Time to delirium resolution
Early 2017 RCT United States Single centre/multiple ICUs Medical/Surgical/Trauma/CV surgical ICUs n=30	Mean age: NR % Female: 36.7% APACHE II :NR Hypoactive delirium at enrollment: NR Hyperactive delirium at enrollment: NR	**Inclusion:** 1)Adults ≥18yo who are mechanically ventilated and expected, and admitted to the medial, surgical, trauma or cardiothoracic ICU of the University of Pennsylvania Medical Center **Exclusion:** 1) Baseline Qtc>480ms 2)History of Parkinson's disease 3) Pregnancy 4) History of schizophrenia or neurologic disease that would confound the delirium assessment 5) Deafness or inability to understand English or Spanish 6) Extubation prior to enrollment 7)Previously enrolled in the study 8)Haloperidol use within 2 days prior to ICU admission 9)Prisoners	Haloperidol 5mg IV q12h n=16	Placebo n=14	90-day mortality

Garg 2022 RCT India Singe center Unclear type of ICU n=45	Mean Age: 56.5 ±11.6 % Females: 44.4% APACHE II: 29.5±3.7 Hypoactive delirium at enrollment: NR Hyperactive delirium at enrollment: NR	**Inclusion criteria:** Patients ≥18yo admitted in ICU with delirium (defined by CAM-ICU) who were accepting enteral medication **Exclusion criteria:** 1)Patients who at baseline had severe cognitive impairment, 2)High risk for medication side-effects because of pregnancy and breast feeding. 3)Patients with history of torsade de pointes, neuroleptic malignant syndrome, or allergy to haloperidol or quetiapine 4)Ongoing treatment with antipsychotics 5)Rapidly resolving organ failure 6)Moribund patients 7)Blind or unable to speak or understand	Group A: Haloperidol 30mg daily PO daily maximum n=15 Group B: Quetiapine 300 mg PO daily maximum n=15	Matched Placebo n=15	Alive without Delirium
Girard 2018 RCT United States Medical or Surgical ICU Multi-centered n=566	Mean Age: 60.3 ± 12.8 % Females: 42.9% APACHE II: 28.8 ± 7.9 Hypoactive delirium at enrollment: 89.2% Hyperactive delirium at enrollment: 10.1%	**Inclusion criteria:** 1)≥18 years admitted to an ICU on invasive or non-invasive positive pressure ventilation, vasopressors, or an intra-aortic balloon pump, and diagnosis of delirium (defined by CAM-ICU). **Exclusion criteria:** 1)Baseline severe cognitive impairment 2)High risk for medication side effects because of pregnancy, breast-feeding, a history of torsades de pointes, QT prolongation, a history of neuroleptic malignant syndrome, or allergy to haloperidol or ziprasidone 3)Receiving ongoing treatment with an antipsychotic medication 4)Moribund state 5)Rapidly resolving organ failure 6)Blind, deaf, or unable to speak or understand English 7)Incarcerated 8)Enrolled in another study or trial that prohibited co-enrollment	Group A: Haldoperidol 2.5mg IV (if <70yo) or 1.25mg IV (if≥70yo) q12h (up to 10mg per dose and 20mg per day) n=192 Group B: Ziprasidone 5mg IV (if <70yo) or 2.5mg IV (if≥70yo) q12h (up to 20mg per dose and 40mg per day) n=190	Placebo n=184	Days alive without delirium or coma
Reade 2009 RCT	Mean Age: 60.3 ±23 % Females: 15%	**Inclusion criteria:**	Haloperidol was administered as a	Dexmedeto-midine was	Time to extubation

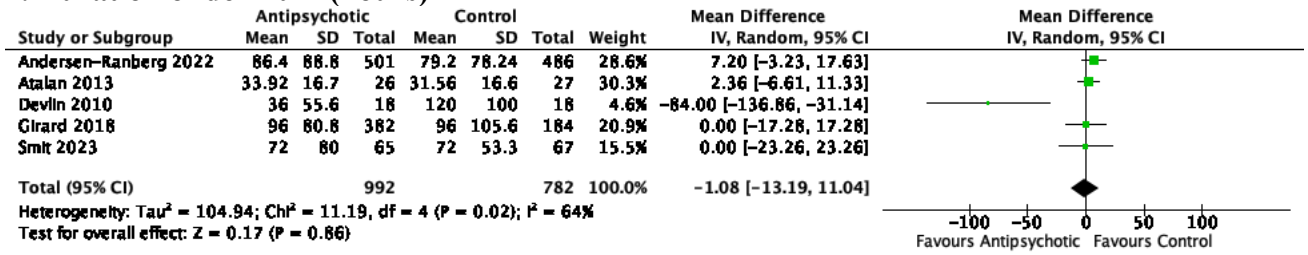
Australia Single center Medical/surgical ICU n=20	APACHE II: 14.4 ± 55.9 Hypoactive delirium at enrollment: 0% Hyperactive delirium at enrollment: 100%	1) Patients requiring mechanical ventilation and sedation only because of severe delirium (RASS>2) **Exclusion:** 1)Plan to return to the OR 2)High dose opioids for pain 3)Need for ongoing airway protection or ventilatory support 4)Unstable such that extubation was not feasible 5)Adverse reaction to alpha-2 agonists or haloperidol	continuous intravenous infusion of 0.5 to 2 mg/hour for as long as necessary, preceded by a loading dose of 2.5 mg if desired. -Titrated to RASS of 0 n=10	administered intravenously as a maintenance infusion of 0.2 to 0.7 µg/kg/hour for as long as deemed necessary by the treating physician. The clinician was given the option of using a loading dose of 1.0 µg/kg intravenously over 20 minutes, as recommended by the manufacturer. -Titrates to RASS of 0 -n=10	
Smit 2023 RCT Netherlands Multi-center Medical-surgical ICU n=132	Mean age: 64 years ± 15.3 % Females: 32% Mean APACHE II: NR Hypoactive delirium at enrollment: 25.7% Hyperactive delirium at enrollment: NR	**Inclusion criteria:** 1. Age≥18 years 2. Admitted to the ICU with delirium (ICDSC ≥4 or a positive CAM-ICU) **Exclusion criteria:** 1-Admitted to the ICU with an acute neurological diagnosis 2-Pregnancy or breast-feeding 3-History of ventricular arrhythmia including torsade de pointes 4-Known allergy to haloperidol 5-History of dementia or an Informant Questionnaire on Cognitive Decline in the Elderly score ≥412 6-History of malignant neuroleptic syndrome or parkinsonism (either Parkinson's disease or another hypokinetic rigid syndrome)	Haloperidol 2.5mg IV q8hours (if patient ≥80yo, 1mg) and increased to a maximum dose of 5mg IV q8 hours n=65 - When delirium had resolved (or was not assessable due to coma) for 24 h, study drug was decreased (from 5 to 2.5 mg for patients < 80 years or from 2.5 to 1 mg for patients ≥ 80 years) or stopped (if at a dose of	Placebo n=67	ICU delirium and coma-free days (up to 14 days after randomisation).

		7-Schizophrenia or other psychotic disorder 8-Inability to conduct valid delirium screening assessment (eg, coma, deaf, blind) or inability to speak the Dutch language. 9-Expected to die within 24hours or leave the ICU within 24hours 10-Already treated with haloperidol in the ICU for >24h or received >3 doses	2.5 mg for patients < 80 years or 1 mg for patients ≥ 80 years). The study drug was restarted if delirium re-occurred within the 14-day intervention period and the patient remained at the ICU.		

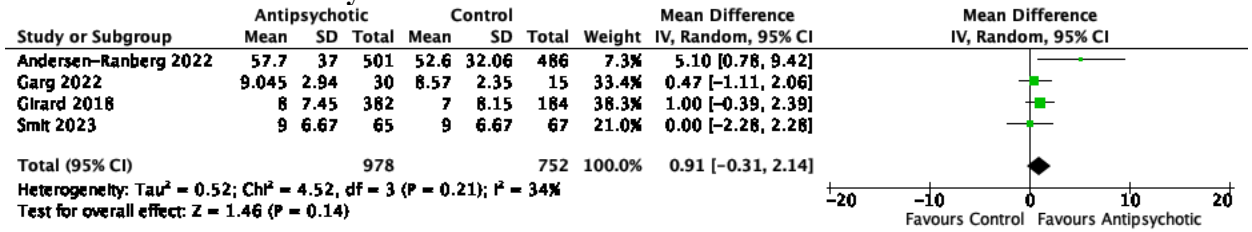
APACHE=Acute Physiology and Chronic Health Evaluation; BID=Dis in die; CAM=Confusion Assessment Method for ICU; CV=Cardiovascular; ICDSC=Intensive Care Delirium Screening Chesklist; ICU=Intensive care unit; IM=Intramusclar; IV=Intravenous; NR=Not recorded; OR=Operating room; PO=Per os; PRN=Pro re nata; RASS= Richmond Agitation-Sedation Scale; RCT=Randomized clinical exam; TID=Ter in die

2. Forest Plots

1. Duration of delirium (hours)



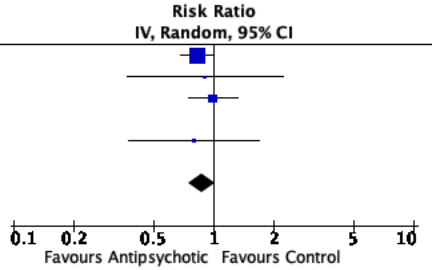
2. Delirium-coma free days



3. Mortality at 28 days

Study or Subgroup	Antipsychotic Events	Antipsychotic Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Andersen–Ranberg 2022	138	501	162	485	64.9%	0.82 [0.68, 1.00]
Garg 2022	9	30	5	15	2.9%	0.90 [0.37, 2.21]
Girard 2018	103	382	50	184	28.1%	0.99 [0.74, 1.32]
Reade 2019	0	10	0	10		Not estimable
Smit 2023	10	65	13	67	4.1%	0.79 [0.37, 1.68]
Total (95% CI)		988		761	100.0%	0.87 [0.75, 1.01]
Total events	260		230			

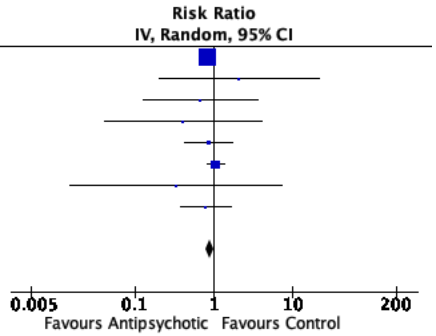
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.17$, $df = 3$ ($P = 0.76$); $I^2 = 0\%$
Test for overall effect: $Z = 1.80$ ($P = 0.07$)



4. Mortality at longest follow-up

Study or Subgroup	Antipsychotic Events	Antipsychotic Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Andersen–Ranberg 2022	182	501	210	485	65.7%	0.84 [0.72, 0.98]
Atalan 2013	2	26	1	27	0.3%	2.08 [0.20, 21.55]
Devlin 2010	2	18	3	18	0.6%	0.67 [0.13, 3.53]
Early 2017	1	16	2	13	0.3%	0.41 [0.04, 4.00]
Garg 2022	12	30	7	15	3.2%	0.86 [0.43, 1.72]
Girard 2018	138	382	63	184	27.0%	1.06 [0.83, 1.34]
Reade 2019	0	10	1	10	0.2%	0.33 [0.02, 7.32]
Smit 2023	10	65	13	67	2.8%	0.79 [0.37, 1.68]
Total (95% CI)		1048		819	100.0%	0.89 [0.79, 1.01]
Total events	347		300			

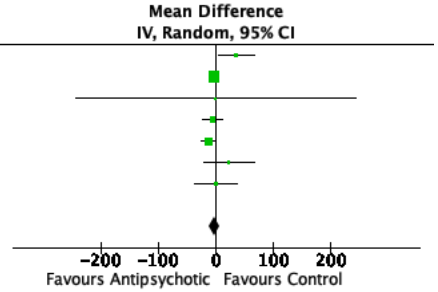
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.05$, $df = 7$ ($P = 0.77$); $I^2 = 0\%$
Test for overall effect: $Z = 1.83$ ($P = 0.07$)



5. Duration of invasive mechanical ventilation (hours)

Study or Subgroup	Antipsychotic Mean	Antipsychotic SD	Antipsychotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Andersen–Ranberg 2022	177.6	268.8	501	141.6	216	485	7.5%	36.00 [5.61, 66.39]
Atalan 2013	10.73	4.49	26	13.52	10.81	27	41.8%	−2.79 [−7.22, 1.64]
Devlin 2010	264	284.4	18	264	444.4	18	0.1%	0.00 [−243.74, 243.74]
Garg 2022	77.7	30.8	30	83	26.4	15	17.3%	−5.30 [−22.62, 12.02]
Girard 2018	59.9	74.3	382	72	71.1	184	24.3%	−12.10 [−24.79, 0.59]
Reade 2019	42.2	70.1	10	19.9	12.4	10	3.9%	22.30 [−21.82, 66.42]
Smit 2023	48	115.6	65	48	106.7	67	5.1%	0.00 [−37.98, 37.98]
Total (95% CI)			1032			806	100.0%	−1.47 [−10.55, 7.61]

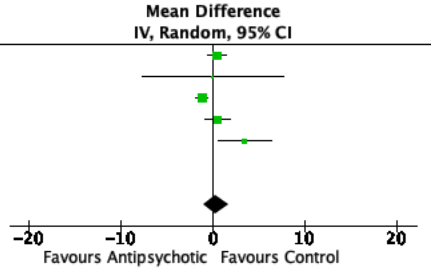
Heterogeneity: $Tau^2 = 46.21$; $Chi^2 = 9.66$, $df = 6$ ($P = 0.14$); $I^2 = 38\%$
Test for overall effect: $Z = 0.32$ ($P = 0.75$)



6. ICU Length of stay (days)

Study or Subgroup	Antipsychotic Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Atalan 2013	3.31	2.32	26	2.85	1.48	27	27.9%	0.46 [−0.59, 1.51]
Devlin 2010	16	8.89	18	16	14.07	18	2.9%	0.00 [−7.69, 7.69]
Garg 2022	5.37	1.16	30	6.56	1.01	15	31.0%	−1.19 [−1.85, −0.53]
Girard 2018	5.5	6.43	382	5	8.15	184	25.2%	0.50 [−0.84, 1.84]
Reade 2019	8	3	10	4.5	3.7	10	13.0%	3.50 [0.55, 6.45]
Smit 2023	18.1	33.4964	65	15.5	13.1191	67	0.0%	2.60 [−6.13, 11.33]
Total (95% CI)			466			254	100.0%	0.34 [−1.02, 1.71]

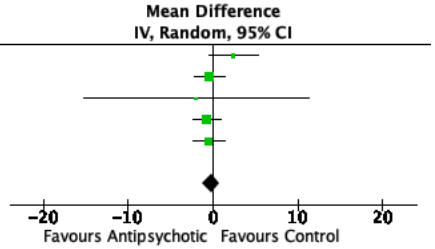
Heterogeneity: Tau² = 1.46; Chi² = 16.53, df = 4 (P = 0.002); I² = 76%
Test for overall effect: Z = 0.49 (P = 0.62)



7. Hospital Length of stay (days)

Study or Subgroup	Antipsychotic Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Andersen−Ranberg 2022	28.8	23.18	501	26.4	22.72	486	11.1%	2.40 [−0.46, 5.26]
Atalan 2013	8.54	3.44	26	8.93	3.11	27	29.2%	−0.39 [−2.16, 1.38]
Devlin 2010	24	16.3	18	26	23.7	18	0.5%	−2.00 [−15.29, 11.29]
Garg 2022	13.13	2.69	30	13.86	2.52	15	33.8%	−0.73 [−2.37, 0.91]
Girard 2018	12.5	10.01	382	13	11.11	184	25.4%	−0.50 [−2.39, 1.39]
Total (95% CI)			957			730	100.0%	−0.23 [−1.19, 0.72]

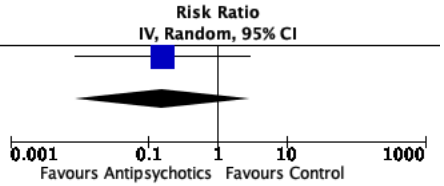
Heterogeneity: Tau² = 0.00; Chi² = 3.77, df = 4 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.63)



8. Incidence of PTSD post-ICU (IES-R)

Study or Subgroup	Antipsychotic Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Smit 2023	0	19	3	21	100.0%	0.16 [0.01, 2.86]
Total (95% CI)		19		21	100.0%	0.16 [0.01, 2.86]
Total events	0		3			

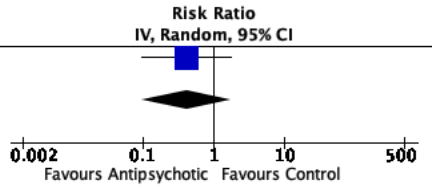
Heterogeneity: Not applicable
Test for overall effect: Z = 1.25 (P = 0.21)



9. Incidence of anxiety post-ICU (HADS)

Study or Subgroup	Antipsychotic Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Smit 2023	2	16	6	20	100.0%	0.42 [0.10, 1.79]
Total (95% CI)		16		20	100.0%	0.42 [0.10, 1.79]
Total events	2		6			

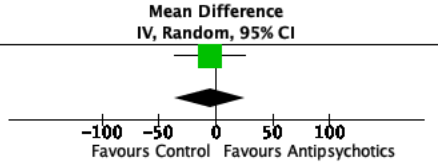
Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)



10. Functional status post-ICU (SF-36 physical function)

Study or Subgroup	Antipsychotics Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Smit 2023	40	56.4	18	45	43.5	24	100.0%	-5.00 [-36.33, 26.33]
Total (95% CI)			18			24	100.0%	-5.00 [-36.33, 26.33]

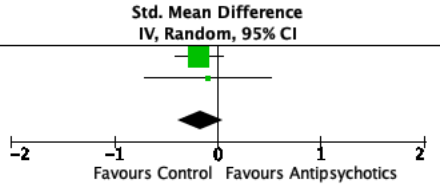
Heterogeneity: Not applicable
Test for overall effect: Z = 0.31 (P = 0.75)



10a. Functional status post-ICU (SMD)

Study or Subgroup	Antipsychotics Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Girard 2018	0.53	2.4	201	1	2.96	103	86.9%	-0.18 [-0.42, 0.06]
Smit 2023	40	56.4	18	45	43.5	24	13.1%	-0.10 [-0.71, 0.51]
Total (95% CI)			219			127	100.0%	-0.17 [-0.39, 0.05]

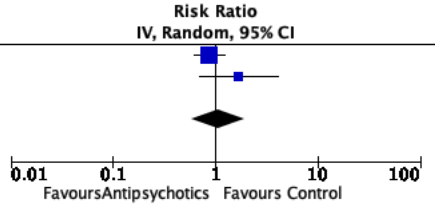
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.50 (P = 0.13)



11. Incidence of cognitive impairment post-ICU

Study or Subgroup	Antipsychotics Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Girard 2018	54	169	33	90	69.2%	0.87 [0.61, 1.24]
Smit 2023	8	16	5	17	30.8%	1.70 [0.70, 4.12]
Total (95% CI)		185		107	100.0%	1.07 [0.58, 1.96]
Total events	62		38			

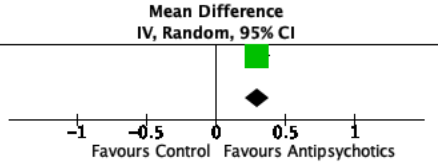
Heterogeneity: Tau² = 0.11; Chi² = 1.90, df = 1 (P = 0.17); I² = 47%
Test for overall effect: Z = 0.22 (P = 0.83)



12. Quality of life

Study or Subgroup	Antipsychotics Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Andersen-Ranberg 2022	0.3	0.67	419	0	0.59	405	100.0%	0.30 [0.21, 0.39]
Total (95% CI)			419			405	100.0%	0.30 [0.21, 0.39]

Heterogeneity: Not applicable
Test for overall effect: Z = 6.83 (P < 0.00001)

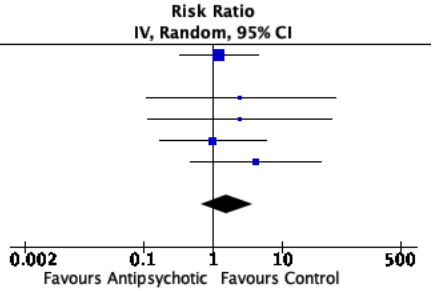


ADVERSE EVENTS

13. Arrythmia

Study or Subgroup	Antipsychotics Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Andersen–Ranberg 2022	5	501	4	486	43.8%	1.21 [0.33, 4.49]
Devlin 2010	0	18	0	18		Not estimable
Early 2017	1	16	0	13	7.7%	2.47 [0.11, 56.03]
Girard 2018	2	382	0	184	8.2%	2.42 [0.12, 50.05]
Reade 2019	2	10	2	10	24.4%	1.00 [0.17, 5.77]
Smit 2023	4	65	1	67	16.0%	4.12 [0.47, 35.92]
Total (95% CI)		992		778	100.0%	1.57 [0.66, 3.74]
Total events	14		7			

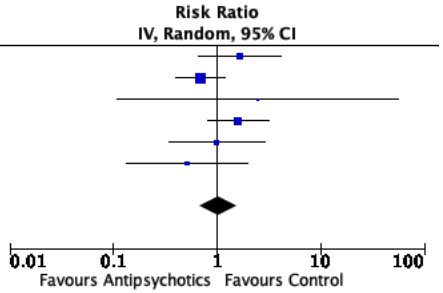
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.33$, $df = 4$ ($P = 0.86$); $I^2 = 0\%$
Test for overall effect: $Z = 1.02$ ($P = 0.31$)



14. Incidence of QtC prolongation

Study or Subgroup	Antipsychotics Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Andersen–Ranberg 2022	12	501	7	486	16.0%	1.66 [0.66, 4.19]
Devlin 2010	9	18	13	18	35.8%	0.69 [0.40, 1.19]
Early 2017	1	16	0	13	1.6%	2.47 [0.11, 56.03]
Girard 2018	33	382	10	184	25.9%	1.59 [0.80, 3.15]
Reade 2019	4	10	4	10	12.4%	1.00 [0.34, 2.93]
Smit 2023	3	65	6	67	8.3%	0.52 [0.13, 1.97]
Total (95% CI)		992		778	100.0%	1.03 [0.69, 1.54]
Total events	62		40			

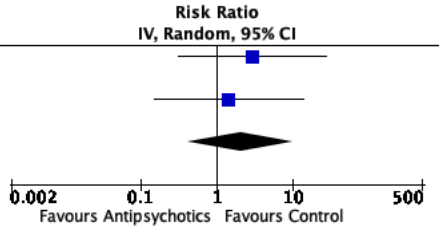
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 5.94$, $df = 5$ ($P = 0.31$); $I^2 = 16\%$
Test for overall effect: $Z = 0.14$ ($P = 0.88$)



15. Extrapyramidal symptoms

Study or Subgroup	Antipsychotics Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Andersen–Ranberg 2022	3	501	1	486	49.9%	2.91 [0.30, 27.88]
Devlin 2010	0	18	0	18		Not estimable
Girard 2018	3	382	1	184	50.1%	1.45 [0.15, 13.80]
Total (95% CI)		901		688	100.0%	2.05 [0.42, 10.12]
Total events	6		2			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.18$, $df = 1$ ($P = 0.67$); $I^2 = 0\%$
Test for overall effect: $Z = 0.88$ ($P = 0.38$)



3. Risk Of Bias

Trial	Random Sequence Generation	Randomized Concealment	Blinding-Clinical Team/Patient	Blinding-Outcome Assessors	Incomplete Data	Selection bias	Other	Overall
Andersen-Ranberg 2022	Low	Possibly low	Low	Low	Low	Low	Low	Low
Atalan 2013	Possibly high	Possibly high	Possibly low	Possibly low	Low	Possibly high	High	High
Devlin 2010	Low	Low	Low	Low	Low	Possibly high	Possibly high	Possibly high
Early 2017	Possibly high	Unclear	Low	Low	Low	Low	Possibly high	Possibly high
Garg 2022	Possibly high	Possibly high	Possibly low	Possibly low	Low	Possibly high	Possibly high	High
Girard 2018	Low	Low	Low	Low	Low	Low	Low	Low
Reade 2019	Low	Possibly high	Possibly high	Possibly high	Low	Low	Low	High
Smit 2023	Low	Low	Low	Low	Low	Low	Low	Low

4. Summary of Findings Table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotics	no antipsychotics	Relative (95% CI)	Absolute (95% CI)		
Duration of delirium (hours)												
5	randomised trials	serious[a]	serious[b]	not serious	serious[c]	none	992	782	-	MD **1.08 lower** (13.19 lower to 11.04 higher)	⨁◯◯◯ Very low	CRITICAL
Delirium Free Days												
3	randomised trials	not serious	serious[d]	not serious	serious[e]	none	913	685	-	MD **1.25 higher** (0.35 lower to 2.86 higher)	⨁⨁◯◯ Low	CRITICAL
28 Day Mortality												
5	randomised trials	not serious	not serious	not serious	very serious[c]	none	260/988 (26.3%)	230/761 (30.2%)	**RR 0.87** (0.75 to 1.01)	**4 fewer per 100** (from 8 fewer to 0 fewer)	⨁⨁◯◯ Low	IMPORTANT
Mortality at Longest Follow-Up												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotics	no antipsychotics	Relative (95% CI)	Absolute (95% CI)		
8	randomised trials	not serious	serious[f]	not serious	serious[g]	none	347/1048 (33.1%)	300/819 (36.6%)	**RR 0.89** (0.79 to 1.01)	**4 fewer per 100** (from 8 fewer to 0 fewer)	⨁⨁◯◯ Low	IMPORTANT
Duration of Mechanical Ventilation (hours)												
7	randomised trials	serious[h]	not serious	not serious	not serious	none	1032	806	-	MD **1.47 lower** (10.55 lower to 7.61 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
ICU LOS (days)												
5	randomised trials	not serious	serious[b]	not serious	very serious[i]	none	466	254	-	MD **0.34 higher** (1.02 lower to 1.71 higher)	⨁◯◯◯ Very low	CRITICAL
Hospital LOS												
5	randomised trials	serious[h]	not serious	not serious	serious[i]	none	957	730	-	MD **0.23 lower** (1.19 lower to 0.72 higher)	⨁⨁◯◯ Low	IMPORTANT
Arrythmia												
6	randomised trials	not serious	not serious	not serious	very serious[k]	none	14/992 (1.4%)	7/778 (0.9%)	**RR 1.57** (0.66 to 3.74)	**1 more per 100** (from 0 fewer to 2 more)	⨁⨁◯◯ Low	CRITICAL
QTc Prolongation												
6	randomised trials	serious[h]	not serious	not serious	serious[k]	none	62/992 (6.3%)	40/778 (5.1%)	**RR 1.03** (0.69 to 1.54)	**0 fewer per 100** (from 2 fewer to 3 more)	⨁⨁◯◯ Low	IMPORTANT
Extrapyrimidal symptoms												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antipsychotics	no antipsychotics	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	not serious	not serious	not serious	very serious[i]	none	6/901 (0.7%)	2/688 (0.3%)	**RR 2.05** (0.42 to 10.12)	**0 fewer per 100** (from 0 fewer to 3 more)	⨁⨁◯◯ Low	CRITICAL
PTSD incidence												
1	randomised trials	not serious	not serious	not serious	extremely serious[i]	none	0/19 (0.0%)	3/21 (14.3%)	**RR 0.16** (0.01 to 2.86)	**12 fewer per 100** (from 14 fewer to 27 more)	⨁◯◯◯ Very low	CRITICAL
Post-ICU Anxiety												
1	randomised trials	not serious	not serious	not serious	extremely serious[i]	none	2/16 (12.5%)	6/20 (30.0%)	**RR 0.42** (0.10 to 1.79)	**17 fewer per 100** (from 27 fewer to 24 more)	⨁◯◯◯ Very low	IMPORTANT
Functional status at 3 months (SF-36)												
1	randomised trials	not serious	not serious	not serious	extremely serious[i]	none	18	24	-	MD **5 lower** (36.33 lower to 26.33 higher)	⨁◯◯◯ Very low	IMPORTANT
Cognitive Impairment Post-ICU												
2	randomised trials	not serious	serious[b]	not serious	very serious[i]	none	62/185 (33.5%)	38/107 (35.5%)	**RR 1.07** (0.58 to 1.96)	**2 more per 100** (from 15 fewer to 34 more)	⨁◯◯◯ Very low	CRITICAL
Quality of life												
1	randomised trials	not serious	not serious	not serious	extremely serious[i]	none	419	405	-	MD **0.3 higher** (0.21 higher to 0.39 higher)	⨁◯◯◯ Very low	IMPORTANT

Explanations

a. Point estimate of effect is lost when high ROB groups are removed
b. High I2, confidence intervals do not all overlap up, point estimates do not all line up
c. The confidence interval demonstrate both harm and benefit

d. Using a MID of 1 day, there is inconsistency
e. Using a MID of 1 day, the lower end of the confidence interval threshold is crossed
f. Using a MID of 1/100, there is inconsistency in the point estimates
g. The lower end of the CI crosses the threshold for MID of 1 per 100
h. Point estimate alters when high ROB trials are removed
i. Using a MID of 1day, the confidence intervals cross thresholds of both important harm and benefit
j. Using a MID of 1 day, the upper end of the CI is crossed
k. Low number of events, and point estimate and confidence interval demonstrates both harm and benefit
l. Very low number of events and wide confidence interval demonstrating both benefit and harm

5. Evidence-To-Decision Framework

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Delirium is a very common occurrence in the critically ill, with prevalence rates quoted to range from 20-80%. The clinical consequences of delirium in the ICU including prolonged ICU length of stay, increased mortality, and increased healthcare costs. Given newly published RCTs since the 2018 PADIS guidelines, we conducted an updated systematic review and meta-analysis to address this issue.	Data we found on this topic: 8 RCTs, 1869 patients -Average age 62.9yo -Mixed ICUs (many med surg, some CV surg, some trauma, some not reported) -2 completed in Europe -1 Australia -3 US -1 Turkey -1 India -All patients had established delirium -Mix of hypo and hyperactive delirium -1 compared to dexmedetomidine, 1 compared to morphine, 6 to placebo
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large	**Slight improvement** **1. Delirium-Free Days**-MD 1.25 more, 95% CI -0.35d fewer to 2.86d more (Low certainty)	

○ Varies ○ Don't know	**2. 28-day mortality**-RR 0.87, 95% CI 0.75 to 1.01; ARR 4 fewer, from 8 fewer to 0 fewer deaths per 100 patients (Low certainty) **3. Mortality at longest follow-up**-RR 0.89, 95% CI 0.79 to 1.01; ARR 4 fewer, from 8 fewer to 0 fewer (Low certainty) **Little to no effect** **1. Duration of IMV (hours)**-MD -1.47h lower, 95% CI -10.55h lower to 7.61h higher (Moderate certainty) **2. ICU length of stay (days)**-MD 0.34d, 95% CI -1.02d lower to 1.71ds higher (Very low certainty) **3. Hospital length of stay (days)**-MD -0.23d lower, 95% CI -1.19d lower to 0.72d higher (Low certainty) **Uncertain** **1. Duration of delirium (hours)**-MD -1.08h lower, 95% CI -13.19h to 11.04h higher (Very low certainty) **2. PTSD incidence**-RR 0.16, 95% CI 0.01 to 2.86 (Very low certainty) **3. Post-ICU Anxiety**-RR 0.42, 95% CI 0.10 to 1.79 (Very low certainty) **4. Functional status at 3 months (SF-36)**-MD -5 lower, 95% CI 36.33 lower to 26.33 more (Very low certainty) **5. Cognitive impairment post-ICU**-RR 1.07, 95% CI 0.58 to 1.96 (Very Low certainty) **6. Quality of life**-MD 0.3 higher, 95% CI 0.21 higher to 0.39 higher (Very low certainty)	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**<u>May increase in arrythmia, little to no effect on Qt prolongation and extrapyramidal symptoms</u>** **1. Arrythmia**-RR 1.57, 95% CI 0.66 to 3.74; ARR 1 more per 100, 95% CI 0 fewer to 2 more (Low certainty) **2. Qt prolongation**-RR 1.03, 95% CI 0.69 to 1.54; ARR 0 fewer per 100, 95% CI from 0 fewer to 3 more (Low certainty) **3. Extrapyramidal symptoms** RR 2.05, 95% CI 0.42 to 10.12; ARR 0 fewer per 100, 95% CI from 0 fewer to 3 more (Low certainty)	No fatal arrythmias noted in the larger trials

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	**<u>Slight improvement</u>** **1. Delirium-Free Days**-MD 1.25 more, 95% CI -0.35d fewer to 2.86d more (Low certainty) **2. 28-day mortality**-RR 0.87, 95% CI 0.75 to 1.01; ARR 4 fewer, from 8 fewer to 0 fewer deaths per 100 patients (Low certainty) **3. Mortality at longest follow-up**-RR 0.89, 95% CI 0.79 to 1.01; ARR 4 fewer, from 8 fewer to 0 fewer (Low certainty) **<u>Little to no effect</u>** **1. Duration of IMV (hours)**-MD -1.47h lower, 95% CI -10.55h lower to 7.61h higher (Moderate certainty) **2. ICU length of stay (days)**-MD 0.34d, 95% CI -1.02d lower to 1.71ds higher (Very low certainty) **3. Hospital length of stay (days)**-MD -0.23d lower, 95% CI -1.19d lower to 0.72d higher (Low certainty) **<u>Uncertain</u>** **1. Duration of delirium (hours)**-MD -1.08h lower, 95% CI -13.19h to 11.04h higher (Very low certainty) **2. PTSD incidence**-RR 0.16, 95% CI 0.01 to 2.86 (Very low certainty)	

	3. Post-ICU Anxiety-RR 0.42, 95% CI 0.10 to 1.79 (Very low certainty) **4. Functional status at 3 months (SF-36)**-MD -5 lower, 95% CI 36.33 lower to 26.33 more (Very low certainty) **5. Cognitive impairment post-ICU**-RR 1.07, 95% CI 0.58 to 1.96 (Very Low certainty) **6. Quality of life**-MD 0.3 higher, 95% CI 0.21 higher to 0.39 higher (Very low certainty) **<u>May increase in arrythmia, little to no effect on Qt prolongation and extrapyramidal symptoms</u>** **1. Arrythmia**-RR 1.57, 95% CI 0.66 to 3.74; ARR 1 more per 100, 95% CI 0 fewer to 2 more (Low certainty) **2. Qt prolongation**-RR 1.03, 95% CI 0.69 to 1.54; ARR 0 fewer per 100, 95% CI from 0 fewer to 3 more (Low certainty) **3. Extrapyramidal symptoms** RR 2.05, 95% CI 0.42 to 10.12; ARR 0 fewer per 100, 95% CI from 0 fewer to 3 more (Low certainty)	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Entire panel voted on outcomes, in addition to the input received from patient partners	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	**<u>Slight improvement</u>** **1. Delirium-Free Days**-MD 1.25 more, 95% CI -0.35d fewer to 2.86d more (Low certainty) **2. 28-day mortality**-RR 0.87, 95% CI 0.75 to 1.01; ARR 4 fewer, from 8 fewer to 0 fewer deaths per 100 patients (Low certainty) **3. Mortality at longest follow-up**-RR 0.89, 95% CI 0.79 to 1.01; ARR 4 fewer, from 8 fewer to 0 fewer (Low certainty) **<u>Little to no effect</u>** **1. Duration of IMV (hours)**-MD -1.47h lower, 95% CI -10.55h lower to 7.61h higher (Moderate certainty) **2. ICU length of stay (days)**-MD 0.34d, 95% CI -1.02d lower to 1.71ds higher (Very low certainty) **3. Hospital length of stay (days)**-MD -0.23d lower, 95% CI -1.19d lower to 0.72d higher (Low certainty) **<u>Uncertain</u>** **1. Duration of delirium (hours)**-MD -1.08h lower, 95% CI -13.19h to 11.04h higher (Very low certainty) **2. PTSD incidence**-RR 0.16, 95% CI 0.01 to 2.86 (Very low certainty) **3. Post-ICU Anxiety**-RR 0.42, 95% CI 0.10 to 1.79 (Very low certainty) **4. Functional status at 3 months (SF-36)**-MD -5 lower, 95% CI 36.33 lower to 26.33 more (Very low certainty) **5. Cognitive impairment post-ICU**-RR 1.07, 95% CI 0.58 to 1.96 (Very Low certainty) **6. Quality of life**-MD 0.3 higher, 95% CI 0.21 higher to 0.39 higher (Very low certainty) **<u>May increase in arrythmia, little to no effect on Qt prolongation and extrapyramidal symptoms</u>** **1. Arrythmia**-RR 1.57, 95% CI 0.66 to 3.74; ARR 1 more per 100, 95% CI 0 fewer to 2 more (Low certainty) **2. Qt prolongation**-RR 1.03, 95% CI 0.69 to 1.54; ARR 0 fewer per 100, 95% CI from 0 fewer to 3 more (Low certainty)	

	3. Extrapyramidal symptoms RR 2.05, 95% CI 0.42 to 10.12; ARR 0 fewer per 100, 95% CI from 0 fewer to 3 more (Low certainty)	

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	-Antipsychotics are very cheap (for example, Haldol, or oral medications cost less than $1.00 per dose in the US) -However, monitoring for side effects may be more expensive (ECG, a cardiologist to review the ECG). We question if this is just established cost that already exists within the ICU	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No trials	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	**<u>Slight improvement</u>** **1. Delirium-Free Days**-MD 1.25 more, 95% CI -0.35d fewer to 2.86d more (Low certainty) **2. 28-day mortality**-RR 0.87, 95% CI 0.75 to 1.01; ARR 4 fewer, from 8 fewer to 0 fewer deaths per 100 patients (Low certainty) **3. Mortality at longest follow-up**-RR 0.89, 95% CI 0.79 to 1.01; ARR 4 fewer, from 8 fewer to 0 fewer (Low certainty) **<u>Little to no effect</u>** **1. Duration of IMV (hours)**-MD -1.47h lower, 95% CI -10.55h lower to 7.61h higher (Moderate certainty) **2. ICU length of stay (days)**-MD 0.34d, 95% CI -1.02d lower to 1.71ds higher (Very low certainty) **3. Hospital length of stay (days)**-MD -0.23d lower, 95% CI -1.19d lower to 0.72d higher (Low certainty) **<u>Uncertain</u>** **1. Duration of delirium (hours)**-MD -1.08h lower, 95% CI -13.19h to 11.04h higher (Very low certainty) **2. PTSD incidence**-RR 0.16, 95% CI 0.01 to 2.86 (Very low certainty) **3. Post-ICU Anxiety**-RR 0.42, 95% CI 0.10 to 1.79 (Very low certainty) **4. Functional status at 3 months (SF-36)**-MD -5 lower, 95% CI 36.33 lower to 26.33 more (Very low certainty) **5. Cognitive impairment post-ICU**-RR 1.07, 95% CI 0.58 to 1.96 (Very Low certainty) **6. Quality of life**-MD 0.3 higher, 95% CI 0.21 higher to 0.39 higher (Very low certainty) **<u>May increase in arrythmia, little to no effect on Qt prolongation and extrapyramidal symptoms</u>** **1. Arrythmia**-RR 1.57, 95% CI 0.66 to 3.74; ARR 1 more per 100, 95% CI 0 fewer to 2 more (Low certainty)	No studies that specifically looked at cost effectiveness analysis

	2. Qt prolongation-RR 1.03, 95% CI 0.69 to 1.54; ARR 0 fewer per 100, 95% CI from 0 fewer to 3 more (Low certainty) **3. Extrapyramidal symptoms** RR 2.05, 95% CI 0.42 to 10.12; ARR 0 fewer per 100, 95% CI from 0 fewer to 3 more (Low certainty)	

Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Given the inexpensive cost, this is unlikely to significantly impact equity in countries of differing economic availability	

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	This is likely to be an acceptable intervention to provide given that there is a signal for improved mortality, but no mechanistic explanation, and no significant harms	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes	Very feasible to administer	

● Yes ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

	JUDGEMENT						
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

CONCLUSIONS

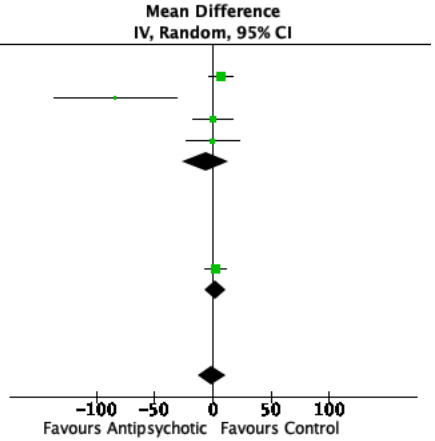
Recommendation
We are unable to issue a recommendation for or against the use of antipsychotics over usual care for the treatment of delirium in adult patients admitted to the intensive care unit (Conditional recommendation, For Intervention or Comparison; Low certainty of evidence).

6. Subgroup Analysis

By Type of ICU (Medsurg vs CV surg)

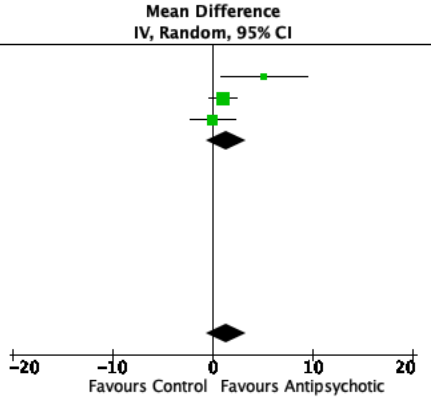
1. Duration of Delirium (hours)

Study or Subgroup	Antipsychotic Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 General Medical/Surgical ICU								
Andersen-Ranberg 2022	86.4	88.8	501	79.2	78.24	486	28.6%	7.20 [-3.23, 17.63]
Devlin 2010	36	55.6	18	120	100	18	4.6%	-84.00 [-136.86, -31.14]
Girard 2018	96	80.8	382	96	105.6	184	20.9%	0.00 [-17.28, 17.28]
Smit 2023	72	80	65	72	53.3	67	15.5%	0.00 [-23.26, 23.26]
Subtotal (95% CI)			966			755	69.7%	-6.15 [-25.98, 13.68]
Heterogeneity: Tau² = 266.00; Chi² = 11.19, df = 3 (P = 0.01); I² = 73%								
Test for overall effect: Z = 0.61 (P = 0.54)								
1.3.2 Post CV-Surgery ICU								
Atalan 2013	33.92	16.7	26	31.56	16.6	27	30.3%	2.36 [-6.61, 11.33]
Subtotal (95% CI)			26			27	30.3%	2.36 [-6.61, 11.33]
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.61)								
Total (95% CI)			992			782	100.0%	-1.08 [-13.19, 11.04]
Heterogeneity: Tau² = 104.94; Chi² = 11.19, df = 4 (P = 0.02); I² = 64%								
Test for overall effect: Z = 0.17 (P = 0.86)								
Test for subgroup differences: Chi² = 0.59, df = 1 (P = 0.44), I² = 0%								

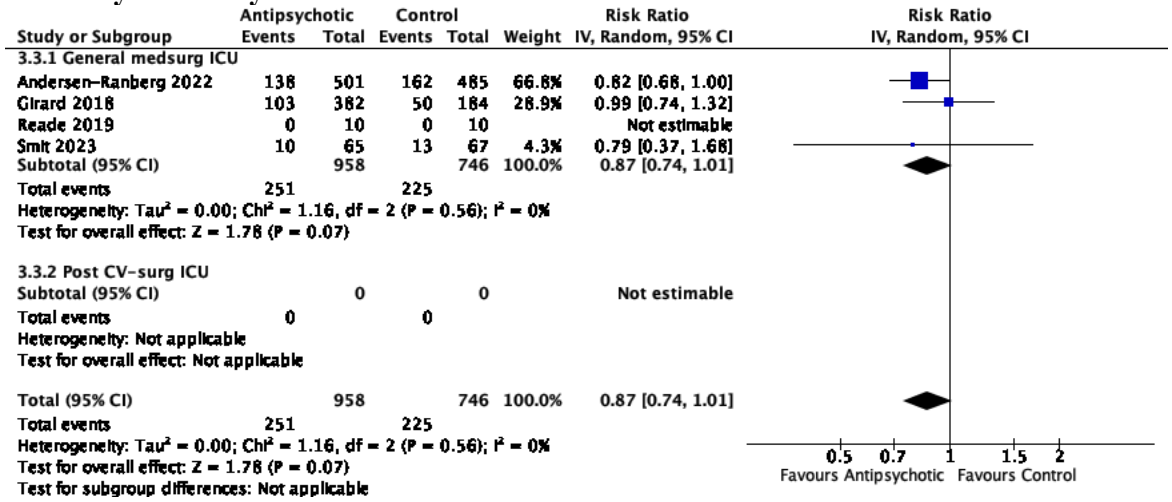


2. Delirium-coma free days

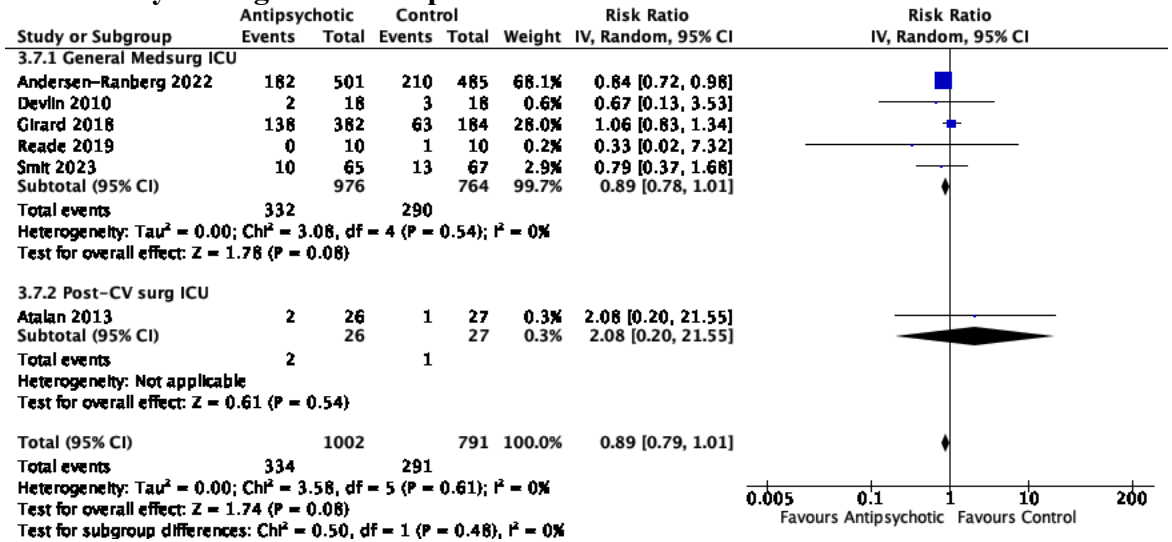
Study or Subgroup	Antipsychotic Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
2.3.1 General medsurg ICU								
Andersen-Ranberg 2022	57.7	37	501	52.6	32.06	486	16.0%	5.10 [0.78, 9.42]
Girard 2018	8	7.45	382	7	8.15	184	49.0%	1.00 [-0.39, 2.39]
Smit 2023	9	6.67	65	9	6.67	67	35.0%	0.00 [-2.28, 2.28]
Subtotal (95% CI)			948			737	100.0%	1.31 [-0.68, 3.29]
Heterogeneity: Tau² = 1.59; Chi² = 4.21, df = 2 (P = 0.12); I² = 52%								
Test for overall effect: Z = 1.29 (P = 0.20)								
2.3.2 Post-CV surgery ICU								
Subtotal (95% CI)			0			0		Not estimable
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			948			737	100.0%	1.31 [-0.68, 3.29]
Heterogeneity: Tau² = 1.59; Chi² = 4.21, df = 2 (P = 0.12); I² = 52%								
Test for overall effect: Z = 1.29 (P = 0.20)								
Test for subgroup differences: Not applicable								



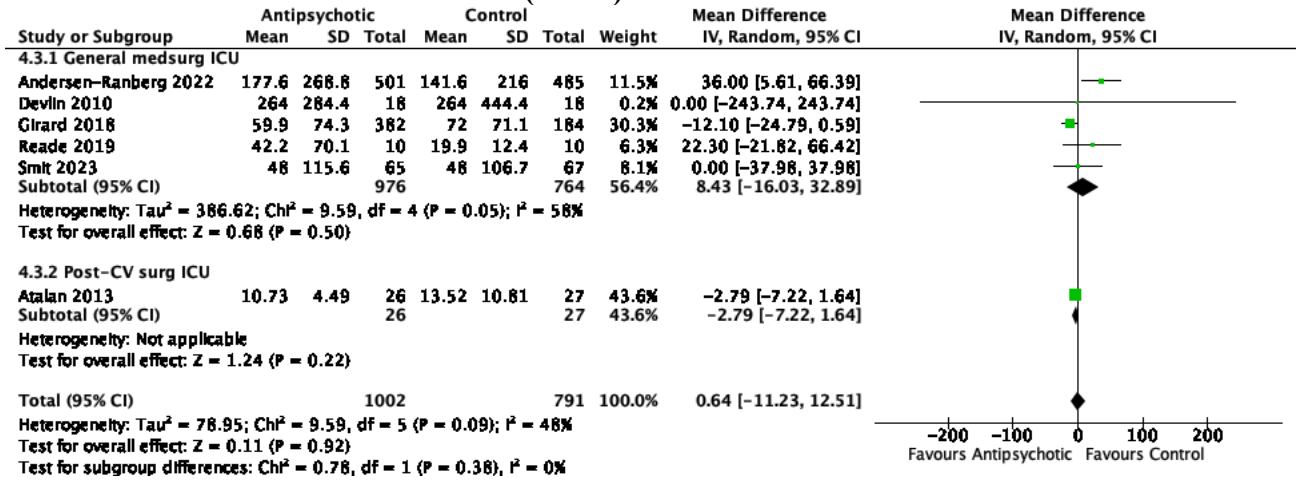
3. 28-day mortality



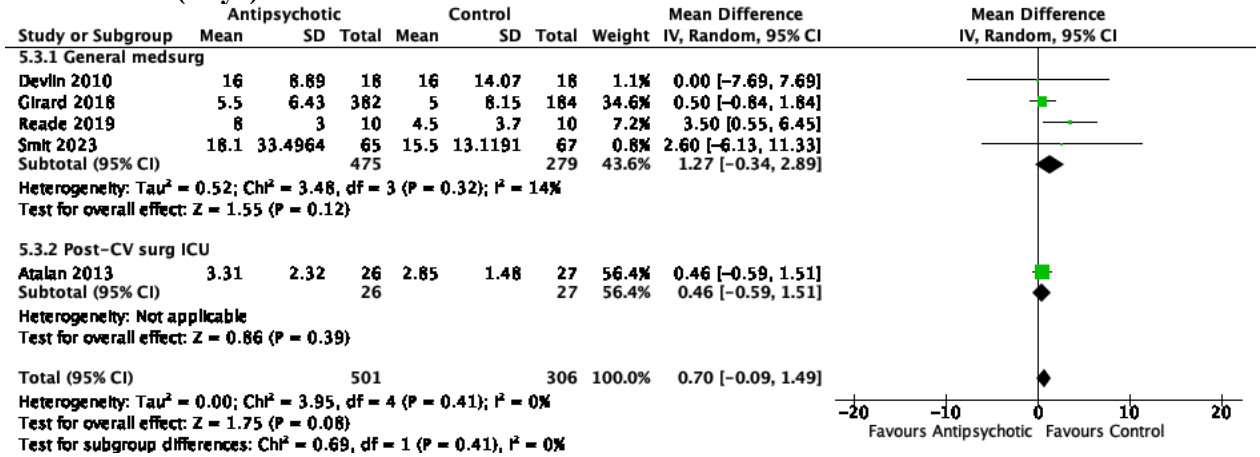
4. Mortality at longest follow-up



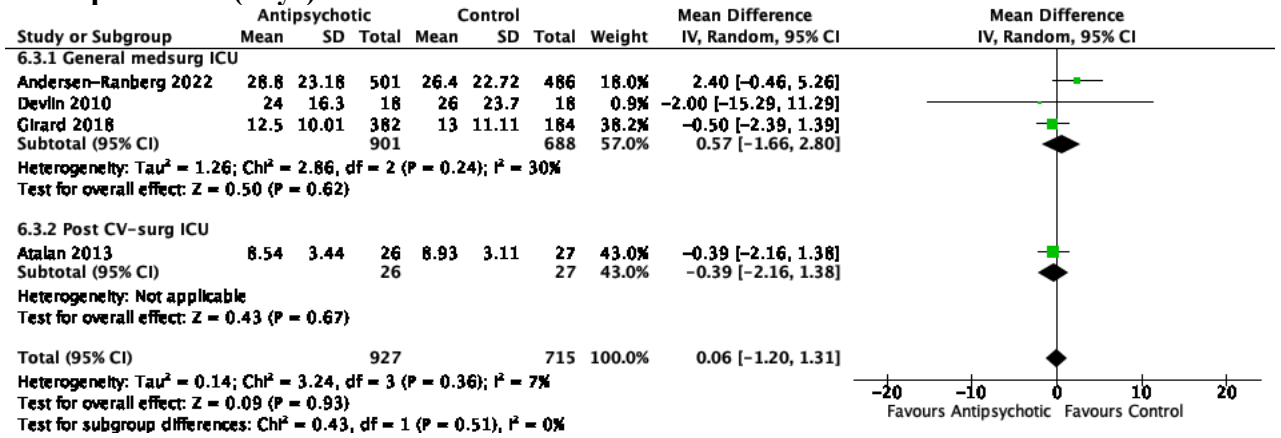
5. Duration of Mechanical ventilation (hours)



6. ICU LOS (days)

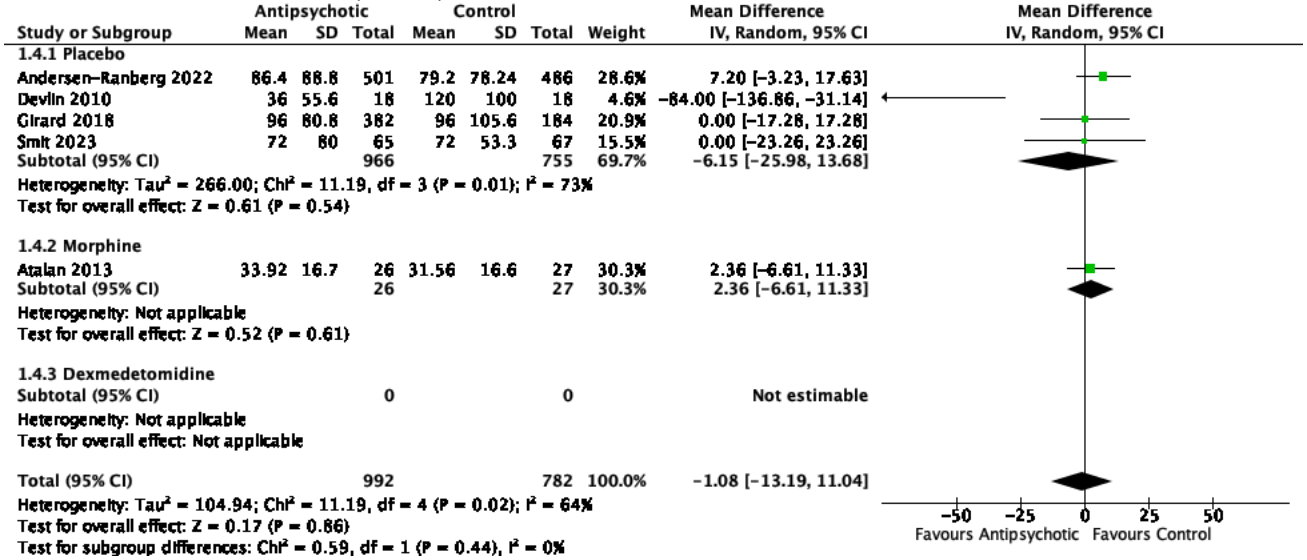


7. Hospital LOS (days)

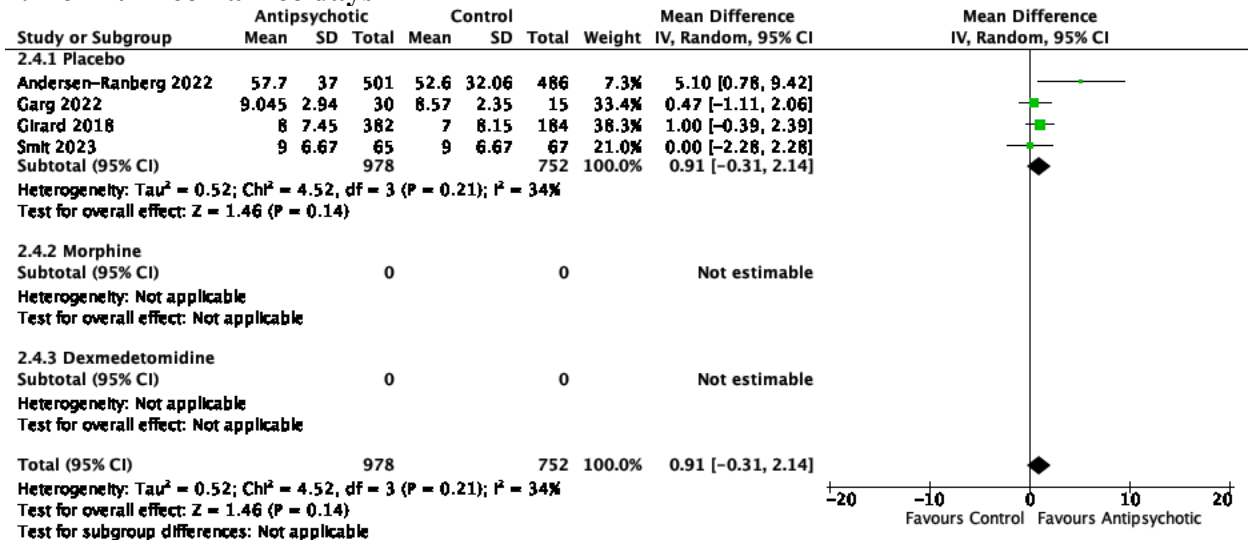


By Comparator (Placebo vs morphine vs dexmedetomidine)-No heterogeneity of treatment effect detected with any outcome here

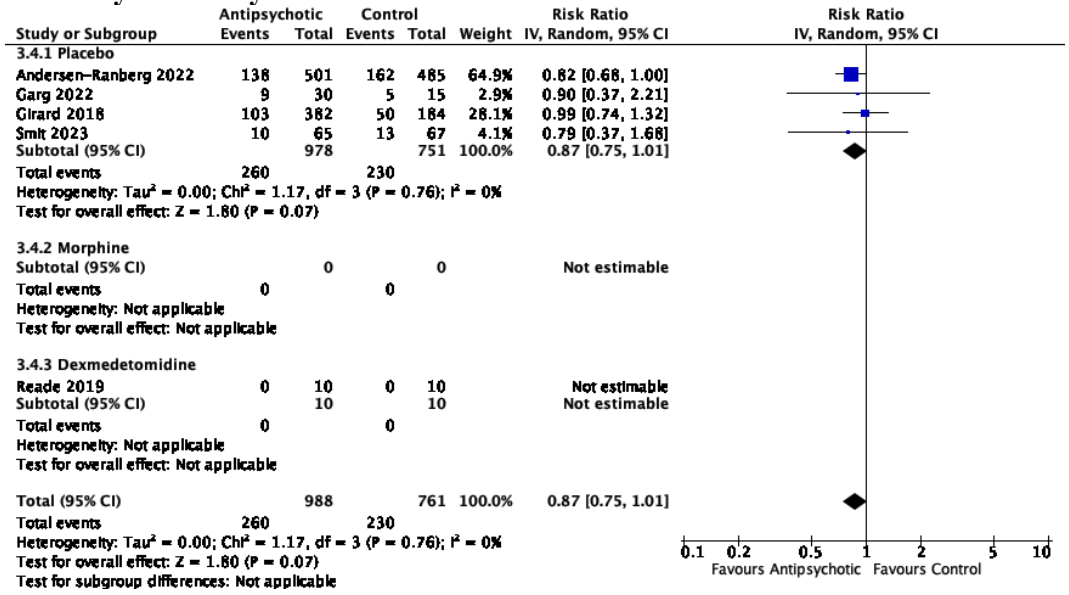
1. Duration of Delirium (hours)



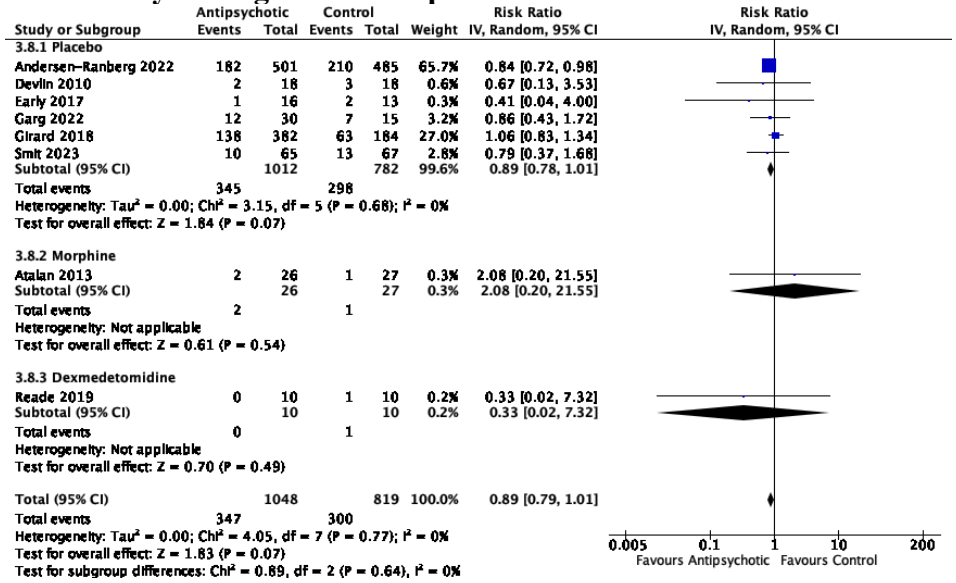
2. Delirium-coma free days



3. 28-day mortality

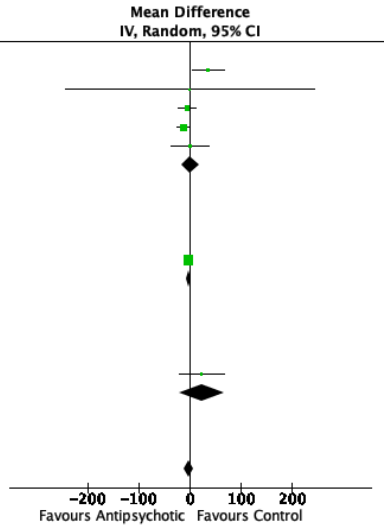


4. Mortality at longest follow-up



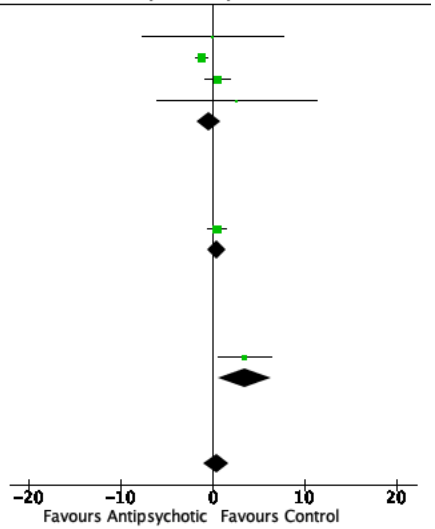
5. Duration of Mechanical ventilation (hours)

Study or Subgroup	Antipsychotic Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
4.4.1 Placebo								
Andersen–Ranberg 2022	177.6	268.8	501	141.6	216	485	7.5%	36.00 [5.61, 66.39]
Devlin 2010	264	284.4	18	264	444.4	18	0.1%	0.00 [−243.74, 243.74]
Garg 2022	77.7	30.8	30	83	26.4	15	17.3%	−5.30 [−22.62, 12.02]
Girard 2018	59.9	74.3	382	72	71.1	184	24.3%	−12.10 [−24.79, 0.59]
Smit 2023	48	115.6	65	48	106.7	67	5.1%	0.00 [−37.98, 37.98]
Subtotal (95% CI)			996			769	54.3%	0.61 [−16.30, 17.52]
Heterogeneity: Tau² = 162.92; Chi² = 8.26, df = 4 (P = 0.08); I² = 52%								
Test for overall effect: Z = 0.07 (P = 0.94)								
4.4.2 Morphine								
Atalan 2013	10.73	4.49	26	13.52	10.81	27	41.8%	−2.79 [−7.22, 1.64]
Subtotal (95% CI)			26			27	41.8%	−2.79 [−7.22, 1.64]
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.24 (P = 0.22)								
4.4.3 Dexmedetomidine								
Reade 2019	42.2	70.1	10	19.9	12.4	10	3.9%	22.30 [−21.82, 66.42]
Subtotal (95% CI)			10			10	3.9%	22.30 [−21.82, 66.42]
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.99 (P = 0.32)								
Total (95% CI)			1032			806	100.0%	−1.47 [−10.55, 7.61]
Heterogeneity: Tau² = 46.21; Chi² = 9.66, df = 6 (P = 0.14); I² = 38%								
Test for overall effect: Z = 0.32 (P = 0.75)								
Test for subgroup differences: Chi² = 1.35, df = 2 (P = 0.51), I² = 0%								

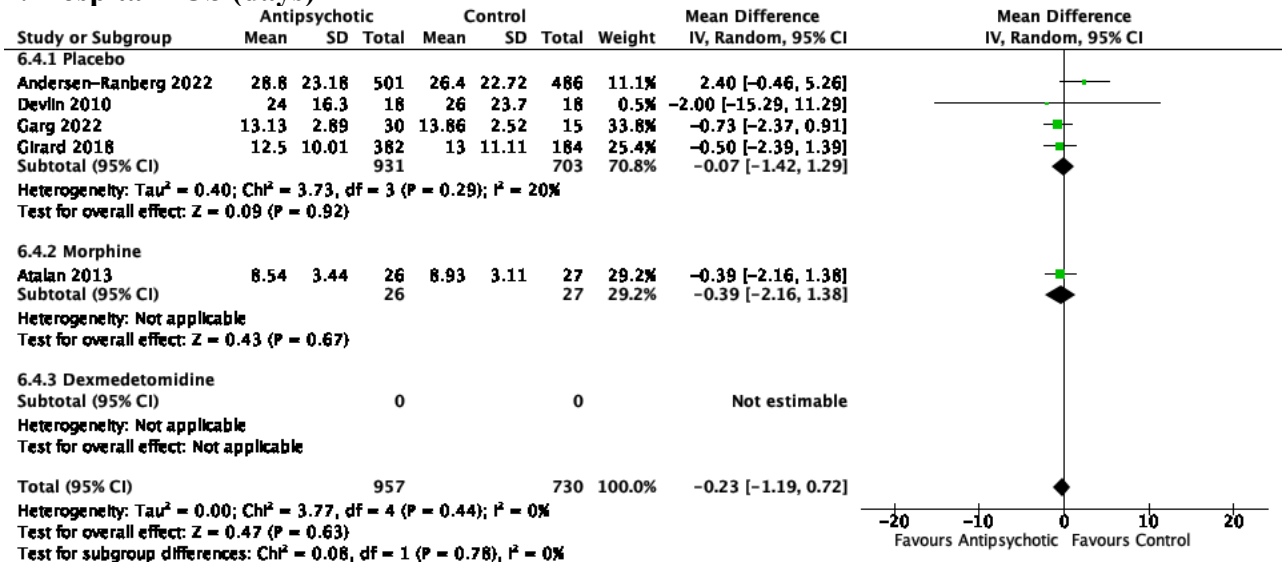


6. ICU LOS (days)

Study or Subgroup	Antipsychotic Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
5.4.1 Placebo								
Devlin 2010	16	8.69	18	16	14.07	18	2.7%	0.00 [−7.69, 7.69]
Garg 2022	5.37	1.16	30	6.56	1.01	15	30.6%	−1.19 [−1.85, −0.53]
Girard 2018	5.5	6.43	382	5	8.15	184	24.7%	0.50 [−0.84, 1.84]
Smit 2023	18.1	33.4964	65	15.5	13.1191	67	2.2%	2.60 [−6.13, 11.33]
Subtotal (95% CI)			495			284	60.1%	−0.41 [−1.74, 0.91]
Heterogeneity: Tau² = 0.70; Chi² = 5.55, df = 3 (P = 0.14); I² = 46%								
Test for overall effect: Z = 0.61 (P = 0.54)								
5.4.2 Morphine								
Atalan 2013	3.31	2.32	26	2.85	1.48	27	27.4%	0.46 [−0.59, 1.51]
Subtotal (95% CI)			26			27	27.4%	0.46 [−0.59, 1.51]
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								
5.4.3 Dexmedetomidine								
Reade 2019	8	3	10	4.5	3.7	10	12.5%	3.50 [0.55, 6.45]
Subtotal (95% CI)			10			10	12.5%	3.50 [0.55, 6.45]
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.32 (P = 0.02)								
Total (95% CI)			531			321	100.0%	0.38 [−0.95, 1.70]
Heterogeneity: Tau² = 1.38; Chi² = 16.99, df = 5 (P = 0.005); I² = 71%								
Test for overall effect: Z = 0.56 (P = 0.57)								
Test for subgroup differences: Chi² = 5.69, df = 2 (P = 0.06), I² = 64.8%								



7. Hospital LOS (days)



9.4 PICO 4-Enhanced Mobilization For Immobility

PICO 4-In adults admitted to the ICU, does enhanced mobilization vs usual care impact patient outcomes?

Population: Adults admitted to the ICU
Intervention: Enhanced Mobilization (Mobilization defined as the process of moving oneself, and of changing and maintaining postures-excluding pulmonary rehabilitation, NMES/TMES)
Comparison: Usual care (assuming usual care/standard of care includes some form of physiotherapy/rehabilitation)
Outcomes:1. Incidence of delirium; 2. Duration of delirium; 3. Incidence of agitation; 4. Duration of mechanical ventilation; 5. Adverse events; 6. ICU LOS; 7. Quality of life post-ICU; 8. Functional status post-ICU; 9. Cognitive abilities post-ICU; 10. Mortality

1. Characteristics Of Included Trials

-Author -Year -Type of RCT -Location -Multi-center vs single center n=	**Patient characteristics**	**Inclusion/ Exclusion**	**Intervention (n=)**	**Comparator (n=)**	**Outcomes**
Amundadottir 2019 -Parallel RCT -Iceland -Single center -n=50	Age: 63 Female: 34% APACHE II: 22.8 Intubated: 100% BMI: 32.6	**Inclusion:** 1. Adults aged 18–80yo, requiring mechanical ventilation for >48 hours 2. Able to ambulate independently before the onset of acute illness 3. Able to cooperate and comply with assessment and intervention for one year after ICU discharge **Exclusion:** 1. Poor survival prognoses 2. Admitted to the hospital more than two weeks prior to admission to the ICU 3. Progressive upright mobilization was C/I (e.g. hemodynamic instability, severe head injuries or substantial	Intensive twice-daily mobilization -Intervention commenced after 48 hours of mechanical ventilation and consisted of two sessions of progressive upright mobilization (mobilization levels 3–10 on the ICU Mobility Scale) daily, until ICU discharge unless upright mobilization was contraindicated. The first mobilization session of the day was scheduled late morning, to coincide with the daily arousal protocol. The focus of each intervention was on individualized and response-driven progressive upright mobilization including sitting over the edge of the bed or a higher level of mobilization. Components of the intervention were functional, strength, balance and transfer training, with the specific aim of progressing patients to standing and walking n=29	Usual care "Daily mobilization" -Intervention commenced after 96 hours of mechanical ventilation and performed once daily until ICU discharge. For patients who were mechanically ventilated, mobilization was scheduled for approximately 9 am. The patients were often not awake, thus passive range of motion exercises were performed once daily, progressing to active assisted and active exercises commensurate with increased patient arousal, unless upright	1. Duration of IMV 2. ICU LOS 3. Hospital LOS 4. HrQoL ICU discharge, hospital discharge, 3, 6 and 12 months 5. 6-min walk test 6. MRC sum-score 7. Functional independence 8. Mortality at 30, 90 and 12 months 9. Disposition at 12 months after discharge 10. Employment 12 months after discharge 13. Time to first upright mobilization session 14. Time to first ambulation session

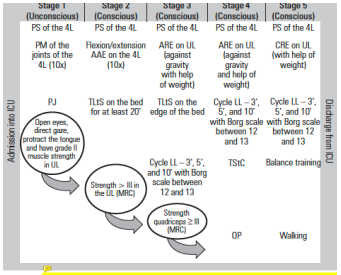
		unstable fractures)		positioning was contraindicated. When considered appropriate by the physiotherapist, passive transfer to a reclining chair or sitting over the edge of the bed was initiated, followed by functional transfer training n=21	
Berney 2020 -Parallel RCT -Australia and United States -Multi-center -n=162	Age: 60yo# Female: 34.0% APACHE II: 22.5 Intubated: 100% BMI:NR	**Inclusion:** 1. Adults >18yo admitted to the ICU and receiving IMV 2. SIRS, sepsis or severe sepsis 3. Expected to require mechanical ventilation ≥48 hours and an ICU stay >4 days post randomisation. **Exclusion:** 1. Primary neurological diagnosis 2. Lower limb amputation or malignancies 3. Unable to perform outcome measures due to pre-morbid physical, intellectual or cognitive impairment 4. Not expected to survive ICU; 5. Pregnant 6. BMI> 40 7. External fixation device or superficial metal in the lower limb 8. Open wounds or skin abrasions at electrode application points 9. Pacemaker without an underlying rhythm 10. Were transferred	Functional-electrical stimulation cycling in addition to usual care -FES included synchronized stimulation of 4 muscle groups -The intervention was performed up to 60min/day for ≥5days/week -Commenced as early as possible n=80	Usual care -Defined as usual care rehabilitation n=82	1. Quadriceps muscle strength at hospital discharge 2. Cognitive impairment at 6months 3. All-cause mortality 4. Incidence and duration of delirium 5. Hand grip strength 6. Physical Function in ICU Test scored 7. Functional Status Score for the ICU 8. The Short Physical Performance Battery 9. 6 min walk test 10. Katz Index of independence in activities of daily living, 11. Lawton's instrumental activities of daily living 12. Hospital Anxiety and Depression Scale 12. Impact of Events Scale-Revised 13. Short Form Health Survey SF-36 v2 14. 5- level EQ- 5D version

		from another ICU after >2 days of consecutive mechanical ventilation. 11. Score of >3.3 on the Informant Questionnaire on Cognitive Decline in the Elderly at baseline prior to randomisation in ICU 12.Score of >10 on the Alcohol Use Disorders Identification Test assessment at baseline 13. No fixed address			
Brummel 2014 -Parallel RCT -United States -Single-center -n=87	Age: 61yo# Female: 52.3% APACHE II: 24.3 Intubated: 88.6% BMI: NR	**Inclusion:** 1. Adults ≥18yo being treated for respiratory failure, sepsis, cardiogenic or hemorrhagic shock who reside within 120 miles of Nashville TN **Exclusion:** 1. Critically ill for > 72 h since the opportunity to administer early physical and cognitive therapy had passed 2. ICU admission >5 days in the previous 30 days 3.Moribund state, severe preexisting dementia or physical disability in activities of daily living 4. Unlikely to continue the intervention in the outpatient setting because of active substance abuse, active psychiatric disorder, or homelessness	Group 1: Early physical therapy -Done daily -Comatose or stuporous patients (RASS -4 or -5) received passive range of motion of all major joints (e.g., fingers, wrists, elbows, shoulders, ankles, knees and hips). Patients who were aroused to voice (RASS –3 or –2) also received passive range of motion exercises and were placed in the sitting position in the bed for at least 20 minutes. Patients who were a RASS -1 to +1 progressed, as able, through active range of motion exercises of all major joints, bed mobility exercises (e.g., lateral rolling and supine to sit), dangling at the edge of the bed, postural re-training, balance exercises (such as reaching in and out of the base of support), activities of daily living training (eating/simulated eating, grooming, bathing, dressing and toileting), transferring from seated to standing and from bed to chair, reaching in and out of the base of support, mini-squats, marching, and ambulation (with or without assist devices). n=22	Usual care -Physical therapy after it was ordered by the treating physicians and per the routine hospital treatment protocol and schedule (usually 1-2 sessions/week) n=22	1. Feasibility outcomes 2. Days free of coma and delirium 3. Days free of mechanical ventilation 4. ICU LOS 5. Hospital LOS 6. Mortality 7. HrQoL 8. Executive functioning 9. Global cognitive status 10. Functional mobility
Burtin 2009	Age: 59yo (17)	**Inclusion:**	Cycling exercise + Usual Care	Usual care	1. 6-minute walk test at hospital

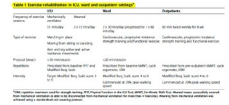
-Parallel RCT -Belgium -Single-center -n=90	Female: 28.4% APACHE II: 25.5 Intubated: NR BMI: 24	Patients admitted to the ICU who had been there for 5 days and expected to have an ICU stay of at least 7 days **Exclusion:** 1. Trauma or surgery of leg, pelvis, or lumbar spine 2. Open abdominal wounds 3. Extreme obesity (body mass index >35 kg/m2) 4.Serious bedsore or venous ulcers 5.An anticipated fatal outcome 6.Body length <1.5 m 7.Preexisting diagnosis causing neuromuscular weakness, acute stroke, status epilepticus 8.Coagulation disorders (international normalized ratio >1.5 or concentration of blood platelets <50) 9.Intracranial pressure >20 mm Hg 10. Psychiatric disorders or severe agitation 11.Cardiorespiratory instability 12.Inspiratory oxygen fraction (FiO_2) >55% 13.Arterial partial pressure of oxygen (PaO_2) <65 torr 14.Minute ventilation <150 mL/kg body weight 15. Respiratory rate >30 breaths/min on adequate ventilatory support 16. Need for significant vasopressive support	-5x a week patients were placed in a comfortable position in between the supine and the semirecumbent position. In sedated patients, cycling was performed in a passive manner for 20 consecutive minutes at a fixed pedaling rate of 20 cycles/min. When patients were able to cycle actively, the cycling session was divided into two bouts of 10 mins or into more intervals when needed. At every session, training intensity was evaluated and an attempt was made to increase the resistance with one level, as tolerated by the patient. n=45	-Respiratory physiotherapy adjusted to the individual needs and a standardized mobilization session of the upper and lower extremities on 5 days per week. Passive motion was applied in sedated subjects, whereas awake patients were asked to participate actively. Intensity of the exercises was increased according to the patient's capability. Ambulation was started when considered appropriate by the medical Staff. n=32	discharge 2. Weaning time 3. ICU LOS 4. Hospital LOS 5. Mortality at 1yr 6. Handgrip force 7. Functional status-Berg Balance Scale 8. Functional Ambulation Category Scale 9. Physical Function in the SF-36 QoL
Carvalho 2019 -Parallel RCT -Brazil	Age: 51yo (18.2) Female: 33.3% APACHE II: 15.2 (6.0)	**Inclusion:** 1. Adults >18 years-old, admitted to an ICU and	Passive cycling and conventional physical therapy -Patient placed in decubitus position and	Conventional physical therapy (respiratory and motor therapy) was	1. Quadriceps femoris thickness 2. Adverse events (there were no adverse events that interrupted the

-Single center -n=96	Intubated: 100% BMI: 25.6	have been IMV for 24-48h, with deep sedation level assessed by the Richmond Agitation Sedation Scale (RASS=–4) and hemodynamically stable. **Exclusion:** 1. Palliative care 2. amputees 3. Lower limb fracture, 4. Neuromuscular or neurological diseases 5. Pre-existing articular and/or musculoskeletal dysfunctions	head elevation at 30 degrees, for 20 minutes, with a fixed cadence of 20 cycles/min, once a day, during the first ICU hospitalization week n=16	conducted by ICU physical therapists twice a day, for around 30 minutes for 7 days. The protocol Included vibrocompression maneuvers, hyperinflation through mechanical ventilator and tracheal suctioning, if needed, besides motor exercises for upper and lower limbs, passive and active-assisted ones, according to the patient's clinical evolution. n=16	protocol) 3. In ICU mortality
Carvalho 2023 -Parallel RCT -Portugal -Single center -n=96	Age: 67.5yo (18.2) Female: 56.3% APACHE II: 15.2 (6.0) Intubated: NR BMI:28.9	**Inclusion:** 1. Adults ≥18yo with respiratory insufficiency due to COVID-19 who are hospitalized at the ICU 2. Referred for respiratory and functional rehabilitation by the ICU medical team 3. Independent in activities of daily living before the onset of critical illness 4. A score of −2 or higher in the Richmond Agitation–Sedation Scale **Exclusion:** 1. Prior muscle weakness (eg., pre-existing neurological or neuromuscular disease) 2. Prior pulmonary disease affecting FEV1 3. Acute thrombosis 4. Diagnosis on admission that excludes	Functional and respiratory multidisciplinary rehabilitation program -Included medical, nursing, physiotherapy and occupational therapy interventions -Duration of their entire hospital stay, starting within the first 24 h from ICU admission, 15–30 min per session, twice per day, 6 days per week. n=48	Usual care -Usual medical and nursing care in the ICU, which involved assessment and treatment of the respiratory system, and active bed exercises and mobility were encouraged as soon as possible n=48	1. Functional capacity using the 6 minute walk test 2. Chelsea Critical Care Physical Assessment tool 3. Medical Research Council sum-score 4. Handgrip strength test 5. Borg Rating of Perceived Exertion 6. ICU LOS 7. Need for IMV

		the possibility of walking at hospital discharge 5. Patients transferred from other hospitals			
Chen 2011 -Parallel RCT -Taiwan -Single center -n=34	Age: 77 Female: 26.5% APACHE II: NR Intubated: 100% BMI: NR	**Inclusion:** 1. Underlying disease stable and cause of respiratory failure resolved 2. IMV for more than 14d, at least 6h/day, trach in situ, attempting SBP daily 3. Partially supported vent mode with PEEP 5-10, SpO2 >92% with FiO2 40 or less 4. Alert, motivated, cooperative, compliant, and psychologically stable 5. Cooperative and stable caregiver **Exclusion:** 1. Overt neuromuscular disease or receiving sedative or paralytic agent that would interfere with strength measurements and limb exercises	Physical training 5 days/week for 6 weeks including: 1. Diaphragmatic breathing control facilitation followed by active coughing induction 2. Strengthening exercises including weight lifting and straight leg raises 3. Active transfer to a chair and maintenance of sitting position form minimum 20 minutes/day 4. Functional activity training n=18	Standard care - weaning trials with SBT daily, optimum bronchodilator inhalation, nutritional support, postural drainage, encouragement of mobility n=16	1. Functional status as measured by functional independence measure questionnaire 2. Survival 3. Home residency and free from ventilation
Coutinho 2016 -Parallel RCT -Brazil -Single center -n=25	Age: 58.5 Female: 52% APACHE II: 25.7 Intubated: 100% BMI: 25.55	**Inclusion:** 1. Age 18 and older, admitted to ICU with at least 24hrs but no more than 48hrs IMV 2. No more than 1 week of hospitalization **Exclusion:** 1. Neuromuscular disease with motor deficit 2. Extubated less than 48hrs after inclusion 3. Hemodynamic instability 4. Complications during the protocol	Standard physiotherapy + passive cycle ergometer exercises with 20 cycles/min for 20mins before physio n=14	30 minute physiotherapy session n=11	1. Duration IMV 2. ICU LOS 3. Hospital LOS 4. Mortality

		5. Shilley catheter in femoral being 6. Need for reintubation 7. Prolonged weaning (3 failed SBTs) 8. BMI >35 9. Development of eschar in calcaneal area during protocol			
Dantas 2012 -Parallel RCT -Brazil -Single center -n=28	Age: 54.8 Female: 60.7% APACHE II: 22.4 Intubated: 100% BMI: NR	**Inclusion:** 1. Adults on IMV for <7days who have adequate cardiac reserve, $Sp0_2$>90% on <60% $Fi0_2$, RR <25, and no physical exercise program prior to study enrollment **Exclusion:** 1. Inability to walk without assistance prior to ICU admission 2. Intracranial hypertension 3. Cognitive impairment prior to ICU admission 4. Neuromuscular disease 5. BMI>40 6. Unconsolidated fractures 7. Recurrence of cancer within the previous 6 months	Early mobilization n=14 -Defined as a systematic early mobilization protocol, BID, every daily  Figure 1 – Early mobilization protocol for critically ill patients on mechanical ventilation. ICU – intensive care unit; PS – passive stretching; 4L – four limbs; PM – passive mobilization; PJ – positioning of the joint; UL – upper limbs; AAE – active-assisted exercise; TLtS – transfer from lying to sitting position; MRC – Medical Research Council; ARE – active-resistive exercise; LL – lower limbs; Cycle LL – cycle ergometry for lower limbs; TStC – transfer from sitting to chair; OP – orthostatic posture; CRE – counter-resistance exercise. Source: Adapted from Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med. 2008;36(8):2238-43.[29] n=26	Standard physiotherapy -Defined as passive mobilization of the four limbs five times a week and active-assisted exercises according to patient improvement and Cooperation n=14	1. Respiratory muscle strength (Maximal inspiratory pressure, maximal expiratory pressure) 2. Peripheral muscle strength 3. Duration of ICU LOS 4. Adverse events (i.e. tachycardia, bradycardia, respiratory distress, change in hemodynamics)
De Azevedo 2021 -Parallel RCT -Brazil -Single center -n=181	Age: 56.5 Female: 45.3% APACHE II: NR Intubated: 100% BMI: NR	**Inclusion:** 1. Adults >18yo admitted to the ICU for ≥3days and were undergoing IMV for <96h **Exclusion:** 1. Pregnant 2. Moribund 3. Unable to walk without assistance before the acute illness that led to ICU admission 4. Severe cognitive impairment before hospitalization	High-protein and early exercise group -Two daily 15min sessions of cycle ergometry -The resistance was gradually increased after the first week -Sessions were continues until discharge, death, day 21 of the study n=87	Standard physiotherapy -Included twice daily active or passive motions n=94	1. Physical component summary score at 3 and 6 months (measured using the SF-36) 2. ICU acquire weakness (handgrip strengths)-weakness defines s <11kg of force for men or <7kg of force for women-done at ICU discharge or day 21 3. Duration IMV 4. ICU LOS 5. ICU Mortality 6. Hospital Mortality

		5. Neuromuscular diseases that compromised weaning from ventilation 6. Acute pelvic fracture 7. Unstable spinal trauma 8. Severe liver disease 9. Impossible to start a diet according to the institutional Protocols 10. Neuromuscular blockers 11. High dose vasoactive mediations 12. Fi02>60% of PEEP ≥ 13. Intracranial hypertension 14. Open abdomen 15. Status epilepticus			
de Paula 2023 -Parallel RCT -Brazil -Single center -n=85	Age: 63.5 Female: 50.6% APACHE II: NR Intubated: 36.5% BMI: 24.9	**Inclusion:** 1. 18 years or older 2. Admitted to the ICU and enrolled in the study within 48 h of ICU admission **Exclusion:** 1. Physical or mental conditions that prevent walking before ICU admission 2.Any physical limitations, including neurological, musculoskeletal, and osteoarticular diseases, which prevented the execution of early mobilization 3. Intracranial hypertension 4. Cardiac arrest or acute coronary syndrome during hospitalization 5. Hemodynamic instability or uncontrolled arrhythmia 6. Decision to withhold	Early mobilization in addition to conventional physiotherapy Early Mobilization:-A physiotherapy score was provided to the patient each day, A physiotherapist would verify the patient's achievements and goals daily, and the intervention delivered on that day was based on that conversation. n=40	Conventional physiotherapy -Done twice per day and included breathing exercises, patient positioning, upper and lower limb exercises (passive or active), sitting on the edge of bed, standing up, and walking away from the bed. n=45	1. Muscle strength using the MRC Manual Muscle Test 2. KATZ index of daily living 3. Level of activities at ICU discharge and at 30 days

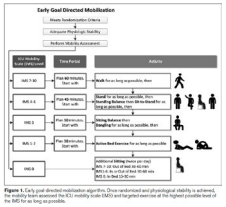
		life-sustaining treatment			
Denhey 2013 -Parallel RCT -Australia -Single center -n=150	Age: 61.1 Female: 36.7% APACHE II: 19.9 Intubated: NR BMI: 27.4	**Inclusion:** 1. Adults admitted to the ICU for ≥5days who lived within a 50-km radius of the hospital, who had no neurological, spinal or musculoskeletal dysfunction preventing participation in physical rehabilitation **Exclusion:** NR	Active functional rehabilitation based on the physiologic principles of exercise prescription  n=74	Usual care -Physiotherapists provided both respiratory and mobility management based upon individual patient assessment according to unit protocols. Mobility may have included active bed exercises, sitting out of bed and/or marching or walking. Usual care was available 7 days per week for 12 hours per day. Acute ward physiotherapy services emphasized functional recovery and discharge planning n=76	1. 6-minute walk test 2. 28d mortality 3. Duration IMV 4. ICU LOS 6. Hospital LOS 7. ICU acquired weakness 8. Disposition 9. 12 month mortality 10. Quality of Life 11. Physical component summary score at 3 and 6 months (measured using the SF-36) 12. MRC score
Deng 2022 -Parallel RCT -China -Single center -n=83	Age: 54.1 Female: 30.1% APACHE II: 18.5 Intubated: 100% BMI: 22.6	**Inclusion:** 1.Patients between the ages of 18-70 who were admitted to the ICU and undergoing IMV for >48h, with an APACHE II score ≥8 2. Expected ICU LOS≥ 7days 3. Receiving enteral nutrition 4. Stable respiratory and circulatory systems who were permitted early out-of-bed mobilization after evaluation by the medical staff **Exclusion:** 1. Inability to communicate prior to ICU admission 2. Bleeding tendency 3.Use of two vasoactive drugs	Abdominal based progressive mobilization program -3 progressive mobilization types, namely passive abdominal massage, physical therapy (bed-side bicycle), and ambulating according to the patient's consciousness and vital signs, and was implemented by the ICU mobility team comprising a physical therapist and two ICU nurses. The program was conducted progressively during the patient's hospitalization 7 days after implementation of enteral nutrition. n=41	Usual care -Included conventional physical therapy, performed twice a day as prescribed by the patient's physician n=42	1. Antral motility index 2. Full enteral feeding rate on the third day 3. Duration IMV 4. ICU LOS 5. Adverse events (diarrhea, vomiting, abdomen distention)

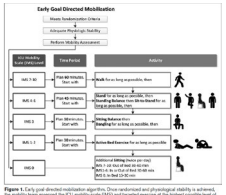
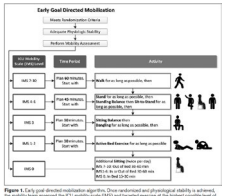
		4. ICP ≥ 20 mmHg 5. Acute coronary syndrome 6. Unstable spinal injury and unstable fracture 7. Gastrointestinal disease 8.Gastric motility drugs			
Dos Santos 2018 -Parallel RCT -Brazil -Single center -n=51	Age: 53.2 Female: 31.0% APACHE II: 15.7 Intubated: 100% BMI: NR	**Inclusion:** 1.Age ≥18 years admitted to the ICU and undergoing I MV for less than 72 hours 2.No known neuromuscular disease **Exclusion:** 1. Patients with cardiopulmonary arrest, end stage malignancy, increased intracranial pressure, or technical obstacles that did not allow the use of NMES, such as bone fractures or skin lesions 2. Prolonged IMV	Group 1: Exercise -The protocol assisted active exercises were initiated at the time that the patient reached sufficient consciousness level, progressing to active (independent) and resistance exercises with elastic bands in the major muscle groups (i.e., biceps, triceps, and lower limbs), according to the degree of cooperation of the patient n=13	Usual care: The usual care group was the control and received no standardized exercises intervention besides usual care of the physical therapy, consisting of and in-bed exercises (i.e., passive mobilization, positio-ning, and stretching). n=15	1. Duration of IMV 2. Duration of sedation 3. ICU LOS 4. Mortality
Eggman 2018 -Parallel RCT -Switzerland -Single center -n=115	Age: 64 Female: 33.0% APACHE II: 22.5 Intubated: NR BMI: 27.5	**Inclusion:** 1. Adults (≥18 years) expected to stay on MV for at least 72 hours and who had been independent before the onset of critical illness **Exclusion:** 1. Previous muscle weakness 2 Contraindications to cycling 3. Enrolment in another intervention study 4 .Palliative care 5. Admission diagnosis that excluded the possibility of walking at hospital discharge 6 Patients who did not	Endurance and resistance training (ERT) -In patients in the experimental group an early, progressive ERT program combined with early mobilization was initiated and each component implemented as intensive as possible and tolerated in individual patients. -To this end, sedation was reduced if medically permitted prior to physiotherapy. Physiotherapists were encouraged to split therapy into two or more sessions to prevent overexertion. -Therapy visits occurred from Monday to Friday up to a maximum of three sessions per day and on weekends if deemed helpful to patient's progress. n=58	Standard care -Patients in the control group received European standard physiotherapy including early mobilization, respiratory therapy and passive or active exercises. -These were physiotherapy-initiated and individually tailored, but subject to a medical prescription. -Treatments took place once daily on weekdays and on weekends if the responsible therapists deemed an interruption of therapy to	1. Functional capacity 2. Functional Independence Measure at hospital discharge 3. ICU acquired weakness 4. Handgrip strength 5. Functional mobility-Timed get up and go 6. Duration of IMV 7. Quality of life (using the Short Form 36) at 6 months after hospital discharge 8. ICU LOS 9. Hospital LOS 10. % that mobilized in ICU

		understand German or French		be harmful to patient's previous progress n=57	
Farzammanesh 2020 -Parallel RCT -Iran -Multi-center -n=168	Age: 45 Female: 49% APACHE II: NR Intubated: 21.4% BMI: NR	**Inclusion:** 1. Age 18 and older 2. Minimum 24h stay in ICU 3. No visual impairment 4. No amputation of lower limbs 5. No history of cognitive impairment including dementia or psychosis 6. No drug poisoning 7. No myocardial ischemia or arrhythmias 8. No hyperthermia 9. Not post cardiac arrest 10. No mobility limiting conditions **Exclusion:** 1. Onset of active GI hemorrhage during study 2. Hemodynamic instability 3. Arterial hemoglobin saturation 88% or less 4. Respiratory rate 5 or less or 40 or more 5. Heart rhythm disorders during the study	ROM exercises twice a day, 10 reps/exercise in upper and lower extremities n=84	"Routine treatment of care and hospital rehabilitation groups" - ROM exercises only on mechanical ventilation and after 3-4d of ICU admission with physician order n=84	1. Duration of ICU stay 2. Incidence of delirium 3. Duration of delirium
Fossat 2018 - Parallel RCT - France -Single center -n=314	Age: 65.5 Female: 35.5% APACHE II: NR Intubated:76% BMI: 26.6	**Inclusion:** 1. Age 18 or older 2. Admitted <72hrs before randomization 3. Deemed to need more than 48hrs ICU care 4. Independent walking ability and Barthel Index >55 within 15 days before ICU admission **Exclusion:** 1. Pregnancy 2. Cardiac arrest as cause of admission or before screening 3. Pacemaker or ICD	15 minute session of leg cycling exercise on a cycle ergometer and at a different time of day a 50 minute electrical stimulation session of quadriceps muscle delivered by a 4-channel electrical stimulator each weekday, in addition to standardized early rehabilitation n=159	Standardized early rehabilitation each weekday from randomization to ICU discharge following a progressive multistep program n=155	1. Muscle strength at discharge from ICU 2. Number of ventilator free days 3. ICU mobility scale score 4. HrQoL at 6 months 5. Functional autonomy at 6 months

		4. Acute cerebral disease requiring deep sedation for at least 72hrs 5. Acute polyradiculone-uropathy 6. Myasthenia 7. Advanced dementia 8. DVT or PE treated for <48hrs 9. Contraindication to electrical muscle stimulation or leg cycling for MSK, dermatological, or surgical reasons 10. Contraindication to standing or transfer to a chair 11. Lower limb amputation 12. Previously included in present study			
Frazzitta 2016 -Parallel RCT -Brazil -Single center -n=31	Age: 61 Female: 35.5% APACHE II: NR Intubated: NR BMI: NR (9.7% reported as obese)	**Inclusion:** 1. ≥18 years old admitted with the neuroICU with severe acquired brain injury 2.GCS ≤8 for ≥24h from the event 3. Diagnosis of vegetative state or minimally conscious state on the third day after the injury 4. Adequate pulmonary gas exchanging function (arterial O2 pressure/O2 flux ratio >250) 5. Stable hemodynamics **Exclusion:** 1. Unstable ICP 2. Cerebral perfusion pressure <60 mmHg 3. Fractures or skin lesions in thorax, abdomen or lower limbs 4. Deep vein thrombosis 5. Body weight>130 kg	Very early verticalized stepping -Single daily sessions of verticalization, using a tilt table with an integrated robotic stepping device located in the ICU room. The upper body of the patient was secured to the table by fastening the chest and the shoulders with a harness. The feet were strapped to the two footplates and the distal thighs secured to the stepping device. Legs stepping movements were passively obtained with the rhythmic alternating pushing up of the feet, and controlled by a computer. After patient positioning, the slope of the tilt table was gradually increased from 0° to 20°, 40° and then 60° in a time span of nine minutes. The stepping frequency was set at 20 steps/min for the entire treatment. The net time of the session was 30 minutes. Sessions were performed five times per week (Monday-Friday) for three consecutive weeks (a total of 15 sessions per patient). Before the verticalization period the experimental group received conventional in-bed physiotherapy for 60 minutes a day. n=15	Usual care -conventional in-bed physiotherapy (mobilization exercises in supine and sitting position on bed, without out-of-bed mobilization nor verticalization) for 60 minutes a day, from Monday to Friday, throughout the ICU stay. n=16	1. ICU LOS 2. Hospital LOS 3. Disability Rating Scale 4. Level of cognitive functioning at ICU and rehabilitation discharge

		6. Height >210 cm.			
Hickmann 2018 -Parallel RCT -Belgium -Single center -n=19	Age: 58 Female: 42.1% APACHE II: 18.5 Intubated: 94.7% BMI: 28	**Inclusion:** 1. Adults with septic shock were included within the 72 hours after ICU admission **Exclusion**: 1. Preexisting cognitive abnormalities 2. Malnutrition 3. Inability to walk independently 4. Leg amputation, fractures 5. Ongoing chemotherapy 6. Long-term steroid treatment 7. Cardiorespiratory arrest 8. Expected ICU stay less than 7 days 9. Therapy withdrawal/ imminent death	Early physiotherapy -The intervention group had two physiotherapy sessions per day (7/7 d) including 30 minutes (1 hr/d) of continuous passive/active leg chair/bed cycling followed by manual passive/active limbs mobilization n=9	Usual care -Daily physiotherapy session through manual passive/active limbs mobilization (5/7 d) n=10	1. Duration IMV 2. ICU LOS 3. 28-day mortality 4. Adverse events 5. Feasibility
Hodgson 2016 -Parallel RCT -Australia -Multi-center -n=47	Age: 58.5 Female: 39.5% APACHE II: 17.9 Intubated: 100% BMI: NR	**Inclusion:** 1. Adults >18yo expected to be invasively ventilated for 48h, and within 48h of eligibility **Exclusion:** 1. Second or subsequent ICU admission during a single hospital admission 2. Unable to follow simple verbal commands in English 3. Death was deemed inevitable and imminent 4. Unable to walk without assistance of another person prior to the ICU admission 5. Diagnosed with dementia prior to current acute illness as assessed by hospital records	Early-goal directed mobilization -Protocol included active functional activities, comprising walking, standing, sitting, and rolling. The patient could receive assistance from staff or equipment but the patient actively participated in the exercise at the highest functional level -The goal for patients allocated to EGDM was to undertake active exercises with a mobility team who was allocated 1 hour/d. -Performed by physio team -The amount of time that active exercise was conducted depended on the patients ICU mobility scale (IMS) score. A score of 1 or 2 indicated a very low mobility level, and active exercise was prescribed for 30 minutes. An IMS of 4–6 indicated a medium level of mobility, and 45 minutes of active exercise was prescribed. An IMS of 7–10 indicated a high level of mobility, and an hour of active mobilization was prescribed. This hour	Usual care -Standard care in mechanically ventilated patients in this region involves passive movements for 5–10 minutes/d. Standard care does not usually involve active exercise during mechanical ventilation, and we have previously shown that active exercise occurs in less than 16% of mechanically ventilated patients n=27	1. The ICU mobility scale 2. Strength 3. Duration of IMV 4. ICU LOS 5. Hospital LOS 6. 6-month post-ICU discharge health-related quality of life activities of daily living 7. Anxiety 8. Depression 9. Adverse events 10. ICU-free days 11. Ventilator free days 12. ICU-acquired weakness n=16

		6. Rest in bed orders due to documented injury or process that precluded mobilization such as suspected or proven instability of spine or pelvis 7. Severe acute brain injury 8. Opinion of the treating clinician it was unsafe to commence mobility therapy.	could be completed in one session of treatment or divided into several sessions throughout the day at the discretion of the treating physiotherapist n=29 		
Hodgson 2020 -Parallel RCT -Australia -Multi-center -n=20	Age: 50 Female: 20% APACHE II: NR Intubated: NR BMI: NR	**Inclusion:** 1. ≥18yo on ECMO for at least 24h, less than 72 though **Exclusion:** 1. In ICU for more than five days prior to the commencement of ECMO 2.Not expected to recover physical function in 90 days 3.Unable to communicate in English	Early-goal directed mobilization -Protocol included active functional activities, comprising walking, standing, sitting, and rolling. The patient could receive assistance from staff or equipment but the patient actively participated in the exercise at the highest functional level -The goal for patients allocated to EGDM was to undertake active exercises with a mobility team who was allocated 1 hour/d. -Performed by physio team -The amount of time that active exercise was conducted depended on the patients ICU mobility scale (IMS) score. A score of 1 or 2 indicated a very low mobility level, and active exercise was prescribed for 30 minutes. An IMS of 4–6 indicated a medium level of mobility, and 45 minutes of active exercise was prescribed. An IMS of 7–10 indicated a high level of mobility, and an hour of active mobilization was prescribed. This hour could be completed in one session of treatment or divided into several sessions throughout the day at the discretion of the treating physiotherapist n=10	Usual care - Standard care included non-protocolised assessment of the patient for strength, range of movement, ability to participate in rehabilitation and early mobilisation. There was no dosage specified for the delivery of rehabilitation or early mobilisation, and all care was at the discretion of the treating clinicians. n=10	1. Feasibility 2. Safety 3. Strength and function 4. ICU LOS 5. Hospital LOS 6. Mortality 7. Disposition 8. 90d quality of life

					
Hodgson 2022 -Parallel RCT -Australia -Multi-center -n=741	Age: 60 Female: 37% APACHE II: 18.1 Intubated: 100% BMI: 30.2	**Inclusion:** 1. Aged ≥18 years 2. IMV in ICU for ≥24h 3. Expected to remain IMV the day after tomorrow 4. Sufficient cardiovascular stability to make mobilization potentially possible, as indicated by: a. the absence of current brady-arrhythmia requiring pharmacological support b. a current ventricular rate ≤ 150bpm c. most recent lactate ≤ 4.0mmol/L d. current noradrenaline infusion rate of ≤ 0.2mcg/kg/min, OR a noradrenaline infusion rate between 0.1 and 0.2mcg/kg/min (without an increase in the infusion rate of more than 25% in the last 6 hours) e. most recent cardiac index ≥ 2.0L/min/m2 (where measured) f. no current requirement for VA ECMO 5. Sufficient respiratory stability to make mobilization potentially possible, as indicated by: a. current FiO_2 ≤ 0.6 b. current PEEP ≤ 16cm H_20 c. an absence of current requirement for	Early-goal directed mobilization -Protocol included active functional activities, comprising walking, standing, sitting, and rolling. The patient could receive assistance from staff or equipment but the patient actively participated in the exercise at the highest functional level -The goal for patients allocated to EGDM was to undertake active exercises with a mobility team who was allocated 1 hour/d. -Performed by physio team -The amount of time that active exercise was conducted depended on the patients ICU mobility scale (IMS) score. A score of 1 or 2 indicated a very low mobility level, and active exercise was prescribed for 30 minutes. An IMS of 4–6 indicated a medium level of mobility, and 45 minutes of active exercise was prescribed. An IMS of 7–10 indicated a high level of mobility, and an hour of active mobilization was prescribed. This hour could be completed in one session of treatment or divided into several sessions throughout the day at the discretion of the treating physiotherapist n=369 	Usual care The control group will receive standard care from physiotherapy staff not involved in delivering the intervention, whenever feasible. We have previously established that standard care in Australia for a patient receiving prolonged IMV (control group intervention) frequently involves no active exercise out of bed n=364	1. The primary outcome will be the number of days alive and out of hospital between randomisation and 180 days 2. All-cause mortality at 180 days 3.. Time from randomisation until death 4. Ventilator-free days to day 28 5. ICU-free days to day 28 6. Quality of life and physical function at 180days measured using: (i) European Quality of Life 5 Dimensions 5 Level (ii) Independent activities of daily living measured with Barthel Activities of Daily Living Index and The Lawton Instrumental Activities of Daily Living Scale (ADL and IADL) (iii) Generic function and disability measured with the World Health Organization's Disability Assessment Schedule 7. Delirium-free days to day 28 or ICU discharge 8. Cognitive function and Psychological function at 180days measured using: (i) Montreal Cognitive Assessment 9. Hospital Anxiety and Depression scale 10. PTSD-Impact of Event Scale – Revised

		NO, prone ventilation, neuromuscular blockers, prostacyclin, VV ECMO or HFOV d. Current RR ≤ 45 **Exclusion** 1. Not independent in activities of daily living in the month prior to current ICU admission (gait aids are acceptable). i.e: living in assisted living accommodation. 2. Documented cognitive impairment 3. Proven or suspected acute primary brain lesion (e.g. traumatic brain injury, stroke, hypoxic brain injury) 4. Proven or suspected spinal cord injury or other neuromuscular disease that will result in permanent or prolonged weakness (not including ICU acquired weakness) 5. Life expectancy less than 180 days due to a chronic or underlying medical condition 6. Death is deemed inevitable as a result of the current illness and either the patient or treating clinical or substitute decision maker are not committed to full active treatment 7. Unable to communicate in English 8. This is not the first ICU admission in the index hospital admission. 9. Fulfilled all inclusion criteria and none of the exclusion criteria ≥ 48 hours			

Kagan 2022 -Parallel group RCT -Israel -Single-center -n=41	Age: 62.7 Female: 35.9% APACHE II: 21 Intubated: 100% BMI: 29.3	**Inclusion:** 1. Adult patients (age 18–90 years) who had been mechanically ventilated for at least 48 h with an expected period of ventilation of a minimum of 7 days **Exclusion:** 1. Conditions that impaired the cycling movement 2. Trauma, arthritis, or surgery of the leg, pelvis, or lumbar spine 3. Open abdominal wounds or abdominal compartment syndrome 4. Anticipated fatal outcome of ICU 5.Pre-existing diagnosis of neuromuscular weakness, acute stroke, or status epilepticus 6.Cardiorespiratory instability (need for significant vasopressor support (noradrenaline) >0.2 mcg/kg/min, dopamine >8 mcg/kg/min, FIO_2 up to 60% or PEEP up to 10 cm H_2O or treatment by nitric oxide, minute ventilation 150 mL/kg body weight, respiratory rate 30 breaths/min on adequate ventilatory support) 7.Contraindication for EN, including mechanical or functional bowel obstruction, high output fistula, severe necrotizing pancreatitis 8. Pregnancy	Cycle ergometry with enteral nutrition -Quadricep muscle strength was evaluated in conscious patients using manual muscle testing, where the individual was asked to hold a limb or other body part at the end of its available range, or at another point in its range of motion, while the clinician provided manual resistance. The active passive trainer (cycling ergometry) was used to mobilize and strengthen the subjects. When patients were able to cycle actively, the cycling session was divided into two bouts of 10 min or into more intervals when needed. At the start, after 10 min and the end of every session, training intensity was evaluated and vital signs were recorded. Patients were placed in a comfortable position in between the supine and the semi recumbent position. For sedated patients, cycling was performed in a passive manner for 20 consecutive minutes n=21	Conventional physiotherapy with enteral nutrition -Conventional (respiratory) physiotherapy adjusted to the individual needs and a standardized mobilization session of the upper and lower extremities, 5 days per week. Passive motion was applied in sedated subjects, whereas awake patients were asked to participate actively. The intensity of the exercises was increased according to the patient's capability. Each session was continued for a minimum of 20 min n=22	1. Duration of IMV 2. ICU mortality 3. ICU LOS 4. Hospital LOS 5. Reintubation rate
Kayambu 2015 -Parallel RCT	Age: 64 Female: 36%	**Inclusion:** 1. Participants ≥18 years	Early rehabilitation -Early targeted physical rehabilitation	Usual care -Standard care group	1. Physical function using the acute care index of

-Australia -Single-center -n=50	APACHE II: 27.5 Intubated: NR BMI: 28	who remained mechanically ventilated ≥48 h and diagnosed with sepsis **Exclusion:** 1. Patients with head injuries, burns, spinal injuries, or multiple fractured lower limbs 2. Patients with septic shock who were unresponsive to maximal treatment, moribund or had an expected mortality within 48 h	program prescribed by the ICU research physiotherapist for 30 min, one to two times daily until discharge from the ICU within 48 h of the diagnosis of sepsis -Physical rehabilitation strategies included electrical muscle stimulation (EMS), passive range of motion, active range of motion, sitting out of bed, transfers, ambulation and other mobilization techniques as appropriate. Targeted muscle groups for EMS were vastus medialis, vastus lateralis, tibialis anterior and brachioradialis. A frequency of 40–45 Hz at 20–25 mA with pulse duration at 400 ls of 12 s on and 6 s off was used n=26	received standard ICU care which included physical therapy strategies provided by the ICU physiotherapist n=24	function at 6 months post discharge 2. Self-reported health-related quality of life at 6 months post discharge 3. Exercise capacity 4. Overall muscle 5. Anxiety using the hospital anxiety and depression scale on ICU discharge 6. ICU LOS 7. Hospital LOS 8. Mortality (ICU and 90-day) 9. Ventilator-free days
Kho 2019 -Parallel group RCT -Canada -Multi-center -n=66	Age: 61.6 Female: 26% APACHE II: 23.5 Intubated:100% BMI: NR	**Inclusion:** 1. Adult ICU patients who could ambulate independently at baseline 3. Within the first 4 days of IMV and the first 7 days of ICU admission **Exclusion:** 1. Patients who could not follow simple commands in English at baseline 2. Could not receive cycling (e.g., did not fit equipment, acute leg fracture) 3. Confirmed or suspected neuromuscular weakness 4. Temporary pacemaker 5. Were not likely to survive their hospital stay or had palliative goals of care 6. Pregnant 7. Temporary exemptions unresolved within the first 4 days of IMV (eg, hemodynamic	Cycling -30 min of cycling/day and routine physical therapy interventions -Until ICU discharge or 28 days n=36	Usual care (routine physiotherapy) n=30	1. Feasibility 2. Duration of IMV
Kim 2014 -Parallel group RCT	Age: 61.1 Female: 40.5%	**Inclusion:** 1. Adults admitted to a	Passive ROM -Passive ROM exercise twice a day, once in	Usual care	1. Manual function test 2. Ability to perform ADLS

-South Korea -Multi-center -n=37	APACHE II: NR Intubated: NR BMI: NR	neurosurgical ICU within 72 hours **Exclusion:** 1. Less than G3 in muscle strength 2. No pre-existing conditions that would disrupt medical treatment (i.e. no amputations, disfigurements, external wounds, or other deformations with regard to either upper extremity) n=19	the morning and once at evening - 5 days per week for 4 weeks -15-minute-long sessions -each move of the exercise routine was repeated 10 times. -The exercise routine was sequenced in a way that the active upper extremities were worked out before the paralyzed side, and consisted of: shoulder joint exercise (forward and side elevation of the upper extremities, internal and external rotation of the shoulder) elbow exercise (bending and extending), wrist exercise (flexion, extension, radial deviation, and ulnar deviation), and finger exercise (flexion and extension)	- Standard care included non-protocolised assessment of the patient for strength, range of movement, ability to participate in rehabilitation and early mobilisation. There was no dosage specified for the delivery of rehabilitation or early mobilisation, and all care was at the discretion of the treating clinicians. n=18	
Kwakman 2022 -Parallel group RCT -Netherlands -Single-center -n=40	Age: 63 Female: 47.5% APACHE II:20 Intubated:100% BMI: NR	**Inclusion:** 1. Mechanically ventilated for ≥48 h in the ICU and able to follow instructions 2. Bilateral quadriceps muscle strength≥2 according to the MRC and were able to sit unsupported on the edge of the bed **Exclusion:** 1. Contraindications for physiotherapy according to the evidence statement for ICU physiotherapy 2. Insufficient use of the Dutch language 3. Inability to walk independently prior to ICU admission 4. ICU readmission 5. Amputations or fractures in the lower extremities 6.Cognitive impairments 7.Imminent to death 8.Traumatic brain injury or stroke patients	Body weight-supported treadmill training (BWSTT) - A mobile treadmill with weight bearing utility was used at the bedside. The body weight-supported treadmill enables ambulation in patients with insufficient motor control or muscle strength to fully bear their weight. We provided BWSTT on a daily basis, except weekend days. If BWSTT was not possible (e.g. due to medical circumstances), usual care physiotherapy was provided instead. During BWSTT, patients were instructed to walk at a self-chosen comfortable walking speed. Perceived exertion and vital signs were monitored during training and used to adjust the bodyweight support or walking speed if needed. The duration of BWSTT was individually determined by the performance of the initial training session and varied between walking just a few steps and walking for several minutes. The training session was stopped when the perceived exertion was scored as very hard on the Borg scale, or if the vital signs exceeded the safety criteria. Intensity of BWSTT increased over the course of the program, by increasing walking speed and distance and by reducing body weight support. BWSTT was provided by two	Usual care Usual care physiotherapy consisted of supervised physiotherapy sessions on a daily basis and included ambulation training, pulmonary physiotherapy, active strength exercises, transfer training, cycling, balance training, inspiratory muscle training (IMT) and mobilizing out of bed. Treatment goals were to improve impairments in the cardiorespiratory- and muscular systems as well as improvement of mobility (in bed mobility, transfers and ambulation) and to regain functional independence in preparation for hospital discharge. Exercise prescription was based on the current (medical) status, the preference and tolerance	1. ICU LOS 2. Duration of IMV 3. MRC score 4. Staff requirements

			trained physiotherapists. After ICU discharge, BWSTT was continued on the regular ward until the patient was able to ambulate with walking aids and minimal physical support for balance assistance as measured with the Functional Ambulation Categories n=19	of the patient at the time of the treatment session and available guidelines regarding evaluation of safety criteria and clinical observation.. Physiotherapy sessions were provided by experienced ICU physiotherapists and were continued until hospital discharge or until pre-admission functional status was achieved and all treatment goals had been reached n=21	
Lin 2023 -RCT -China -Single centre -n=77	Age: 53 Female: 23.3% APACHE II: NR Intubated: NR BMI: NR	**Inclusion:** 1. Patients undergoing surgical repair of Type A aortic dissection 2. Age 18 and older 3. Stable respiratory indicators (SpO_2 90 and above, FiO2 <55%, PEEP <10) 4. MAP >75mmHg 5. Urine volume >1mL/kg/h 6. Barthel index >70 in first 2 weeks of ICU admission 7. Cardiac function grade 3 or below **Exclusion:** 1. ICU stay <48hrs 2. Unstable postoperative conditions (thrombosis or improper blood perfusion) 3. Pacemaker or ICD 4. Defect in limbs affecting walking function 5. Schizophrenia	Early goal-directed mobilization - theory-based and goal-oriented with total goal divided into several small goals, prescribed 48hrs after surgery n=39	Starting time of rehabilitation exercises determined by physiotherapists. Usual care offered by unit PTs such as active assistance and active mobilization, bed positioning, bedside and armchair transfers, orthostatism, and ambulation. Intervention was not standardized and did not follow any particular protocols. n=38	1. Functional status 2. Changes in vital signs during exercise 3. Serious adverse events 4. Grip strength 5. Duration of mechanical ventilation 6. ICU LOS 7. Total LOS 8. Muscle strength 9. ICU acquired weakness 10. HrQoL and readmission rate after 3 months

Lorenz 2024 -RCT -Berlin -Single center -n=19	Age: 58.3 Female: 25% APACHE II: 19 Intubated:100% BMI: 27.9	**Inclusion:** 1. Adults admitted with COVID-19 who were expected to be mechanically ventilated for at least 24hours after randomization 2. Clinical stability (defined as pressor dose less than or equal to 0.3mcg/kg/min, HR 40-150, not on ECMO, $Fi0_2 \geq 0.6$, PEEP ≤18, RR45, no hemorrhage, no multiorgan failure, lactate <4mmol/L **Exclusion:** 1. Confinement to bed before critical illness 2. Bed rest or contraindications of weight load of the lower extremity or spine 3. Body height outside the range of 150–195 cm 4. Body weight outside the scope of 45–135 kg 5. Severe skin lesions or fasciitis in the area of contact with the device or rhabdomyolysis 6. Pacemakers or other electrical stimulators or implanted medical pumps. 7. Acute subarachnoid or intracerebral hemorrhage 8.Increased ICP 9. Status epilepticus 10. Acute intoxication 11. Peripheral artery disease 12. Pregnancy 13.Patients receiving palliative care or those with therapy limitations	2 sessions of at least 20 minutes of mobilization per protocol with the VEMOTION system (Reactive Robotics GmbH), an AI-enhanced system combining a bed cycle and tilt table. The intervention lasted 5 days or until extubation, whichever came first n=9	standard mobilization program throughout their stay in the ICU n=10	1. ICU Mobility Scale 2. Surgical ICU Optimal Mobilization Score 3. Feasibility criteria 4. ICU LOS 5. Hospital LOS 6. Mortality 180 days 7. WHO disability assessment schedule Instrumental activities of daily living scale 8. Duration IMV 9. Discharge disposition
Maca 2023	Age: 60	**Inclusion:**	Conventional therapy plus in-bed cycling	1. Chest physiotherapy	1. Duration of mechanical

-Parallel RCT -Czech Republic -Single centre -n=40	Female: 45% APACHE II: 12 Intubated: 100% BMI: 28.5	1. Age 18 and over 2. ICU admission 3. Weaning from IMV **Exclusion:** 1. Inability to use cycling exercise 2. Encephalopathy 3. Cardiac arrest 4. Symptomatic chronic neuromuscular disease 5. Extreme obesity 6. Anticipated survival 7 days or less 7. Patient height 1.5m or less	performed once daily 5 days/week except for Saturday & Sunday. -The therapy was targeted to at least 10 minutes of active cycling in servo mode, without resistance, or against resistance, depending upon the patients ability n=20	encompassing manual therapy, ventilation support (contact breathing, activation of diaphragm, reflex stimulation of breathing), and airway clearance techniques (vibration, breathing exercises on the side or in sitting position, cough assistance, instrument support-vest airway clearance system) 2. Functional mobility training using reconditioning (reeducation of the range of motion and muscle strength, coordination and endurance training), mobilization according to the mobility protocol. In passive patients, we performed a passive exercise to prevent secondary changes n=19	ventilation 2. Change in intensity of muscle strength and speed of recovery 3. Presence of adverse alterations of vital (respiratory and cardiovascular) parameters related to use of cycling device
Machado 2017 -Parallel RCT -Brazil -Single centre -n=38	Age: 45 Female: 39.5% APACHE II: 17.13 Intubated: 100% BMI: NR	**Inclusion:** 1. Invasive mechanical ventilation 2. Maintained at a light level of sedation 3. Hemodynamically stable **Exclusion:** 1. Receiving palliative care 2. Amputees 3. Patients with leg fractures 4. Patients with neuromuscular disease, neurologic disease, and/or ICU-acquired weakness 5. Patients who are unable to cycle because	Conventional therapy plus passive exercise on a leg cycle ergometer 20 minute sessions at a fixed rate of 20 cycles/min performed 5 days/week until the last day of ICU stay n=22	Conventional physical and respiratory therapy are provided by the ICU physical therapists twice daily, for approximately 30 min, 7 days per week. The protocol included vibro-compression maneuvers; lung hyperinflation by the mechanical ventilator; endotracheal aspiration, when necessary; as well as passive and active-assisted motor exercises for arms and legs, depending on the clinical course of patients n=16	1. Peripheral muscle strength in arms and legs as measured by MRC scale 2. Duration of IMV 3. ICU LOS 4. Hospital LOS

		of pre-existing joint and MSK disorders			
Maffei 2017 -Parallel RCT -France -Single centre -n=40	Age: 53 Female: 45% APACHE II: NR BMI: 26 Intubated: 100%	**Inclusion:** 1. Patients aged >18 years and registered on the liver transplant waiting list 2. Absence of motor paralysis and major Neuromyopathy before transplant **Exclusion:** 1. Important hemodynamic instability or severe sepsis.	Intensive early rehabilitation twice daily 5d/week "In phase 1 (with the patient sedated and intubated), the physiotherapist positioned the patient in semi-seated position twice a day for 1 hour and applied 10 repetitions of passive range of motion for each joint of the limbs (flexion, extension, abduction, adduction, and rotation). In phase 2 (with the patient awake and intubated), if hemodynamic, cardiovascular, and respiratory criteria were established, the physiotherapist assessed the level of consciousness through responses to the following 5 statements: "open your eyes," "look at me," "open your mouth and put out your tongue," "move your head," "raise your eyebrows." One point was assigned to each appropriate response. If the score was 3 (out of 5), the patient was deemed to undergo phase 2 exercises: physiotherapist began active-assistive and active range of motion according to the MRC score, 10 repetitions for each joint twice a day, then including sitting on a chair if not against medical or surgical advice. In phase 3 (with the patient awake and extubated), active range of motion and resistance training for the arms and legs was applied according to MRC score (10 movements each joint and if necessary increase the resistance), and then included sitting on the edge of bed with active training leg (10 movements of knee extension, ankle dorsiflexion, and plantarflexion). Then standing, sitting on a chair, and walking were intended, according to the patient's capacities." n=20	Usual treatment - rehabilitation carried out under medical prescription for physiotherapist with 1 session/day 5d/week (usual treatment in ICU) n=20	1. Tolerance - assessed by number of adverse events during rehabilitation sessions 2. Feasibility - number of sessions discontinued 3. ICU LOS
McWilliams 2018 -Parallel RCT -United Kingdom -Single centre -n=103	Age: 61.5 Female: 61% APACHE II: 17.5 BMI: NR Intubated: 10)%	**Inclusion:** 1. Adults (≥16 years of age) who had been invasively ventilated for at least 4 days and expected to continue for	Enhanced rehabilitation - Physiotherapy sessions delivered by members of a specialist critical care rehabilitation team who were separate to the normal physiotherapy team. Following recruitment and randomisation subjects in the	Standard care - assessed by the physiotherapy team within 24 h of admission to critical care to obtain background in-formation on reason for	1. Feasibility - recruitment, compliance & differentiation from standard care 2. Time to first mobilization 3. Dose of physiotherapy in terms of therapy time

		at least 24h **Exclusion:** 1. Profound neurological deficit (defined as unlikely to return to a GCS of at least 14) 2. Orthopedic injury with contraindications to mobilize (e.g. pelvic fracture) 3. Unable to mobilize at least 10m prior to admission (with or without an aid) 4. Pre-existing neuromuscular disease 5. Invasively ventilated at another facility for >48h prior to admission or in hospital for >7 days prior to the onset of mechanical ventilation 6. Withdrawal of treatment was expected within 24 h of potential recruitment	intervention group were assigned a physiotherapy key worker who completed a standardized comprehensive assessment. Following this assessment an individually tailored rehabilitation program was devised, with the rehabilitation plan displayed in the subjects' bed space to aid communication and track daily achievements. Weekly goal setting meetings were held to review progress and update treatment plans as required. To facilitate ongoing rehabilitation following critical care discharge both verbal and written handovers were provided to ward therapy staff. For patients achieving a Manchester Mobility Score (MMS) of ≤4 at critical care discharge (unable to stand independently), ongoing rehabilitation was provided by the key worker in conjunction with the ward therapists for the first week following discharge from critical care. n=53	admission, as well as any pre-existing conditions that may be relevant. They then continue to be seen on a daily basis on weekdays, with rehabilitation commencing based on the individual physiotherapists own clinical reasoning. Physiotherapy provision is funded at a ratio of 1 physiotherapist to 10 patients, with an average treatment time of 30 – 45 min per patient per day Monday to Friday with one physiotherapist. When discharged to the ward environment, a telephone handover is provided to the receiving therapist who then continues the rehabilitation until the patient is deemed safe for discharge, with no further input provided by the critical care team n=50	4. Reasons for missed sessions 5. Mobility level at ICU discharge 6. ICU LOS 7. Hospital LOS 8. Mortality 9. Barthel Index 10. Strength (MRC score and grip dynamometry) 11. HrQoL
McWilliams 2023 -Parallel RCT -United Kingdom -Multi-centre -n=58	Age: 66 Female: 52% APACHE II: NR BMI: 26.7 Intubated: NR	**Inclusion:** 1. Patients admitted to the ICU with a RASS≥-3 and expected to stay in the ICU for ≥24h **Exclusion:** 1)Immobility prior to hospital admission 2)Diagnosis of delirium prior to screening or severe neurological deficit or injury	1)An evening mobilization session between 1200 and 2100h delivered by a dedicated mobilization team that included trained ICU physiotherapists in conjunction with bedside nursing staff as required -This was done in addition to usual care n=29	Usual care consisted of routine care delivered during normal working hours (between 08:00 and 17:00 h), including physiotherapy-led mobilization and rehabilitation interventions, and activities of daily living n=29	1. Feasibility 2. ICU and hospital LOS 3. Delirium 4. Duration of delirium 5. Duration IMV 6. In ICU and hospital mortality 7. Mobility and function
Morris 2016 - Parallel RCT	Age: 56 Female: 55.3	**Inclusion:** 1. Admission to a	Daily therapy until hospital discharge consisting of passive range of motion,	Weekday physical therapy when ordered by	1. Hospital LOS 2. Physical function

-USA -Single center -n = 300	APACHE III: 76 BMI: NR Intubated: NR	medical ICU 2. Age 18 years or older 3. Mechanical ventilation via endotracheal tube or noninvasive ventilation by mask 4. Arterial PaO_2/FIO_2 ratio less than 300 **Exclusion:** 1. Inability to walk without assistance prior to the acute ICU illness (use of cane or walkers were not exclusions) 2. Cognitive impairment prior to acute ICU illness described by surrogate, as nonverbal 3. Acute stroke 4. BMI > 50 5. Neuromuscular dis-ease impairing weaning from IMV 5. Acute hip fracture 6. Unstable cervical spine or pathologic fracture 7. Mechanically ventilated more than 80 hours or current hospitalization (including transferring hospital) more than 7 days 8. Orders for do not intubate on admission 9. Considered to be moribund by the primary attending 10. Enrolled in another research study	physical therapy, and progressive resistance exercise n=150	clinical team n=150	3. HrQoL
Moss 2016 -Parallel RCT -United State -Multi-center -n = 120	Age: 52.5 Female: 59% APACHE II: 17.65 Intubation: 100% BMI: NR	**Inclusion:** 1. At least 18 years of age who required mechanical ventilation for at least 5 days (subsequently modified for 4 or more days after 78 patients enrolled)	Therapy conducted for up to 28 days after randomization or until the patient successfully completed all stages of the program. While a patient was an inpatient, PT was delivered 7 days per week by a licensed physical therapist. After hospital discharge to a home environment, the protocol was continued in the home or on	As inpatients, patients assigned to the standard-of-care PT program received range-of-motion exercises, positioning, and functional mobility retraining 3	1. Short form of Continuous Scale Physical Functional Performance Test 2. ICU free days 3. Hospital free days 4. Discharge to home 5. All-cause mortality 6. Institution free days

		Exclusion: 1. Myocardial infarction within the last 3 weeks 2. Presence of signs or symptoms of unstable angina or history of unstable arrhythmias 3. Acute dissecting aortic aneurysm 4. Pulmonary embolism within the last six weeks 5. Severe aortic stenosis 6. Significant language barrier that would limit the ability to participate in the physical therapy program 7. Currently living > 45 miles from the University of Colorado Hospital 8. Unlikely to survive 6 months 9. Severe physical or cognitive impairment that would impair participation in physical therapy 10. Patient or physician declined.	an outpatient basis 3 days per week until the subject completed 28 days of therapy or was able to successfully complete all stages of the program. PT sessions were planned for 30 minutes while the patient was in the ICU and for up to 60 minutes while the patient was on a regular hospital floor, in an outpatient setting, or at home. The components of the PT program consisted of five elements delivered in a graduated manner: (1)techniques for proper breathing during exercise, (2) progressive range of motion, (3)therapeutic exercises emphasizing muscle strengthening, (4)exercises designed to improve core mobility and strength, and (5)functional mobility retraining, including bed mobility, transfers, gait, and balance. n=59	days per week by a licensed physical therapist. Once participants were able, they were assisted in daily activities such as transfers to bedside or chair and ambulation in their room. Similarly to the patients in the intensive PT arm, standard-of-care patients received their intervention for up to a total of 28 days. However, at hospital discharge to home, these patients received only information on the importance of daily exercise and were encouraged to initiate their own exercise program. No formal outpatient therapy program was delivered to the patients receiving standard care. n=61	
Nava 1998 -Parallel RCT -Italy -Single center -n= 80	Age: NR Female: NR APACHE II: NR Intubation: NR BMI: NR	**Inclusion:** 1. 3 to 5 days after admission to the RICU 2. Clinical stability defined as: (1)absence of Hyperthermia, (2)stable Hemodynamics (mean arterial blood pressure not varying by more than 10mmHg in the preceding 3 days, with systolic pressure of >90 and <170mmHg), (3)conscious and cooperative state, (4)no use of respiratory-depressant drugs. **Exclusion:**	Comprehensive rehabilitation program - 2 daily sessions of 30-45mins each consisting of four different steps of increasing difficulty. Steps I and II were considered progressive ambulation training and were common to both groups of patients Step 1 - maintaining optimal postural position i.e. sitting upright, as well as passive and active training of lower extremities Step 2 - progressive walking retraining Step 3 - specific respiratory muscle training & lower extremity training (cycling and stair climbing) Step 4 - 3 week complete lower extremity rehab program consisting of 2x daily 30min sessions of continuous treadmill walking n=60	Standard therapy plus progressive ambulation Medical therapy for underlying disease, nutritional support, and progressive ambulation (steps 1 and 2) n=20	1. Length of RICU stay 2. Mortality 3. Ventilator dependence 4. Walking autonomy 5. 6min walk test

		1. Systemic neurologic diseases 2. Severe orthopedic problems 3. Cardiovascular instability, 4. Severe arrhythmia			
Nickels 2020 -Parallel RCT -Australia -Single center -n=72	Age: 56.5 Female: 31.9% APACHE III: 66 Intubation: 100% BMI: 29.5	**Inclusion:** 1. Expected to be mechanically ventilated for more than 48 h 2. Recruited within 96 h of ICU admission 3. Expected to remain in ICU for more than 48 h from study enrolment **Exclusion:** 1. Under 18yo 2. Pre-existing condition that impaired mobility 3. New neurological disorder 4. Injuries precluding in-bed cycling 5. Over 135 kg (cycle ergometer maximum weight capacity) 6. Pregnant 7. Uncontrolled seizures or status epilepticus 8. Unlikely to survive the current hospital admission	Same usual care interventions PLUS once daily (up to 6d per week) in bed cycling sessions lasting a maximum of 30min n=36	Routine physiotherapy interventions that included a daily assessment of physical and respiratory status and treatment. Physical treatments were directed to functional task achievement including; sitting, standing and mobilizing n=36	1. Muscle atrophy of rectus femoris cross-sectional area 2. Manual muscle strength 3. Handgrip strength 4. ICU mobility score 5. 6min walk test 6. HrQoL
Nydal 2019 - Stepped-wedge cluster RCT -Germany -Multi-center -n=272	Age: 72 Female: 44.9% APACHE II: NR Intubated: 33% BMI: 26.2	**Inclusion:** 1. ≥18 years 2. Order for mobilization present **Exclusion:** 1. Palliative GOC 2. Had not previously consented to their data being used for research 3. Had already been included in a previous phase of this study 4. Had an immobility order	Protocol template with traffic light system for mobilization. Inter-professional meeting to adapt intervention template to local populations and conditions, with potential barriers for early mobilization identified. Possible strategies reducing barriers to mobilization discussed. Team members received pocket cards, posters and laminated posters for the bedside to define patients' daily mobility goals. n=122	Mobilization as usual based on clinicians' individual decision n=152	1. % of patients mobilized out of bed (level 3 on ICU mobility scale or higher) 2. Duration IMV 3. Duration delirium 4. ICU LOS 5. Hospital LOS 6. Adverse events

		5. If mobilization was not documented			
Nydal 2021 -RCT -Germany -Multi-center -n = 46	Age: 62.5 Female: 28.3% APACHE II: NR Intubated: 4.5% BMI: NR	**Inclusion:** 1. ≥18 years old 2. RASS≥-3 and were responsive 3. Could be assessed for delirium 4. Were able to being mobilized out of bed according to local policies 5. Expected to spend at least one night in the ICU **Exclusion:** 1. Expectation of death within the next 72 hours 2. No informed consent for the study 3. Pre-existing immobility 4. Contraindication against mobilization 5. Delirium already present before recruitment 6. Positive pregnancy test 7. Delirium assessment not possible (coma, foreign language, aphasia, etc.) 8. Participation in a competitive study with the outcome of delirium	Early mobilization provided by mobilization team. Patients approached between 2100 and 2300, informed and mobilized after consent. Aim for minimum mobility level was sitting on the edge of the bed, which progressed to standing, sitting in a chair or walking as tolerated. Duration was between minimum of 3mins and maximum 2hrs. Carried out for 3 consecutive evenings (i.e. each patient received maximum of 3 interventions) n=26	Usual care - Were mobilized during the day by physiotherapists and nurses. If necessary, they received the same pharmacological treatment as patients in the intervention group, as per local policies. Patients in the control group could be mobilized during the evening, too, on the basis of nurses' clinical judgement. n=20	1. Feasibility 2. Duration of delirium 3. Incidence of delirium 4. Mortality 5. Duration IMV 6. Hospital LOS
Patel 2023 -Parallel RCT -United States -Single center -n=198	Age: 56.7 Female: 42.5% APACHE II: 23 Intubated: 100% BMI: 29	**Inclusion:** 1. Adult patients (aged ≥18 years) 2. Mechanically ventilated for less than 96hrs but expected to continue for at least 24h 3. Functionally independent at baseline, defined as a Barthel Score of more than 70	Early mobilization (physical and occupational therapy) at enrollment after interruption of sedation. Daily cotreatment with a physical therapist and occupational therapist throughout hospital treatment until discharge or return to baseline level of function. Sessions ranged from 25-30min. n=100	Physical and occupational therapy initiated at the discretion of primary team or on extubation, whichever occurred first. n=100	1. Cognitive impairment at 1 year 2. Cognitive impairment at hospital discharge 3. ICU-AW 4. Functional independence 5. QoL 6. Institution free days

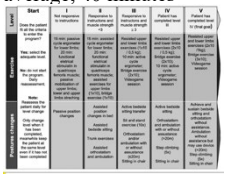
		Exclusion: 1. Rapidly changing neurological conditions (large stroke, status epilepticus, or intracranial hemorrhage or swelling) 2. Cardiac arrest 3. Elevated ICP 4. Pregnancy 5. Life expectancy <6 months 6. Severe chronic pain syndrome 7. Traumatic brain injury 8. Multiple limb fractures, pelvic fractures, or more than one absent limb			
Pinkaew 2020 -Parallel RCT -Thailand -Single center -n = 75	Age: 73.0 Female: 53.5% APACHE II:NR Intubated: 100% BMI: NR	**Inclusion:** 1. On ventilation for at least 72 hours and had a hemodynamic stable 2. Aged over 18 years 3. Physicians consult with physical therapy 4. Physiologically stable were with <50% variation in resting heart rate (HR), systolic blood pressure (SBP) < 200 mmHg or > 90 mmHg, SpO_2 >90%, FiO_2 < 60%, RR)<25 breaths per minute 4. No invasive femoral arterial lines 5. Not receiving treatment with a no physical exercise program **Exclusion:** 1. Pregnancy 2. BMI > 40 kg/m2 3.MSK diseases such as myasthenia gravis, Guillain-Barré syndrome	1) Early mobilization n=25 2) Early mobilization + elastic band exercise n=25	Conventional treatment -including, lung therapy techniques, pulmonary shaking, breathing exercises, coughing training, active exercise, chest mobilization etc n=25	1. Duration of IMV 2. Strength of arm muscle

		4. Vascular diseases such as lupus erythematous 5. Broken bones or skin ulcers (such as burns) 6. Metastatic lung disease 7. Acute traumatic brain injuries, the neuro-deficit condition, cognitive dysfunction and coma 8. Pacemaker			
Qie 2022 -Parallel RCT -China -Single center -n=190	Age: 53.15 Female: 42.1% APACHE II: 17.65 Intubated: 100% BMI: NR	**Inclusion:** 1. Age≥18years 2. ICU stay >24h, mechanical ventilation time >72h 3. APACHE II 15–21 points 4. Consent to participate in the study **Exclusion:** 1. Neurological or craniocerebral diseases 2. Patients with severe disturbance of consciousness or mental diseases who cannot cooperate with nursing instructions 3. Limb movement disorder, motor dysfunction, neuromuscular disease, unstable fracture, and limb disability 4. Hemodynamic instability, and malignant arrhythmia	Progressive early rehabilitation. Patients comprehensively evaluated using functional independence measure. Individualized early rehab program developed and modified every other day. Level 1 patients: passive training in bed. Training methods included stretching flexion, external rotation, internal rotation, and abduction. Patients in both groups were trained 10 times each day for about 30min each time Level 2 patients: active training in bed. The rehabilitation therapist guided and encouraged the patients to take the initiative to perform lower limb functional exercises. During exercise, the head of the bed was raised by 60°, and patients were instructed to buckle the legs and sit on the bed, while the pillows were placed on both sides to prevent lateral deviation. Then, according to the tolerance, the head of the bed was raised to 65°, and the legs were fully buckled. The active training was carried out with the help of the foot pedal type lower limb exercise device twice a day for 5-10 min each time. In addition, the patient was assisted to sit upright twice a day for 10-15 min each time Level 3 patients: bedside activities. When the leg can be lifted skillfully, a table with appropriate height was placed at the bedside to assist sitting at the edge of the bed, holding the chest with both hands while holding the elbows on the table. The feet	ICU routine nursing, diet guidance, traditional rehabilitation training guidance. The specific measures were as follows: close monitoring of vital signs such as respiration, blood pressure, pulse, and blood oxygen; adjusting mechanical ventilation parameters based on the condition; use of an air cushion to prevent bedsores and turning over; patting back and airway humidification; patients were given either passive or active training of limbs and joints, such as internal retraction, internal rotation, abduction, external rotation, flexion, and extension, twice each day for 30min; psychological counseling for patients and improving treatment compliance; and actively preventing the complications such as bed sores, ventilator-associated pneumonia,	1. Incidence and duration of delirium 2. Duration mechanical ventilation 3. ICU LOS 4. Functional status 5. Barthel index

			were naturally drooping and standing on the ground. The training time was appropriately controlled according to the degree of tolerance of the body for twice a day/10-60min each time, where the maximum time was not more than 2h Level 4 patients: standing by the bed or walking indoor. Twice a day/10-20min each time; for patients with rapid recovery and permitted condition, according to the standing condition, they were assisted in short-distance walking training. The number and degree of training were customized to be suitable for patients. n=95	and deep vein thrombosis n=95	
Rahiminezhad 2022 -Parallel RCT -Single center -Iran -n=71	Age: 47.05 Female: NR APACHE II: NR Intubated: NR BMI: NR	**Inclusion:** 1. Age 18y and above 2. On 1st day of ICU admission 3. No amputation, no fractures in the lower or upper extremities, no neuromuscular diseases (myasthenia gravis, Guillain–Barre syndrome, botulism and pesticide poisoning) 4. No deep vein thrombosis 5. No skin diseases 6. No metabolic disorders, including hypokalemia, hypophosphatemia, hypomagnesemia 7. No allergy to olive oil in the massage group **Exclusion:** 1. Having been transferred to the ward during the intervention 2. Having any of the disorders listed in the inclusion criteria	ROM exercise group: intervention started on the first day of admission. In addition to routine care, passive, active, and active-assistive ROM exercises were done once a day for seven consecutive days. Passive and active ROM exercises were done according to the patient's condition. Upper extremity ROM exercises include shoulder flexion, shoulder extension, shoulder abduction, elbow flexion and extension, wrist flexion and extension, joints of the thumb and fingers) and the lower extremity ROM exercises include hip and knee flexion, hip extension, hip abduction, ankle dorsiflexion, plantar flexion. Ten repetitions. The ROM exercises lasted 30–60 min n=36	Routine care as usual - physiotherapist performed routine care once a day in the morning, including respiratory and limb physiotherapy n=35	1. Mean muscle strength of right arm 2. Mean muscle strength left arm 3. Mean muscle strength right and left legs 4. Adverse events
Rezvani 2022 -RCT	Age: 54.38 Female: 44.9%	**Inclusion:** 1. Being intubated for at	Standard 4-level protocol 1. Limited joint movement exercise was	Routine ICU care, which was to change patient	1. Respiratory markers 2. Duration of IMV

-Single center -Iran -n = 49	APACHE II: NR Intubated: 100% BMI: NR	least 48 hours and using mechanical ventilation 2. Age 18-65 3. RASS more than −3 and less than 2 4. Stable hemodynamic conditions with the minimum dose of supportive drugs 5. PEEP < 8, FiO_2 <60%, SpO_2> 89%, and RR 12-30 **Exclusion:** 1. Any mobilization disorder before admission 2. Cognitive impairment and psychosis 3. Neuromuscular disorders 4. Acute stroke 5. BMI above 40 6. Femoral or spinal fracture 7. Undergoing cardiopulmonary resuscitation 8. Any disturbance in hemodynamic conditions (instability), death, discharge, or weaning off ventilator	performed on unconscious patients 5 times for each joint 2. Physiotherapy protocol was started, by which the patient had to answer 3 of the commands until the researcher knew he or she was ready to enter the next stage. The commands included: open your eyes, look at me, open your mouth and stick out your tongue, bring your head up and down, and raise your eyebrows when you hear the number 5. If the patient responded to 3 of the researcher's 5 commands, his or her condition was appropriate for initiating physiotherapy. When the patient gained sufficient strength and alertness to participate in occupational therapy, directed to either active supporter approach or active limited joint movement approach and moved from level 2 to level 4. Measures performed at this level included changing the position every 2 hours, inactive movement of the joint range 3 times a day, and being placed in a full sitting position at least 2 times for 20 minutes. All measures in the second level were also performed in levels 3 and 4. As patient progressed, the activities focused on a variety of functions such as sitting on the edge of the bed, getting out of bed, balance activity in a sitting position, and pre-walking exercises such as weight transfer on the legs, walking in a same spot, and moving. n=26	position once or twice in each shift n=23	3. Length of ICU stay
Schaller 2016 -Parallel RCT -International (Austria, Germany, USA) -Multi-center -n=200	Age: 65 Female:37% APACHE II: 16 Intubated:100% BMI: NR	**Inclusion:** 1. Patients aged 18 years or older 2. Mechanically ventilated for less than 48 h, and expected to require mechanical ventilation for at least another 24 h at the time of screening 3. Functionally independent at baseline with a Barthel Index Score of at least 70 at 2	1. Mobilization goal defined during daily morning rounds 2. Goal implementation across shifts facilitated by inter-professional closed-loop communication Began no later than 1d after enrollment n=104	Mobilization in line with the individual center's practice guidelines for mobilization and physical therapy n=96	1. Mean Surgical ICU Optimal Mobilization Score 2. ICU LOS 3. Mini-modified functional independence measure 4. MRC sum score 5. QoL 6. Hospital LOS 7. Mortality 8. Delirium free days 9. Sedation free days 10. Neuromuscular blocking drug free days 11. Vasopressor free days

		weeks before admission to the SICU, based on patient or proxy completion of the measure **Exclusion:** 1. Admitted to hospital for more than 5 days before screening 2. Motor component of GCS lower than 5 3. Irreversible disorder with a 6-month mortality of greater than 50% 4. Raised intracranial pressure 5. Cardiopulmonary arrest 6. Unstable fractures contributing to probable Immobility 7. Included in another trial at the same time as our trial 8. Acute myocardial infarction 9. Did not have lower part of their legs 10. Rapidly developing neuromuscular disease 11. Pregnant 12. Ruptured or leaking aortic aneurysm			12. Ventilator free days 13. Mean daily morphine equivalent dose 14. Corticosteroid days
Schujmann 2020 -Parallel RCT -Brazil -Single center -n=135	Age: 51.5 Female: 37.0% APACHE II: NR Intubated: 40% BMI: NR	**Inclusion:** 1. 18 years old or older 2. Scoring 100 points on the Barthel index in the 2 weeks prior to ICU admission **Exclusion:** 1. Previously hospitalized at other hospitals 2. Neurologic alterations 3. Stayed less than 4 days in the ICU 4. Amputees upon admission	Early and progressive mobility program with five levels of activity combined with conventional physiotherapy -A combined therapy consisting of a combination of conventional physiotherapy and a program of early and progressive mobilization at the appropriate level of activity for each patient -The protocol describes exercises for the muscular and cardiorespiratory systems: exercises aimed at gait re-education and cognitive components. The patients were assisted by specific physiotherapists who differed between the groups.	Control Group -Conventional treatment offered by the unit physiotherapists, with active assists and active mobilization as well as bed positioning, bedside and armchair transfers, orthostatism, and ambulation. The physiotherapist defined the type of therapy and did not use a preestablished routine. No equipment was used	1. Barthel Index after ICU discharge 2. Mobility - timed up and go, sit-to-stand, and 2-minute walk test 3. ICU mobility scale

		5. Contraindications for Mobilization 6. Cognitive impairment with an inability to understand commands and perform tests	All patients started physical therapy care within up to 48 hours of ICU admission Both groups received physiotherapy treatment bid, five times a week. Due to the hospital routine, in the morning, both groups received conventional physical therapy. The intervention group received conventional physiotherapy in he morning and the research protocol in the afternoon. The control group received conventional physiotherapyduring both periods. The duration of each session in IG was, on average, 40 minutes  n=68	-Initiation of therapy was decided by the responsible physical therapist. n=67	
Schweickert 2009 -Parallel RCT -United States -Multi-center -n =104	Age: 56.1 Female: 50% APACHE II: 19.5 Intubated: 100% BMI: 27.7	**Inclusion:** 1. Adults (≥18 years of age) who had been on mechanical ventilation for less than 72 h, were expected to continue for at least 24 h 2. Met criteria for baseline functional independence (defined a priori as a Barthel Index score ≥70 obtained from a proxy describing patient function 2 weeks before admission) **Exclusion:** 1. Rapidly developing neuromuscular disease 2. Cardiopulmonary arrest 3. Irreversible disorders with 6-month mortality estimated at more than 50% 4. Raised ICP 5. Absent limbs 6. Enrolment in another	Exercise & mobilization beginning on day of enrolment n=49	Standard care with physical and occupational therapy as ordered by primary care team *Neither site routinely provides physical therapy for patients who are on mechanical ventilation for less than 2 weeks n=55	1. Return to independent functional status at hospital discharge (ability to perform 6 ADLs and walking independently) 2. Number of hospital days with delirium 3. Ventilator free days 4. ICU LOS 5. Hospital LOS 6. Barthel Index score at discharge 7. Number of functionally independent ADLs 8. Distance walked without assistance 9. Incidence of ICU acquired paresis 10. Hand grip strength scoring

		trial			
Schweickert 2023 -Stepped wedge RCT -United States -Multi-center -n=1917	Age: 62.0 Female: 43.0% APACHE II: NR Intubated: 100% BMI: NR	**Inclusion:** 1. IMV for ≥48hours 2. Able to ambulate, independently or with assistance, prior to hospital admission **Exclusion:** 1. Comfort measures only	Designation and posting of daily mobilization goals, interprofessional closed-loop communication coordinated by each ICU's facilitator, and performance feedback n=1069	Usual care - nurses able to document daily mobility goals within electronic health record but no explicit encouragement to do so, and no data related to patient mobility presented on ICU dashboard n=848	1. Maximal Intensive Care Mobility Scale 48hrs prior to ICU discharge 2. Ability to stand before ICU discharge 3. Unplanned extubation
Waldauf 2021 -Parallel RCT -Czech Republic -Single center -n=150	Age: 61.1 Female: 26.7% APACHE II: 22.15 BMI: 30 Intubated: 100%	**Inclusion:** 1. Adult (≥18years) patients who received mechanical ventilation for less than 72 hours but were predicted to need ICU for a week or more **Exclusion:** 1. Bedridden before ICU admission 2. Missing or injured lower limbs 3. Irreversible paralysis or those with pacemakers	Cycle ergometry assisted by functional electrical stimulation Intervention began the calendar day after randomisation and consisted of a progressive mobility program tailored to patients' condition and supplemented by the use of FESCE. The goal was to deliver a total of 90min of active exercise a day until ICU discharge or day 28 whichever occurred earlier. Early in the course of the disease the intervention included FESCE. After warm-up phase (5min of passive cycling), patients received therapy consisting of functional electrical stimulation or active cycling with duration adjusted per protocol and patient's tolerance) followed by relaxation phase (5min of passive cycling). Face-to-face individual therapy was delivered two times a day by a certified physical therapist (MSc) specially trained in FESCE application in ICU n=75	Standard care - usual best medical and nursing care, daily sedation holds, respiratory physiotherapy and management as usual. Standard physiotherapy delivered 2x/day 6d/wk in a routine way n=75	1. Physical component summary score of SF-36 quality of life questionnaire measured at 6 months 2. Four-item physical fitness in intensive care test 3. Rectus muscle cross-sectional diameter on ultrasound 4. Mean daily nitrogen balance 5. Muscle power as per MRC score 6. Ventilator free days 7. ICU LOS 8. Number of episodes of elevated ICP 9. Dialysis interruptions
Winkelman 2018 -Parallel RCT -United States -Multi-center -n=54	Age: 56.2yo (17.0) Female: 53.7% APACHE II: NR Intubated: 100% BMI: 30.3	**Inclusion:** 1.Adults admitted to an ICU who received at least 36h of IMV and were expected to require at least ≥24h more of IMV **Exclusion:** 1. A length of ICU stay of 14 or more days prior to eligibility to	Twice daily early therapeutic mobility n=25	Daily early therapeutic mobility n=29	1. Duration IMV 2. ICU LOS 3. Delirium incidence 4. Mortality

		enroll 2. Weight >350 lb 3. History or acute diagnosis of neurological or orthopedic injury that precluded the ability to participate in volitional and progressive ETM (e.g., new spinal cord injury, delayed lower extremity fracture repair, inability to follow directions due to a chronic brain condition such as severe dementia or stroke/hypoxic coma, or related conditions) 4. New myocardial infarction 5. Presence of open fascia from abdominal or lower extremity surgery (e.g., fasciotomy for infection), or end-stage or end-of-life treatment (e.g., hospice consulted) 6. Intensivist opinion that the individual was moribund.			
Wright 2018 -Parallel RCT -United Kingdom -Multi-center -n=308	Age: 62 (16) Female: 41.6% APACHE II: 19 (7) Intubated: 98.5% BMI:NR	**Inclusion:** 1. 18 years or older and had received 48 hours or more of either invasive or non-invasive ventilation **Exclusion:** 1. End-of-life care 2. Acute brain or spinal cord injury (or admitted following brain or spinal cord surgery) 3. Multiple trauma if mobilization therapy was judged unlikely to be possible	The intervention group had a target delivery of 90 min of physical rehabilitation per day (Monday to Friday), split between at least two sessions. n=150	The standard care group had a target of 30 min of physical rehabilitation per day (Monday to Friday). -The physical rehabilitation therapy received by the standard care group was the same as that provided normally in participating ICUs Respiratory physiotherapy was given as standard in both groups. n=158	1. Mortality 2. ICU LOS 3. Duration IMV 4.Quality of Life at 6 months 5. Physical Component Summary measure of the SF-36 6. Physical ability at ICU discharge 7. Mental health 8. Hospital LOS

		4. Burns 5. Rapidly progressive neuromuscular disease 6. Patients enrolled in another clinical trial without a co-enrolment agreement in place 7. Patients previously enrolled in this trial			
Wu 2022 -Parallel RCT -China -Single-center -n=96	Age: 57.1 (10.95) Female: 14.8% APACHE II: NR Intubated: 100% BMI: NR	**Inclusion:** 1. Aged 18–75yo 2. Lung transplantation 3. Communicate normally **Exclusion:** NR	Early extubation combined with physical training program n=48	Routine nursing intervention -The responsible nurse assisted the patient with ankle pump exercises in bed twice a day. As well as routine nursing, the observation group underwent early tracheal extubation combined with early exercise. n=48	1. Duration IMV 2. ICU LOS 3. 6-minute walk test 4. Hospital LOS
Wu 2023 -Parallel RCT -China -Multi-center -n=56	Age: 59.87 Female: 21.4% APACHE II: 16 Intubated: 30.9% BMI: 22.8	**Inclusion:** 1. Aged 18 to 80 years 2. Expected to stay in the ICU for > 48 h 3. Could walk independently two weeks before transfer to ICU 4. APACHE-II ≥ 8 5. Patients were awake and able to cooperate with five standardized questions **Exclusion:** 1. Incapable of doing the early activity or rehabilitation exercises, such as being in the acute phase of myocardial infarction, having a ruptured thoracic aortic aneurysm, or obstructive hypertrophic	Resistance training and usual care The resistance protocol encompassed three physical function levels: supine, sitting, and standing. Each level consisted of seven to eight actions, such as chest pressing, elbow flexion, rowing, ankle dorsiflexion, ankle plantarflexion, knee extension, hip flexion, bridge exercises, and abdominal breathing. These exercises targeted the upper and lower extremity muscles, as well as the core muscle groups - The RT intervention was conducted under the guidance of trained researchers, both in the ICU and in general ward, starting from randomisation until hospital discharge. Administered five times per week, each session lasted approximately 20 to 30 min and was comprised of warm-up, exercise, and cool-down phases. The exercises incorporated two levels of resistance: using body weight for limb movements and utilizing TheraBand elastic bands (The Hygenic Corporation, Akron, OH, U.S.) with	Usual care-comprehensive rehabilitation and nutrition management, overseen by physicians and charge nurses. Early rehabilitation included activities such as passive joint mobilization, passive sitting, bedside sitting, bicycle-assisted training, active bedside exercises, dynamic standing, assisted walking, or advanced muscular training, and so on n=28	1. 6-minute walk test 2. Short physical performance battery 3 MRC and ICU AW 4. Grip strength 5. SF-36 6. Minim-Mental state exam 7. Hospital anxiety and depression scale 8. Revised impact of event scale

		cardiomyopathy, uncontrolled lethal arrhythmia, pulmonary embolism, acute phase of asthma, severe pulmonary hypertension, myasthenia gravis, Guillain–Barré syndrome, recent deep vein thrombosis (DVT) or venous thromboembolism (VTE) 2. Active uncontrolled bleeding 3.Restriction of activity during hospitalization due to medical condition and other factors; 4. Acute phase of brain injury and possible long-term physical dysfunction and impaired consciousness 5.Cognitive dysfunction or mental impairment 6. Contraindication to enteral nutrition or the need for prolonged fasting; 7. Inability to achieve muscle strength level 3 during ICU hospitalization; 8.Femoral arterial cannulation	colour-coded levels of resistance (yellow and red). n=28		
Yousef-Brauner 2015 -Parallel RCT -Israel -Single-center -n=18	Age: 56.6 (15) Female: 61.1% APACHE II: 20 (7.4) Intubated: 100% BMI: NR	**Inclusion:** 1. Adults >18yo who were independent before current hospitalization, fully conscious and able to perform simple commands, and had a MRC physical strength examination score < 48 points 2. Had been mechanically ventilated	Physical therapy twice a day -Description see below The first phase was passive and included range of motion passive activation in the upright sitting position, with six repetitions per movement for all upper and lower limb joints, change of positions, manual lung hyperinflation and bronchial suction. Patients who were able to actively move at least one joint of every limb at strength of 1	Physical therapy once a day n=9	1. ICU LOS 2. Duration IMV 3. MRC

		for at least 48h, and expected to remain IMV for at least 48h more **Exclusion:** 1. Unconsciousness; central or peripheral neurological damage 2.Hemodynamic instability (i.e., blood pressure >200 or <80 mmHg, heart rate <40 or >130 per minute) 3. Arrhythmias 4. Acute myocardial infarction 5. Respiratory instability (i.e.,O2 saturation <88%).	of 5 or higher based on manual muscle testing crossed to the second phase. The second phase was active, and included breathing exercises for those who were able to breathe spontaneously, manual lung hyperinflation and bronchial suction, active exercises using all the joints of each limb for 15 min, positional changes and bed mobility, including sitting at the edge of the bed, SB and trunk exercises. Patients passed to the third phase if SB was graded 2 of 4 or higher, according to Stolov's Criteria. The third phase was a functional, and included breathing exercises, manual lung hyperinflation and bronchial suction, active exercises using all joints of each limb for 15 min, SB and trunk exercises while sitting at the edge of the bed. Training for bed motilities such as transfer from supine to sitting positions and from sitting to standing, as well as walk training adapted to the individual patient (e.g., mobile oxygen delivery equipment, mobile ventilator and walking aids) were included n=9		
Yu 2020 -Parallel RCT -China -Single-center -n=107	Age: 59.2 (7.7) Female: 49.5% APACHE II: 20.8 (3.2) Intubated: 100% BMI: NR	**Inclusion:** 1. Patient ≥18yo who had been admitted to the ICU and required IMV within the previous 2 days 2. GCS score was 15 before admission, and patients could communicate via gesture or expression before admission 3. Acute resp failure was the main cause of ICU 4. APACHE II score ≥10 **Exclusion:** 1. Pregnant women 2.Diseases such as fractures, muscle weakness, suspected nervous system damage	Intervention group -In bed cycling combined with upper limb passive joining active strategy n=53	Patients in the control group received routine treatments in ICU, including turning over every 2 h and releasing both upper limbs for 5 min. Lower extremities were treated with lower extremity pneumatic pump for 20–30 min twice daily, and ventilator clustering care strategy was employed to prevent ventilator-associated pneumonia: raising the bed, shallow sedation, preventing aspiration, and daily catheter assessment n=54	1. ICU LOS 2. Duration of IMV 3. Proportion of ICU acquired weakness

		that may cause long-term muscle weakness 3. Risk for severe bleeding, the platelet count was <50×109/L, and the activated partial thromboplastin time (APTT) was >50 s; 4.History of myocardial ischemia, malignant arrhythmia, blood purification treatment and ECMO assist.			
Yu 2022 -Parallel RCT -China -Single center -N = 102	Age: 69.9 Female: 17.6% APACHE II: 17.2 Intubated: 100% BMI: 23.2	**Inclusion:** 1.≥18 years of age 2. IMV for 1-2d prior 3. Expected to stay in ICU at least 7 days **Exclusion:** 1.Primary gastrointestinal disease 2. Brain failure 3. Malignant tumor 4. Pregnancy 5. Contraindications to training bedside cycle ergometer 6.Extubated within 48hrs of inclusion 7.Unstable hemodynamics	-Passive or active cycling exercise training for lower extremities using a bedside cycle ergometer (20min sessions at individually adjusted intensity level) in addition to routine BID 20min physical therapy sessions n=52	-Conventional physical therapy 20min BID n=50	1.Gastrointestinal function 2. Days from of MV 3. ICU LOS 4. Hospital LOS
Zhou 2022 -Parallel RCT -China -Multi-center -n=100	Age: 57.2 Female: 44% APACHE II: 14 Intubated: 13.5% BMI: 24.1	**Inclusion:** 1. ≥18 years of age admitted to an ICU for the 1st time and expected to stay ≥72h 2.Conscious enough within the subsequent 24h to respond to at least three of the following orders: “open and/or close your eyes,” “look at me,” “put out your tongue,” “nod your head,” and “raise your eyebrows;” 3. Barthal index ≥70 2	-Early mobilization in addition to standard ICU care. -EM within 24h of ICU admission of the patient, twice daily, 20–30 min/session, until ICU discharge. The mobilization mode that the patients received was determined by their functional independence, measured daily by BI. Patients with different BI were assigned to the corresponding nursing systems, thus receiving individualized mobilization in accordance with their own functional independence n=50	Standard ICU rehabilitation n=50	1. ICU acquired weakness 2 MRC score 3. Functional independence 3. Duration IMV 4. ICU LOS 5. ICU mortality

		weeks before ICU admission **Exclusion:** 1. Pregnancy 2. Deformity, paralysis, fracture, or surgery of limbs 3. Pre-existing primary systemic neuromuscular disease that affects muscle strength (e.g., Guillain Barre, myasthenia gravis, amyotrophic lateral sclerosis) 4. Intracranial or spinal processes affecting motor function 5. Gastrointestinal surgery within 1 month 6. No expectation of any nutritional intake within the subsequent 48 h 7. Terminal cancer, expected death, or extremely poor prognosis			

ADLS-Activities of daily living; APACHE-Acute Physiology and Chronic Health Evaluation; ICU-AW-Intensive care unit acquired weakness; BMI: Body Mass Index; EN-Enteral Nutrition; FES-Functional-electrical stimulation; GCS-Glasgow Coma Scale; GI-Gastrointestinal; HrQoL-Health related quality of life; ICP-Intracranial pressure; ICU-Intensive Care Unit; IMV-Invasive Mechanical Ventilation; LOS-Length of STAY; MRC- Medical research council MSK-musculoskeletal; NR-Not recorded; PEEP-Positive end expiratory pressures; RASS-Richmond Agitation Sedation Scale; RCT: Randomized clinical trial; RR-Respiratory rate; $Sp0_2$-peripheral oxygen saturation

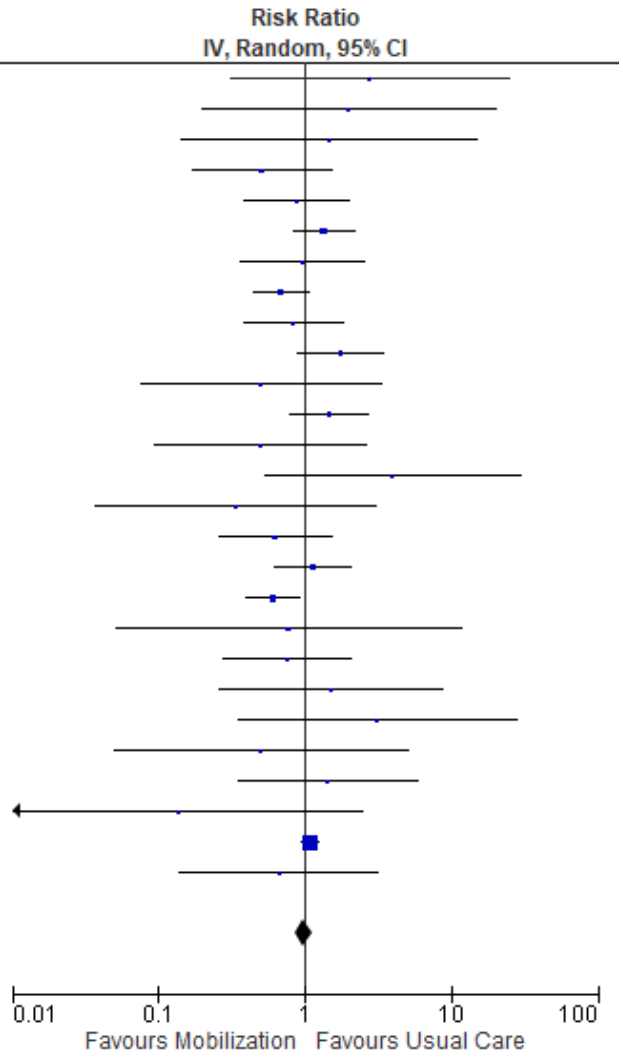
2. Forest Plots

1. ICU Mortality

Study or Subgroup	Enhanced Mobilization Events	Total	Usual Care Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Kayambu 2015	3	26	1	24	0.4%	2.77 [0.31, 24.85]	2015
Frazzitta 2016	2	20	1	20	0.4%	2.00 [0.20, 20.33]	2016
Hodgson 2016	2	29	1	21	0.4%	1.45 [0.14, 14.94]	2016
Machado 2017	4	26	7	23	1.6%	0.51 [0.17, 1.51]	2017
Eggmann 2018	9	58	10	57	2.8%	0.88 [0.39, 2.01]	2018
Fossat 2018	33	158	24	154	7.7%	1.34 [0.83, 2.16]	2018
McWilliams 2018	7	52	7	50	2.1%	0.96 [0.36, 2.54]	2018
Wright 2018	26	150	40	158	8.9%	0.68 [0.44, 1.06]	2018
Kho 2019	9	36	9	30	3.1%	0.83 [0.38, 1.83]	2019
Nydahl 2019	18	120	13	152	4.2%	1.75 [0.90, 3.43]	2019
Pinkaew 2020	2	50	2	25	0.6%	0.50 [0.07, 3.34]	2020
Berney 2020	20	80	14	82	5.0%	1.46 [0.80, 2.69]	2020
Farzammanesh 2020	2	82	4	81	0.7%	0.49 [0.09, 2.62]	2020
Hodgson 2020	4	10	1	10	0.5%	4.00 [0.54, 29.80]	2020
Nickels 2020	1	36	3	36	0.4%	0.33 [0.04, 3.06]	2020
Schujmann 2020	7	68	11	67	2.5%	0.63 [0.26, 1.52]	2020
Waldauf 2021	18	75	16	75	5.2%	1.13 [0.62, 2.03]	2021
De Azevedo 2021	23	87	41	94	9.6%	0.61 [0.40, 0.92]	2021
Nydahl 2021	1	26	1	20	0.3%	0.77 [0.05, 11.56]	2021
Yu 2022	6	76	8	76	1.9%	0.75 [0.27, 2.06]	2022
Zhou 2022	3	50	2	50	0.7%	1.50 [0.26, 8.60]	2022
Kagan 2022	3	21	1	22	0.4%	3.14 [0.35, 27.88]	2022
Kwakman 2022	1	19	2	19	0.4%	0.50 [0.05, 5.06]	2022
McWilliams 2023	4	26	3	28	1.0%	1.44 [0.35, 5.81]	2023
Maca 2023	0	20	3	19	0.2%	0.14 [0.01, 2.47]	2023
Schweickert 2023	337	1069	246	848	38.3%	1.09 [0.95, 1.25]	2023
Lorenz 2024	2	10	3	10	0.8%	0.67 [0.14, 3.17]	2024
Total (95% CI)		**2480**		**2251**	**100.0%**	**0.98 [0.85, 1.13]**	
Total events	547		474				

Heterogeneity: Tau² = 0.01; Chi² = 27.80, df = 26 (P = 0.37); I² = 6%

Test for overall effect: Z = 0.21 (P = 0.83)

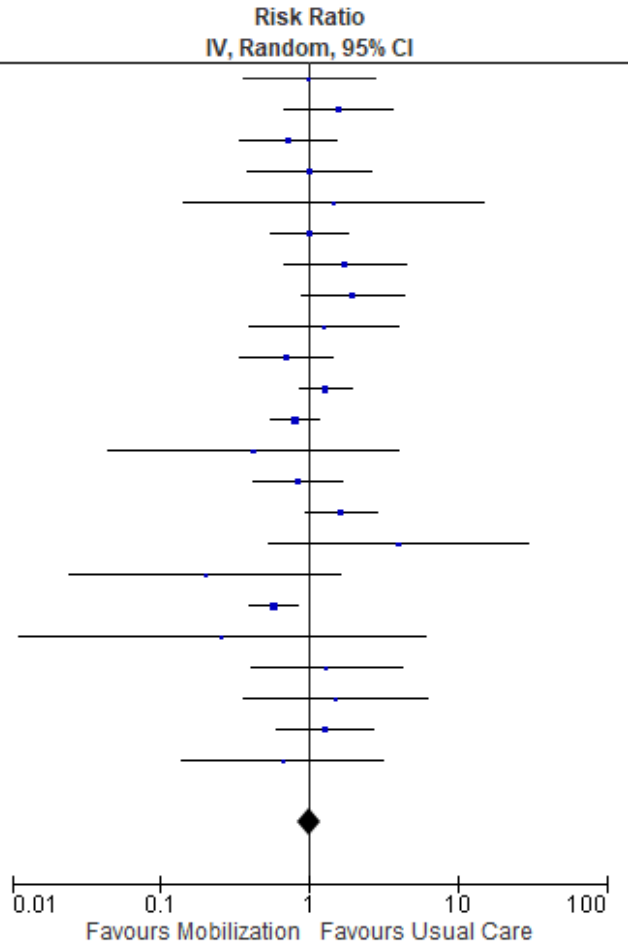


2. Hospital Mortality

Study or Subgroup	Enhanced Mobilization Events	Total	Usual Care Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Nava 1998	12	60	4	20	3.0%	1.00 [0.36, 2.75]	1998
Burtin 2009	11	45	7	45	4.0%	1.57 [0.67, 3.69]	2009
Schweickert 2009	9	49	14	55	5.0%	0.72 [0.34, 1.52]	2009
Brummel 2014	6	22	6	22	3.2%	1.00 [0.38, 2.62]	2014
Hodgson 2016	2	29	1	21	0.6%	1.45 [0.14, 14.94]	2016
Morris 2016	18	150	18	150	6.8%	1.00 [0.54, 1.85]	2016
Moss 2016	10	59	6	61	3.4%	1.72 [0.67, 4.44]	2016
Schaller 2016	17	104	8	96	4.5%	1.96 [0.89, 4.34]	2016
Frazzitta 2016	5	20	4	20	2.3%	1.25 [0.39, 3.99]	2016
Eggmann 2018	10	58	14	57	5.2%	0.70 [0.34, 1.45]	2018
Fossat 2018	42	158	32	154	11.6%	1.28 [0.86, 1.91]	2018
Wright 2018	34	150	45	158	12.1%	0.80 [0.54, 1.17]	2018
Nydahl 2019	1	120	3	152	0.7%	0.42 [0.04, 4.01]	2019
Kho 2019	11	36	11	30	5.8%	0.83 [0.42, 1.65]	2019
Berney 2020	24	80	15	82	7.6%	1.64 [0.93, 2.89]	2020
Hodgson 2020	4	10	1	10	0.8%	4.00 [0.54, 29.80]	2020
Nickels 2020	1	36	5	36	0.8%	0.20 [0.02, 1.63]	2020
De Azevedo 2021	25	87	47	94	12.0%	0.57 [0.39, 0.85]	2021
Nydahl 2021	0	26	1	20	0.3%	0.26 [0.01, 6.05]	2021
Kagan 2022	5	21	4	22	2.3%	1.31 [0.41, 4.22]	2022
de Paula 2023	4	40	3	45	1.6%	1.50 [0.36, 6.30]	2023
Patel 2023	14	99	11	99	5.1%	1.27 [0.61, 2.66]	2023
Lorenz 2024	2	10	3	10	1.3%	0.67 [0.14, 3.17]	2024
Total (95% CI)		**1469**		**1459**	**100.0%**	**1.01 [0.84, 1.22]**	
Total events	267		263				

Heterogeneity: Tau² = 0.04; Chi² = 27.30, df = 22 (P = 0.20); I² = 19%

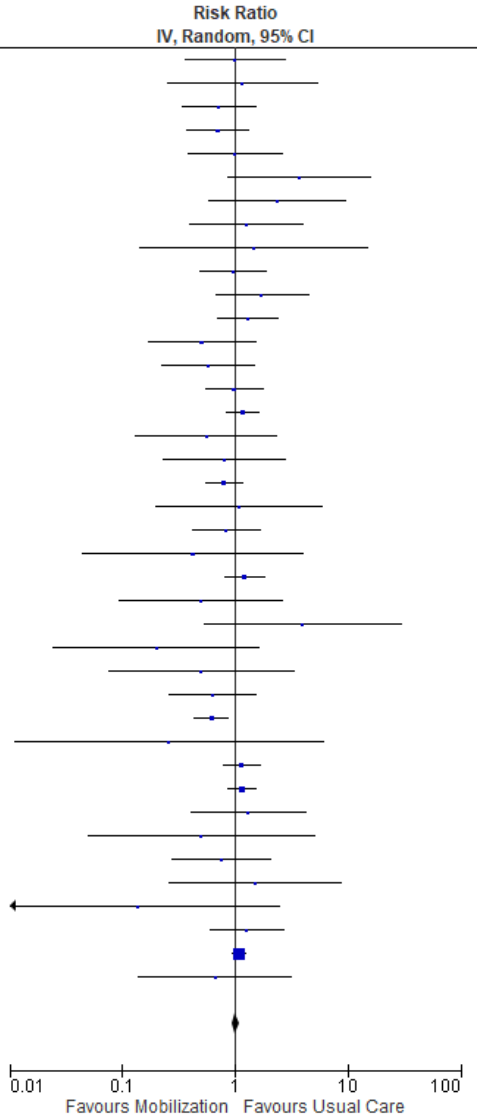
Test for overall effect: Z = 0.09 (P = 0.93)



3. Mortality at Longest Follow-Up

Study or Subgroup	Enhanced Mobilization Events	Total	Usual Care Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Nava 1998	12	60	4	20	0.7%	1.00 [0.36, 2.75]	1998
Burtin 2009	3	31	3	36	0.3%	1.16 [0.25, 5.34]	2009
Schweickert 2009	9	49	14	55	1.4%	0.72 [0.34, 1.52]	2009
Denhey 2013	13	74	19	76	1.9%	0.70 [0.37, 1.32]	2013
Brummel 2015	6	22	6	22	0.8%	1.00 [0.38, 2.62]	2015
Kayambu 2015	8	26	2	24	0.4%	3.69 [0.87, 15.69]	2015
Coutinho 2016	6	14	2	11	0.4%	2.36 [0.59, 9.48]	2016
Frazzitta 2016	5	20	4	20	0.6%	1.25 [0.39, 3.99]	2016
Hodgson 2016	2	29	1	21	0.1%	1.45 [0.14, 14.94]	2016
Morris 2016	15	131	15	126	1.7%	0.96 [0.49, 1.88]	2016
Moss 2016	10	59	6	61	0.8%	1.72 [0.67, 4.44]	2016
Schaller 2016	21	104	15	96	2.1%	1.29 [0.71, 2.36]	2016
Machado 2017	4	26	7	23	0.6%	0.51 [0.17, 1.51]	2017
Dos Santos 2018	4	13	8	15	0.8%	0.58 [0.22, 1.48]	2018
Eggmann 2018	16	58	16	57	2.2%	0.98 [0.55, 1.77]	2018
Fossat 2018	51	158	43	154	6.5%	1.16 [0.82, 1.62]	2018
Hickmann 2018	2	9	4	10	0.4%	0.56 [0.13, 2.34]	2018
McWilliams 2018	4	42	5	42	0.5%	0.80 [0.23, 2.77]	2018
Wright 2018	34	150	45	158	5.1%	0.80 [0.54, 1.17]	2018
Amundadottir 2019	3	29	2	21	0.3%	1.09 [0.20, 5.94]	2019
Kho 2019	11	36	11	30	1.6%	0.83 [0.42, 1.65]	2019
Nydahl 2019	1	120	3	152	0.1%	0.42 [0.04, 4.01]	2019
Berney 2020	32	80	27	82	4.5%	1.21 [0.81, 1.83]	2020
Farzammanesh 2020	2	82	4	81	0.3%	0.49 [0.09, 2.62]	2020
Hodgson 2020	4	10	1	10	0.2%	4.00 [0.54, 29.80]	2020
Nickels 2020	1	36	5	36	0.2%	0.20 [0.02, 1.63]	2020
Pinkaew 2020	2	50	2	25	0.2%	0.50 [0.07, 3.34]	2020
Schujmann 2020	7	68	11	67	1.0%	0.63 [0.26, 1.52]	2020
De Azevedo 2021	29	87	51	94	6.1%	0.61 [0.43, 0.87]	2021
Nydahl 2021	0	26	1	20	0.1%	0.26 [0.01, 6.05]	2021
Waldauf 2021	33	75	29	75	5.2%	1.14 [0.78, 1.67]	2021
Hodgson 2022	83	369	71	364	9.5%	1.15 [0.87, 1.53]	2022
Kagan 2022	5	21	4	22	0.6%	1.31 [0.41, 4.22]	2022
Kwakman 2022	1	19	2	19	0.1%	0.50 [0.05, 5.06]	2022
Yu 2022	6	76	8	76	0.7%	0.75 [0.27, 2.06]	2022
Zhou 2022	3	50	2	50	0.2%	1.50 [0.26, 8.60]	2022
Maca 2023	0	20	3	19	0.1%	0.14 [0.01, 2.47]	2023
Patel 2023	14	99	11	99	1.4%	1.27 [0.61, 2.66]	2023
Schweickert 2023	337	1069	246	848	40.0%	1.09 [0.95, 1.25]	2023
Lorenz 2024	2	10	3	10	0.3%	0.67 [0.14, 3.17]	2024
Total (95% CI)		**3507**		**3227**	**100.0%**	**1.01 [0.93, 1.10]**	
Total events	801		716				

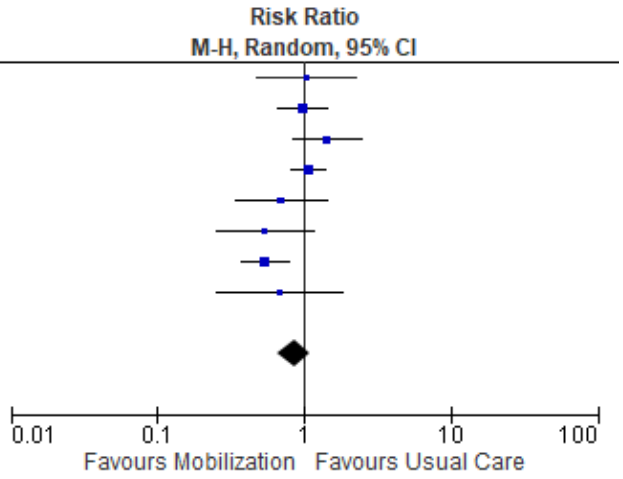
Heterogeneity: Tau² = 0.00; Chi² = 36.92, df = 39 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)



4. Incidence of Delirium

Study or Subgroup	Enhanced Mobilization Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Winkelman 2018	8	25	9	29	7.9%	1.03 [0.47, 2.27]	2018
Fossat 2018	39	158	39	154	17.4%	0.97 [0.66, 1.43]	2018
Nydahl 2019	23	114	20	141	12.6%	1.42 [0.82, 2.46]	2019
Berney 2020	47	82	44	82	21.2%	1.07 [0.81, 1.41]	2020
Nickels 2020	9	36	13	36	9.1%	0.69 [0.34, 1.41]	2020
Nydahl 2021	7	26	10	20	8.2%	0.54 [0.25, 1.16]	2021
Qie 2022	27	95	50	95	17.8%	0.54 [0.37, 0.78]	2022
McWilliams 2023	5	26	8	28	5.7%	0.67 [0.25, 1.80]	2023
Total (95% CI)		**562**		**585**	**100.0%**	**0.85 [0.65, 1.11]**	
Total events	165		193				

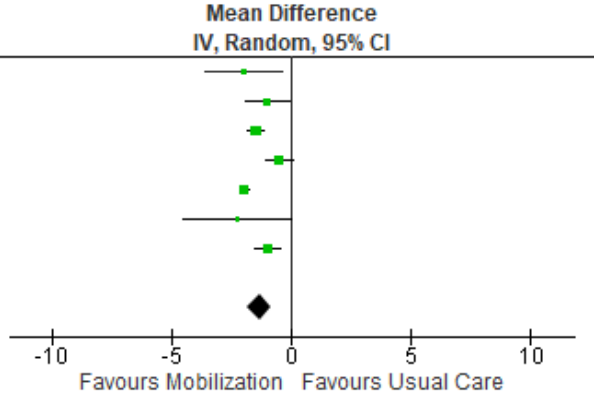
Heterogeneity: Tau² = 0.07; Chi² = 14.24, df = 7 (P = 0.05); I² = 51%
Test for overall effect: Z = 1.19 (P = 0.23)



5. Duration of delirium (days)

Study or Subgroup	Enhanced Mobilization Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Schweickert 2009	2	4.44	49	4	3.7	55	7.0%	-2.00 [-3.58, -0.42]	2009
Berney 2020	2	2.96	80	3	2.96	80	12.8%	-1.00 [-1.92, -0.08]	2020
Farzammanesh 2020	1.75	0.62	82	3.23	1.48	81	19.9%	-1.48 [-1.83, -1.13]	2020
Nydahl 2021	1.5	1.26	26	2	0.74	20	17.0%	-0.50 [-1.08, 0.08]	2021
Qie 2022	2.62	0.43	95	4.59	0.82	95	21.4%	-1.97 [-2.16, -1.78]	2022
McWilliams 2023	2	2	5	4.25	2	8	4.2%	-2.25 [-4.48, -0.02]	2023
Patel 2023	0	1.48	99	1	2.22	99	17.8%	-1.00 [-1.53, -0.47]	2023
Total (95% CI)			**436**			**438**	**100.0%**	**-1.34 [-1.85, -0.83]**	

Heterogeneity: Tau² = 0.30; Chi² = 35.27, df = 6 (P < 0.00001); I² = 83%
Test for overall effect: Z = 5.18 (P < 0.00001)

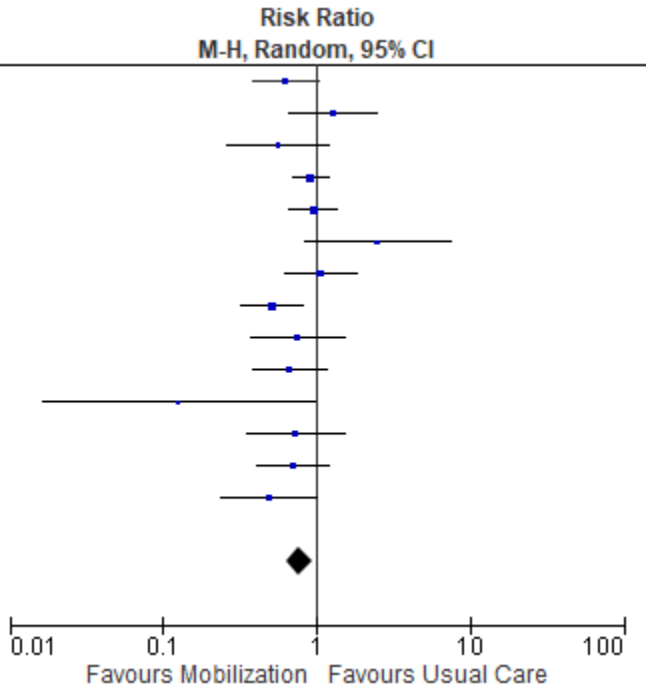


6. ICU Acquired Weakness

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Schweickert 2009	15	49	27	55	8.8%	0.62 [0.38, 1.03]	2009
Denhey 2013	16	74	13	76	6.1%	1.26 [0.65, 2.44]	2013
Hodgson 2016	7	25	10	20	4.8%	0.56 [0.26, 1.20]	2016
Schaller 2016	50	104	51	96	15.3%	0.90 [0.69, 1.19]	2016
Eggmann 2018	23	40	26	43	12.5%	0.95 [0.66, 1.36]	2018
Kho 2019	13	28	3	16	2.7%	2.48 [0.83, 7.40]	2019
Amundadottir 2019	13	20	8	13	8.0%	1.06 [0.62, 1.81]	2019
Yu 2020	16	53	32	54	9.6%	0.51 [0.32, 0.81]	2020
Berney 2020	11	80	15	82	5.4%	0.75 [0.37, 1.54]	2020
De Azevedo 2021	16	87	26	94	7.8%	0.66 [0.38, 1.15]	2021
Zhou 2022	1	50	8	50	0.8%	0.13 [0.02, 0.96]	2022
Wu 2023	8	28	11	28	5.0%	0.73 [0.35, 1.53]	2023
de Paula 2023	13	40	21	45	7.9%	0.70 [0.40, 1.20]	2023
Lin 2023	8	39	16	38	5.3%	0.49 [0.24, 1.00]	2023
Total (95% CI)		**717**		**710**	**100.0%**	**0.77 [0.64, 0.93]**	
Total events	210		267				

Heterogeneity: Tau² = 0.04; Chi² = 20.03, df = 13 (P = 0.09); I² = 35%

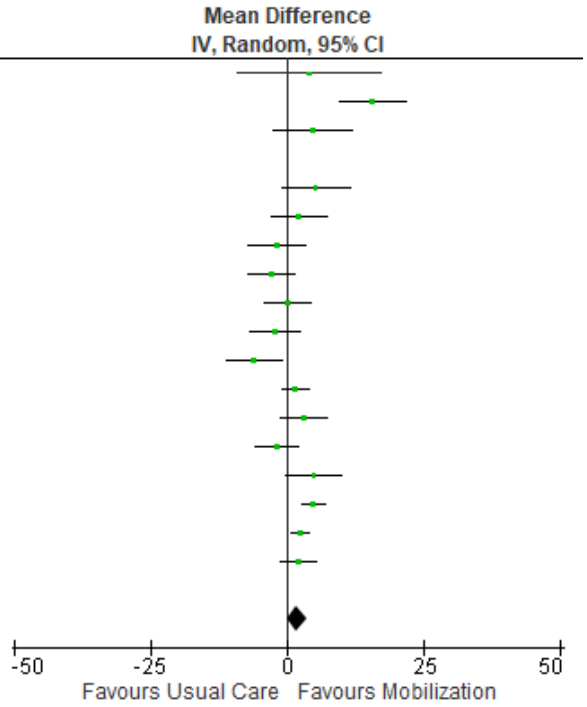
Test for overall effect: Z = 2.69 (P = 0.007)



7. Medical Research Council Score

Study or Subgroup	Enhanced Mobilization Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Schweickert 2009	52	24.44	49	48	42.96	55	1.5%	4.00 [-9.26, 17.26]	2009
Dantas 2012	55.86	4.4	14	40.29	10.51	14	4.6%	15.57 [9.60, 21.54]	2012
Kayambu 2015	51.9	10.5	19	47.3	13.6	23	3.7%	4.60 [-2.69, 11.89]	2015
Yousef-Brauner 2015	0	0	0	0	0	0		Not estimable	2015
Hodgson 2016	50.4	7.5	29	45.2	13.2	21	4.4%	5.20 [-1.07, 11.47]	2016
Machado 2017	47.18	8.75	22	45	6.89	16	5.5%	2.18 [-2.80, 7.16]	2017
Eggmann 2018	42.4	13.1	40	44.4	11.7	43	5.2%	-2.00 [-7.36, 3.36]	2018
Fossat 2018	48	21.5	158	51	15.6	154	6.3%	-3.00 [-7.16, 1.16]	2018
McWilliams 2018	53	10.37	35	53	7.41	34	6.3%	0.00 [-4.24, 4.24]	2018
Amundadottir 2019	40.2	6.6237	20	42.4	6.4538	13	5.9%	-2.20 [-6.75, 2.35]	2019
Kho 2019	46.3	12.1	28	52.4	5.2	16	5.3%	-6.10 [-11.26, -0.94]	2019
Berney 2020	51.8	7.1	80	50.3	8.7	82	8.2%	1.50 [-0.94, 3.94]	2020
Waldauf 2021	42.4	12.0602	57	39.4	11.1281	59	6.3%	3.00 [-1.23, 7.23]	2021
Kwakman 2022	56	5.19	19	58	7.41	21	6.6%	-2.00 [-5.94, 1.94]	2022
Wu 2023	52.28	6.4	28	47.43	12.29	28	5.4%	4.85 [-0.28, 9.98]	2023
Lin 2023	48.59	2.22	39	43.89	6.49	38	8.5%	4.70 [2.52, 6.88]	2023
Carvalho 2023	54.4	3.7	48	52.1	4.1	48	9.1%	2.30 [0.74, 3.86]	2023
de Paula 2023	60	4.44	25	58	8.9	35	7.2%	2.00 [-1.42, 5.42]	2023
Total (95% CI)			**710**			**700**	**100.0%**	**1.74 [-0.03, 3.52]**	

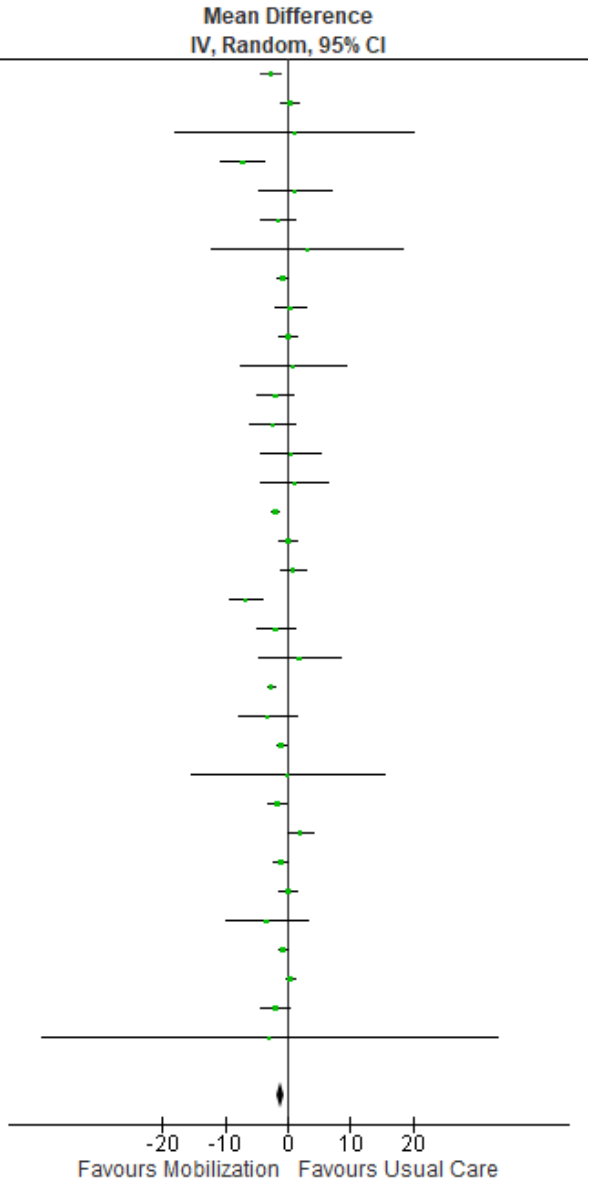
Heterogeneity: Tau² = 8.39; Chi² = 54.31, df = 16 (P < 0.00001); I² = 71%
Test for overall effect: Z = 1.92 (P = 0.05)



8. Duration of Mechanical Ventilation (days)

Study or Subgroup	Enhanced Mobilization Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Schweickert 2009	3.4	3.7	49	6.1	4.15	55	4.4%	-2.70 [-4.21, -1.19]	2009
Denhey 2013	4.4	5.1	74	4.1	3.5	76	4.6%	0.30 [-1.10, 1.70]	2013
Kayambu 2015	8	44.4	26	7	20.8	24	0.1%	1.00 [-17.99, 19.99]	2015
Yousef-Brauner 2015	9	5	9	16.2	2	9	1.9%	-7.20 [-10.72, -3.68]	2015
Coutinho 2016	12.6	5.1	14	11.4	8.8	11	0.9%	1.20 [-4.65, 7.05]	2016
Hodgson 2016	5.4	4.81	29	7	5.19	21	2.6%	-1.60 [-4.43, 1.23]	2016
Machado 2017	18	21.11	22	15	25.19	16	0.1%	3.00 [-12.17, 18.17]	2017
Maffei 2017	0.49	0.54	20	1.3	2.02	20	5.4%	-0.81 [-1.73, 0.11]	2017
Eggmann 2018	5.4	7.11	58	5	6.15	57	3.0%	0.40 [-2.03, 2.83]	2018
Fossat 2018	5	5.93	158	5	6.67	154	4.6%	0.00 [-1.40, 1.40]	2018
Hickmann 2018	5.5	11.19	9	4.7	6.59	10	0.5%	0.80 [-7.57, 9.17]	2018
McWilliams 2018	10	5.93	44	12	8.15	43	2.4%	-2.00 [-5.00, 1.00]	2018
Winkelman 2018	10.4	6.39	25	12.86	7.17	29	1.9%	-2.46 [-6.08, 1.16]	2018
Kho 2019	8.5	8.89	36	8	10.37	30	1.2%	0.50 [-4.21, 5.21]	2019
Amundadottir 2019	8.8	9.6	29	7.8	9.1	20	1.0%	1.00 [-4.30, 6.30]	2019
Yu 2020	8.36	1.08	53	10.34	1.64	54	5.9%	-1.98 [-2.51, -1.45]	2020
Berney 2020	7	5.19	80	7	4.4	82	4.4%	0.00 [-1.48, 1.48]	2020
Nickels 2020	6.3	4.15	36	5.5	4.89	36	3.5%	0.80 [-1.30, 2.90]	2020
Pinkaew 2020	6.15	3.7	48	12.82	5.69	23	2.9%	-6.67 [-9.22, -4.12]	2020
De Azevedo 2021	10	10.4	87	12	10.4	94	2.3%	-2.00 [-5.03, 1.03]	2021
Kagan 2022	12	7.8	14	10.2	9.5	13	0.7%	1.80 [-4.79, 8.39]	2022
Qie 2022	5.74	1.75	95	8.43	2.36	95	5.8%	-2.69 [-3.28, -2.10]	2022
Rezvani 2022	10.5	6.37	26	13.74	9.79	23	1.3%	-3.24 [-7.93, 1.45]	2022
Wu 2022	2	1.48	48	3	2.59	48	5.5%	-1.00 [-1.84, -0.16]	2022
Zhou 2022	0	45.85	50	0	31.26	50	0.1%	0.00 [-15.38, 15.38]	2022
Deng 2022	4.52	2.77	41	6.24	3.9	42	4.5%	-1.72 [-3.17, -0.27]	2022
McWilliams 2023	4	3.5	18	2	2.6	16	3.5%	2.00 [-0.06, 4.06]	2023
Lin 2023	2.6	1.45	39	3.7	3.3	38	5.0%	-1.10 [-2.24, 0.04]	2023
Wu 2023	0	0.2	28	0	3.6	28	4.7%	0.00 [-1.34, 1.34]	2023
Maca 2023	21	9.78	20	24.4	10.88	19	0.7%	-3.40 [-9.90, 3.10]	2023
Patel 2023	2.7	2.15	99	3.4	3.04	99	5.6%	-0.70 [-1.43, 0.03]	2023
Schweickert 2023	6.74	8.42	1069	6.26	6.14	848	5.7%	0.48 [-0.17, 1.13]	2023
Carvalho 2023	4.1	3.6	21	6.1	4.2	23	3.2%	-2.00 [-4.31, 0.31]	2023
Lorenz 2024	29	34.63	10	32	47.2	10	0.0%	-3.00 [-39.28, 33.28]	2024
Total (95% CI)			**2484**			**2216**	**100.0%**	**-1.10 [-1.69, -0.51]**	

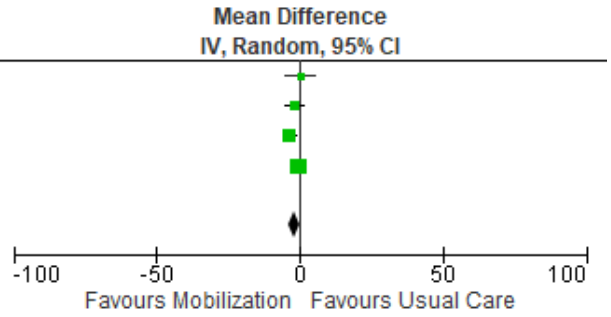
Heterogeneity: Tau² = 1.46; Chi² = 127.43, df = 33 (P < 0.00001); I² = 74%
Test for overall effect: Z = 3.67 (P = 0.0002)



9. Hospital Anxiety and Depression Scale

Study or Subgroup	Enhanced Mobilization Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Hodgson 2016	11.6	9.1	21	11.3	7.1	16	10.7%	0.30 [-4.92, 5.52]	2016
McWilliams 2018	5	6.67	17	7	2.96	18	19.3%	-2.00 [-5.45, 1.45]	2018
Berney 2020	3.3	2.5	25	7	4.9	25	31.3%	-3.70 [-5.86, -1.54]	2020
Wu 2023	4.36	2.75	28	4.84	3.16	28	38.7%	-0.48 [-2.03, 1.07]	2023
Total (95% CI)			**91**			**87**	**100.0%**	**-1.70 [-3.62, 0.22]**	

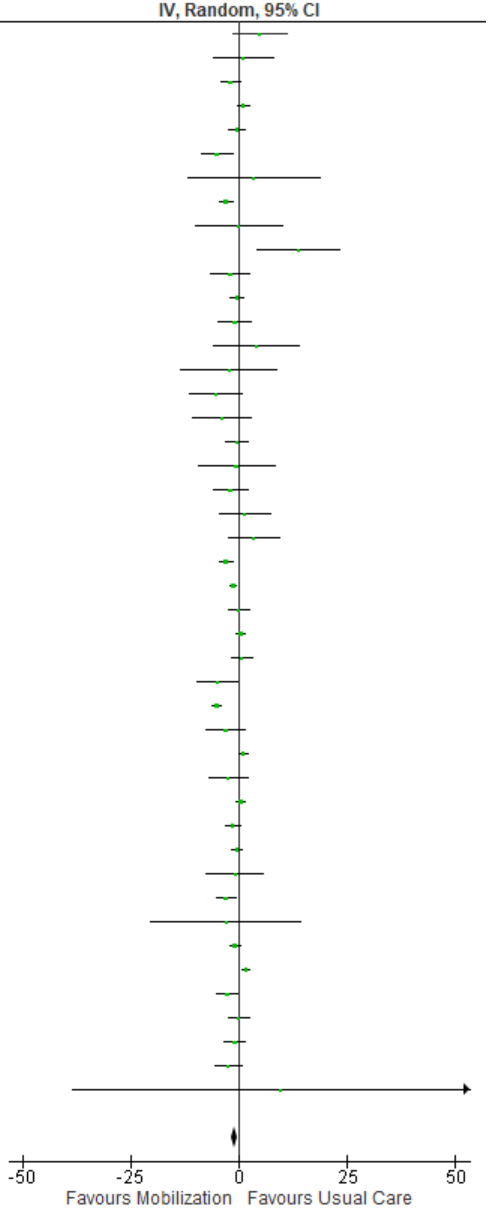
Heterogeneity: Tau² = 1.85; Chi² = 6.19, df = 3 (P = 0.10); I² = 52%
Test for overall effect: Z = 1.73 (P = 0.08)



10. ICU Length of Stay (days)

Study or Subgroup	Enhanced Mobilization Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Nava 1998	38.1	14.3	60	33.2	11.7	20	1.0%	4.90 [-1.38, 11.18]	1998
Burtin 2009	25	16.3	31	24	12.6	36	0.9%	1.00 [-6.06, 8.06]	2009
Schweickert 2009	5.9	6.44	49	7.9	5.04	55	3.0%	-2.00 [-4.24, 0.24]	2009
Denhey 2013	8	4.44	74	7	3.7	76	3.7%	1.00 [-0.31, 2.31]	2013
Brummel 2014	3.5	3.6	22	4	2.7	22	3.3%	-0.50 [-2.38, 1.38]	2014
Yousef-Brauner 2015	13	4.6	9	18.11	3.1	9	2.1%	-5.11 [-8.73, -1.49]	2015
Kayambu 2015	12	30.4	26	8.5	24.4	24	0.2%	3.50 [-11.73, 18.73]	2015
Schaller 2016	7	5.19	104	10	6.67	96	3.5%	-3.00 [-4.67, -1.33]	2016
Coutinho 2016	20.1	9.3	14	20.1	15.1	11	0.5%	0.00 [-10.17, 10.17]	2016
Frazzitta 2016	38.8	15.7	15	25.1	11.2	16	0.5%	13.70 [4.04, 23.36]	2016
Hodgson 2016	9	8.15	29	11	8.15	21	1.6%	-2.00 [-6.58, 2.58]	2016
Morris 2016	7.5	7.41	150	8	6.67	150	3.5%	-0.50 [-2.10, 1.10]	2016
Moss 2016	15	11.11	59	16	10.37	61	2.0%	-1.00 [-4.85, 2.85]	2016
Machado 2017	22	13.33	22	18	17.04	16	0.5%	4.00 [-6.04, 14.04]	2017
Maffei 2017	12	15.7	20	14.3	20	20	0.4%	-2.30 [-13.44, 8.84]	2017
Winkelman 2018	13.4	7.97	25	18.76	14.47	29	1.1%	-5.36 [-11.48, 0.76]	2018
Dos Santos 2018	10.3	8.7	13	14.2	9.7	15	0.9%	-3.90 [-10.72, 2.92]	2018
Eggmann 2018	6.1	6.15	58	6.6	7.48	57	2.8%	-0.50 [-3.01, 2.01]	2018
Hickmann 2018	6.7	12	9	7.3	6.3	10	0.6%	-0.60 [-9.36, 8.16]	2018
McWilliams 2018	16	5.93	45	18	11.85	43	1.9%	-2.00 [-5.94, 1.94]	2018
Amundadottir 2019	12.4	8.3	29	11	11.5	20	1.1%	1.40 [-4.48, 7.28]	2019
Kho 2019	13.5	13.33	36	10	11.11	30	1.1%	3.50 [-2.40, 9.40]	2019
Schujmann 2020	5	2.22	50	8	5.19	49	3.5%	-3.00 [-4.58, -1.42]	2020
Yu 2020	11.87	2	53	13.24	2.32	54	4.0%	-1.37 [-2.19, -0.55]	2020
Berney 2020	10	7.41	80	10	7.41	82	3.0%	0.00 [-2.28, 2.28]	2020
Farzammanesh 2020	5.59	3.19	82	5.14	3.18	81	3.9%	0.45 [-0.53, 1.43]	2020
Nickels 2020	8.4	6	36	7.7	4.59	36	2.9%	0.70 [-1.77, 3.17]	2020
De Azevedo 2021	18	17.8	87	23	14.8	94	1.5%	-5.00 [-9.79, -0.21]	2021
Qie 2022	10.52	2.28	95	15.74	4.24	95	3.9%	-5.22 [-6.19, -4.25]	2022
Rezvani 2022	13.46	6.89	26	16.48	9.05	23	1.6%	-3.02 [-7.57, 1.53]	2022
Wu 2022	5	2.96	48	4	1.85	48	3.9%	1.00 [0.01, 1.99]	2022
Yu 2022	27	10	52	29.5	12.78	50	1.7%	-2.50 [-6.96, 1.96]	2022
Zhou 2022	4.5	3.48	50	4.1	2.07	50	3.8%	0.40 [-0.72, 1.52]	2022
Deng 2022	7.78	3.36	41	9.24	4.47	42	3.4%	-1.46 [-3.16, 0.24]	2022
Hodgson 2022	7.9	8	371	8.4	7.56	370	3.8%	-0.50 [-1.62, 0.62]	2022
Kagan 2022	16.3	7.7	14	17.2	9.6	13	1.0%	-0.90 [-7.50, 5.70]	2022
Lin 2023	7	3.7	39	10	5.93	38	3.0%	-3.00 [-5.21, -0.79]	2023
Maca 2023	25	37.93	20	28	11	19	0.2%	-3.00 [-20.34, 14.34]	2023
Patel 2023	4.7	4.37	99	5.6	5.11	99	3.7%	-0.90 [-2.22, 0.42]	2023
Schweickert 2023	11.48	11.86	1069	9.85	8.61	848	3.9%	1.63 [0.71, 2.55]	2023
Carvalho 2023	12.9	5.8	48	15.6	6.7	48	2.8%	-2.70 [-5.21, -0.19]	2023
de Paula 2023	5	3.6	40	5	7.8	45	2.8%	0.00 [-2.54, 2.54]	2023
McWilliams 2023	5	4.8	26	6	4.4	28	2.9%	-1.00 [-3.46, 1.46]	2023
Wu 2023	5	5	28	7.5	6.7	28	2.4%	-2.50 [-5.60, 0.60]	2023
Lorenz 2024	42.5	45.19	10	33	63.15	10	0.0%	9.50 [-38.63, 57.63]	2024
Total (95% CI)			**3363**			**3087**	**100.0%**	**-1.01 [-1.75, -0.27]**	

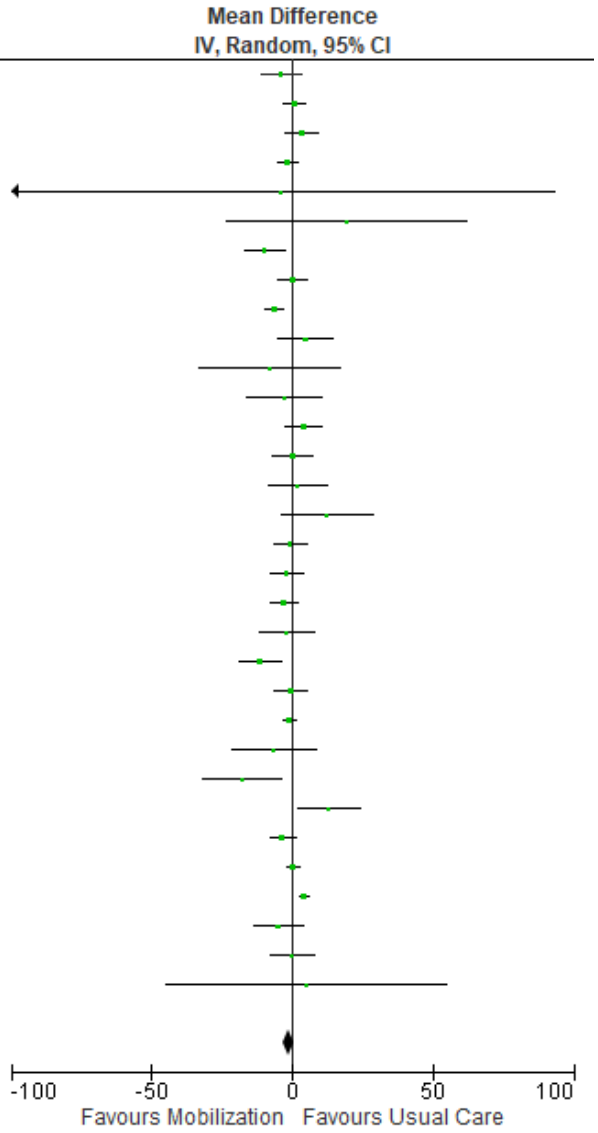
Heterogeneity: Tau² = 3.36; Chi² = 195.06, df = 44 (P < 0.00001); I² = 77%
Test for overall effect: Z = 2.69 (P = 0.007)



11. Hospital Length of Stay (days)

Study or Subgroup	Enhanced Mobilization Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Burtin 2009	36	14.07	31	40	15.6	36	3.3%	-4.00 [-11.11, 3.11]	2009
Schweickert 2009	13.5	11.19	49	12.9	8.07	55	5.2%	0.60 [-3.19, 4.39]	2009
Denhey 2013	23.5	18.89	74	20	17.8	76	3.9%	3.50 [-2.38, 9.38]	2013
Brummel 2014	7	4.1	22	8.6	7.6	22	5.4%	-1.60 [-5.21, 2.01]	2014
Kayambu 2015	41	110.3	26	45	217.8	24	0.0%	-4.00 [-100.90, 92.90]	2015
Frazzitta 2016	153.2	59.6	15	134	61	16	0.2%	19.20 [-23.26, 61.66]	2016
Hodgson 2016	19	11.85	29	29	13.33	21	3.3%	-10.00 [-17.15, -2.85]	2016
Moss 2016	21	11.85	59	21	17.78	61	4.2%	0.00 [-5.39, 5.39]	2016
Schaller 2016	15	11.85	104	21.5	11.11	96	5.6%	-6.50 [-9.68, -3.32]	2016
Coutinho 2016	25.8	12.9	14	21.08	11.8	11	2.3%	4.72 [-4.99, 14.43]	2016
Machado 2017	38	41.48	22	46	37.04	16	0.5%	-8.00 [-33.10, 17.10]	2017
Maffei 2017	27.6	18.5	20	30.6	24.8	20	1.4%	-3.00 [-16.56, 10.56]	2017
Eggmann 2018	25.9	16.96	58	22	17.93	57	3.6%	3.90 [-2.48, 10.28]	2018
McWilliams 2018	29	14.07	43	29	19.26	42	3.2%	0.00 [-7.18, 7.18]	2018
Kho 2019	27	24.81	36	25	19.26	30	2.0%	2.00 [-8.64, 12.64]	2019
Amundadottir 2019	36.9	25.3	27	24.6	30.4	20	1.0%	12.30 [-4.09, 28.69]	2019
Nickels 2020	17.2	14.2	36	17.9	12.14	36	3.8%	-0.70 [-6.80, 5.40]	2020
Berney 2020	21	19.26	80	23	20	82	3.8%	-2.00 [-8.05, 4.05]	2020
Schujmann 2020	16	10	50	19	15.38	49	4.4%	-3.00 [-8.12, 2.12]	2020
De Azevedo 2021	38	38.5	87	40	28.9	94	2.2%	-2.00 [-11.98, 7.98]	2021
Wu 2022	31.2	17.6	48	42.6	18.3	48	3.2%	-11.40 [-18.58, -4.22]	2022
Yu 2022	36.5	11.48	52	37	18.52	50	3.9%	-0.50 [-6.51, 5.51]	2022
Hodgson 2022	17	14.14	371	17.9	16.15	370	6.2%	-0.90 [-3.09, 1.29]	2022
Kagan 2022	26.5	17	14	33.1	22.6	13	1.1%	-6.60 [-21.77, 8.57]	2022
Kwakman 2022	24	20	19	42	25.19	21	1.3%	-18.00 [-32.03, -3.97]	2022
de Paula 2023	36	25.7	40	23	25.9	45	1.9%	13.00 [2.01, 23.99]	2023
Lin 2023	19	7.41	39	22.5	12.04	38	4.8%	-3.50 [-7.98, 0.98]	2023
Patel 2023	9.7	8.07	99	9.5	8.37	99	6.2%	0.20 [-2.09, 2.49]	2023
Schweickert 2023	20.32	19.08	1069	16.13	14.43	848	6.6%	4.19 [2.69, 5.69]	2023
McWilliams 2023	13	19.6	26	18	13.3	28	2.5%	-5.00 [-14.00, 4.00]	2023
Wu 2023	14	7.6	28	14	19.6	28	3.0%	0.00 [-7.79, 7.79]	2023
Lorenz 2024	45	42.59	10	40	68.52	10	0.1%	5.00 [-45.00, 55.00]	2024
Total (95% CI)			**2697**			**2462**	**100.0%**	**-1.16 [-2.94, 0.62]**	

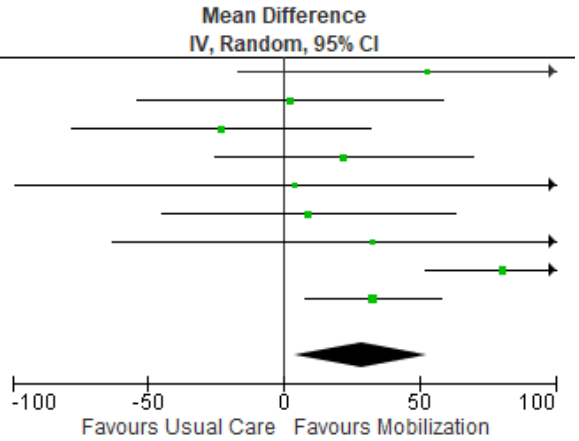
Heterogeneity: Tau² = 11.94; Chi² = 91.01, df = 31 (P < 0.00001); I² = 66%
Test for overall effect: Z = 1.28 (P = 0.20)



12. 6 Minute Walk Test (meters)

Study or Subgroup	Enhanced Mobilization Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Burtin 2009	196	150.37	31	143	140	36	8.1%	53.00 [-16.95, 122.95]	2009
Denhey 2013	384.5	147.9	48	382.1	139.4	52	10.5%	2.40 [-54.05, 58.85]	2013
Eggmann 2018	223	133	58	246	167	57	10.8%	-23.00 [-78.24, 32.24]	2018
Wright 2018	195	103.7	49	173	111.85	34	12.6%	22.00 [-25.50, 69.50]	2018
Amundadottir 2019	419.3	163.5184	22	415.4	156.7009	16	4.6%	3.90 [-98.88, 106.68]	2019
Berney 2020	249	118	39	240	140	49	11.1%	9.00 [-44.93, 62.93]	2020
Nickels 2020	258	219.26	36	225	197.78	36	5.1%	33.00 [-63.46, 129.46]	2020
Wu 2022	393.2	75.1	48	312.6	66.5	48	18.1%	80.60 [52.22, 108.98]	2022
Carvalho 2023	604	67	48	571	57	48	19.2%	33.00 [8.11, 57.89]	2023
Total (95% CI)			**379**			**376**	**100.0%**	**28.62 [4.18, 53.06]**	

Heterogeneity: Tau² = 647.97; Chi² = 17.17, df = 8 (P = 0.03); I² = 53%
Test for overall effect: Z = 2.30 (P = 0.02)

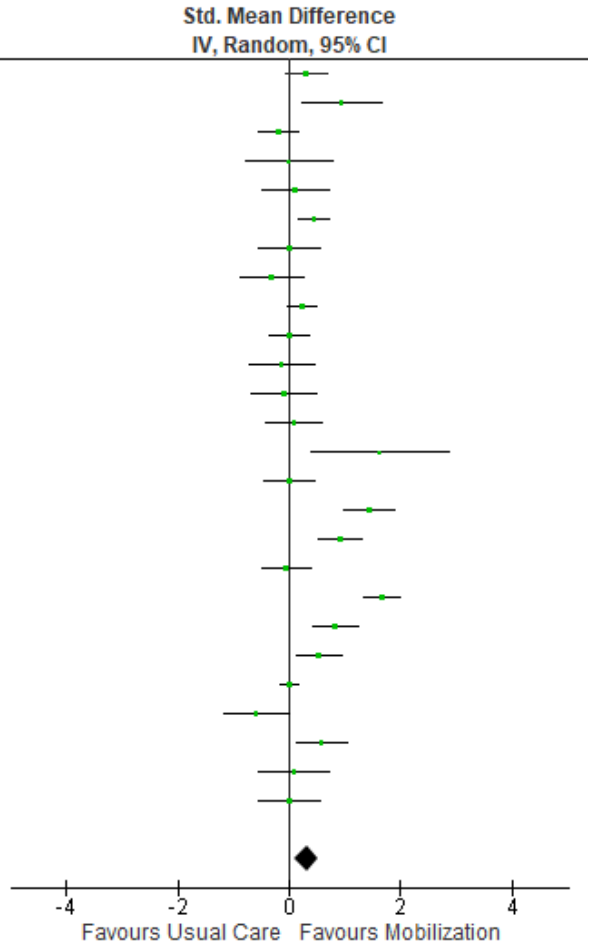


13. Functional Measures (standard mean difference)

Study or Subgroup	Enhanced Mobilization Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Schweickert 2009	75	64.81	49	55	62.96	55	4.2%	0.31 [-0.08, 0.70]	2009
Chen 2011	49	15.78	18	31	21.48	16	3.2%	0.94 [0.23, 1.66]	2011
Denhey 2013	7.7	1.7	61	8	1.5	56	4.3%	-0.19 [-0.55, 0.18]	2013
Brummel 2014	0	0.74	14	0	0.01	12	3.0%	0.00 [-0.77, 0.77]	2014
Kayambu 2015	5.6	2.1	19	5.4	1.7	23	3.5%	0.10 [-0.50, 0.71]	2015
Schaller 2016	4	2.22	104	3	2.22	96	4.5%	0.45 [0.17, 0.73]	2016
Hodgson 2016	7.4	3.6	29	7.4	3.6	21	3.7%	0.00 [-0.56, 0.56]	2016
McWilliams 2018	45	33.33	26	55	29.63	22	3.6%	-0.31 [-0.88, 0.26]	2018
Wright 2018	70	27	114	64	25	107	4.6%	0.23 [-0.04, 0.49]	2018
Eggmann 2018	28.5	15.6	58	28.5	16.3	56	4.3%	0.00 [-0.37, 0.37]	2018
Kho 2019	5.7	2	28	6	2.5	20	3.6%	-0.13 [-0.71, 0.44]	2019
Amundadottir 2019	3	11.1	29	4	10.4	19	3.6%	-0.09 [-0.67, 0.49]	2019
Berney 2020	5.7	1.2	27	5.6	1.1	31	3.8%	0.09 [-0.43, 0.60]	2020
Hodgson 2020	6	0.01	6	5	0.74	9	1.8%	1.62 [0.39, 2.86]	2020
Nickels 2020	35	2.2	36	35	2.2	36	4.0%	0.00 [-0.46, 0.46]	2020
Schujmann 2020	97	5	50	76	20	49	4.0%	1.44 [0.99, 1.88]	2020
Yu 2020	41.04	7.02	53	33.7	8.81	54	4.2%	0.91 [0.51, 1.31]	2020
Waldauf 2021	9.4	4.199	37	9.6	4.1717	42	4.0%	-0.05 [-0.49, 0.39]	2021
Qie 2022	85.45	5.86	95	74.86	6.78	95	4.4%	1.66 [1.33, 2.00]	2022
Wu 2022	86.8	15.9	48	73.2	16.8	48	4.1%	0.82 [0.41, 1.24]	2022
Zhou 2022	70	23.19	50	57.5	23.11	50	4.2%	0.54 [0.14, 0.94]	2022
Hodgson 2022	100	0.01	332	100	3.7	328	4.8%	0.00 [-0.15, 0.15]	2022
McWilliams 2023	4	4.8	22	7	5.2	25	3.6%	-0.59 [-1.17, -0.00]	2023
Lin 2023	87.82	10.93	39	80.79	13.13	38	4.0%	0.58 [0.12, 1.03]	2023
Maca 2023	35	19.1	20	33	24.04	19	3.4%	0.09 [-0.54, 0.72]	2023
de Paula 2023	6	0.74	26	6	0.74	25	3.7%	0.00 [-0.55, 0.55]	2023
Total (95% CI)			**1390**			**1352**	**100.0%**	**0.31 [0.10, 0.52]**	

Heterogeneity: Tau² = 0.24; Chi² = 166.87, df = 25 (P < 0.00001); I² = 85%

Test for overall effect: Z = 2.88 (P = 0.004)

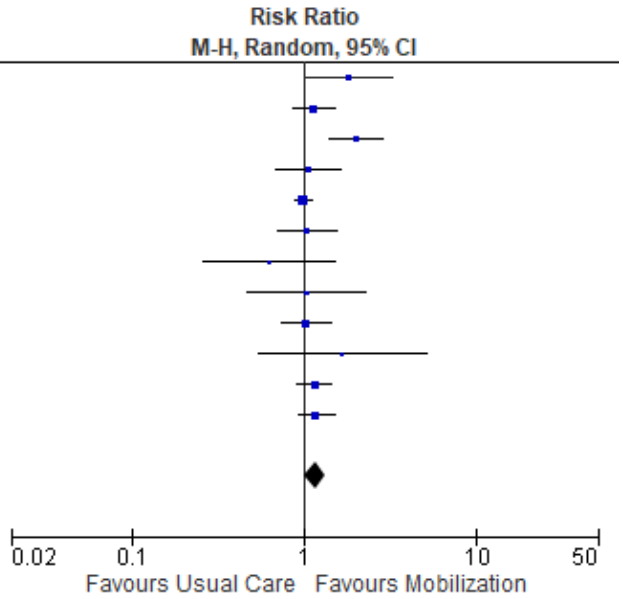


14. Discharge to Home

Study or Subgroup	Enhanced Mobilization Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Schweickert 2009	21	49	13	55	4.6%	1.81 [1.02, 3.22]	2009
Denhey 2013	44	74	40	76	11.1%	1.13 [0.85, 1.50]	2013
Schaller 2016	53	83	26	81	8.8%	1.99 [1.39, 2.84]	2016
Hodgson 2016	19	29	13	21	7.1%	1.06 [0.69, 1.62]	2016
Morris 2016	107	131	105	126	18.3%	0.98 [0.88, 1.10]	2016
Moss 2016	25	49	27	55	8.1%	1.04 [0.71, 1.53]	2016
Eggmann 2018	7	58	11	57	2.3%	0.63 [0.26, 1.50]	2018
Amundadottir 2019	10	29	7	21	2.7%	1.03 [0.47, 2.27]	2019
Berney 2020	37	80	37	82	9.4%	1.02 [0.73, 1.43]	2020
Hodgson 2020	5	10	3	10	1.4%	1.67 [0.54, 5.17]	2020
Nickels 2020	31	36	27	36	13.3%	1.15 [0.91, 1.44]	2020
Patel 2023	62	99	53	99	12.9%	1.17 [0.92, 1.48]	2023
Total (95% CI)		**727**		**719**	**100.0%**	**1.15 [1.00, 1.33]**	
Total events	421		362				

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 22.22$, df = 11 (P = 0.02); $I^2 = 50\%$

Test for overall effect: Z = 2.02 (P = 0.04)

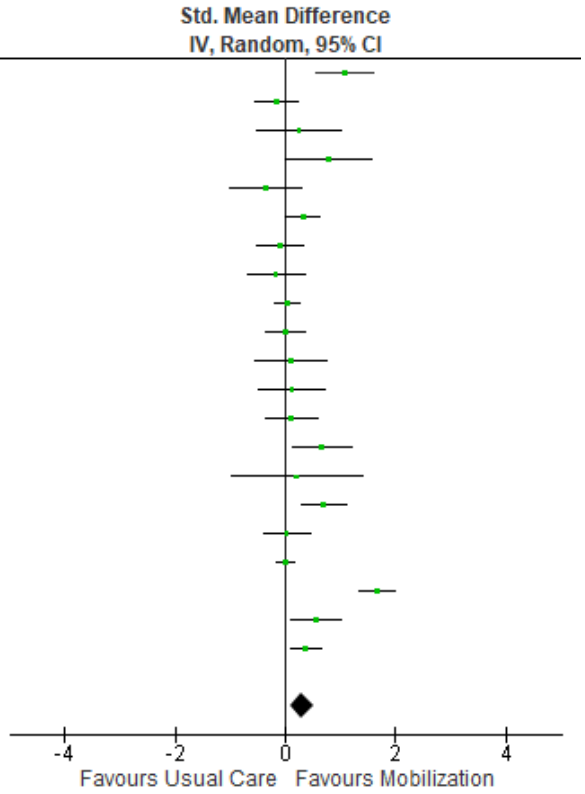


15. Quality of Life Measures (standard mean difference)

Study or Subgroup	Enhanced Mobilization Mean	SD	Total	Usual Care Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Burtin 2009	21	3.7	31	15	6.7	36	4.7%	1.07 [0.56, 1.59]	2009
Denhey 2013	40.1	14.7	48	42.4	13.7	48	5.2%	-0.16 [-0.56, 0.24]	2013
Brummel 2015	80	20	14	75	18.5	12	3.5%	0.25 [-0.52, 1.03]	2015
Kayambu 2015	81.8	22.2	11	60	29.4	19	3.5%	0.78 [0.01, 1.56]	2015
Hodgson 2016	61	19	21	68	19	16	4.0%	-0.36 [-1.02, 0.30]	2016
Morris 2016	36.9	10.4677	82	33.5	10.7149	79	5.6%	0.32 [0.01, 0.63]	2016
Schaller 2016	61.3	18.4	40	63	19.9	44	5.1%	-0.09 [-0.52, 0.34]	2016
Eggmann 2018	40.8	11.1	34	42.7	10.4	24	4.6%	-0.17 [-0.70, 0.35]	2018
Fossat 2018	51	29.6	158	50	24.4	154	6.0%	0.04 [-0.19, 0.26]	2018
Wright 2018	37	12.2	62	37	11.3	54	5.4%	0.00 [-0.36, 0.36]	2018
Kho 2019	0.69	0.2	21	0.67	0.21	17	4.1%	0.10 [-0.54, 0.74]	2019
Amundadottir 2019	38.5	9.7096	24	37.3	10.0545	18	4.2%	0.12 [-0.49, 0.73]	2019
Nickels 2020	75	18	36	73	17	36	4.9%	0.11 [-0.35, 0.58]	2020
Berney 2020	76.3	13.8	26	64.4	20.4	28	4.5%	0.67 [0.12, 1.22]	2020
Hodgson 2020	52.5	14.8	5	50	7.41	6	2.1%	0.20 [-0.99, 1.39]	2020
De Azevedo 2021	33.63	53	58	0	40.8	42	5.2%	0.69 [0.28, 1.10]	2021
Waldauf 2021	50	35.56	42	49	37.78	46	5.1%	0.03 [-0.39, 0.45]	2021
Hodgson 2022	0.7	0.3	333	0.7	0.3	332	6.2%	0.00 [-0.15, 0.15]	2022
Qie 2022	85.45	5.86	95	74.86	6.78	95	5.5%	1.66 [1.33, 2.00]	2022
Lin 2023	50.98	4.89	39	47.13	8.44	38	4.9%	0.55 [0.10, 1.01]	2023
Patel 2023	45.7	19.19	99	39.6	12.37	99	5.7%	0.38 [0.10, 0.66]	2023
Total (95% CI)			**1279**			**1243**	**100.0%**	**0.30 [0.08, 0.51]**	

Heterogeneity: Tau² = 0.19; Chi² = 120.95, df = 20 (P < 0.00001); I² = 83%

Test for overall effect: Z = 2.72 (P = 0.006)

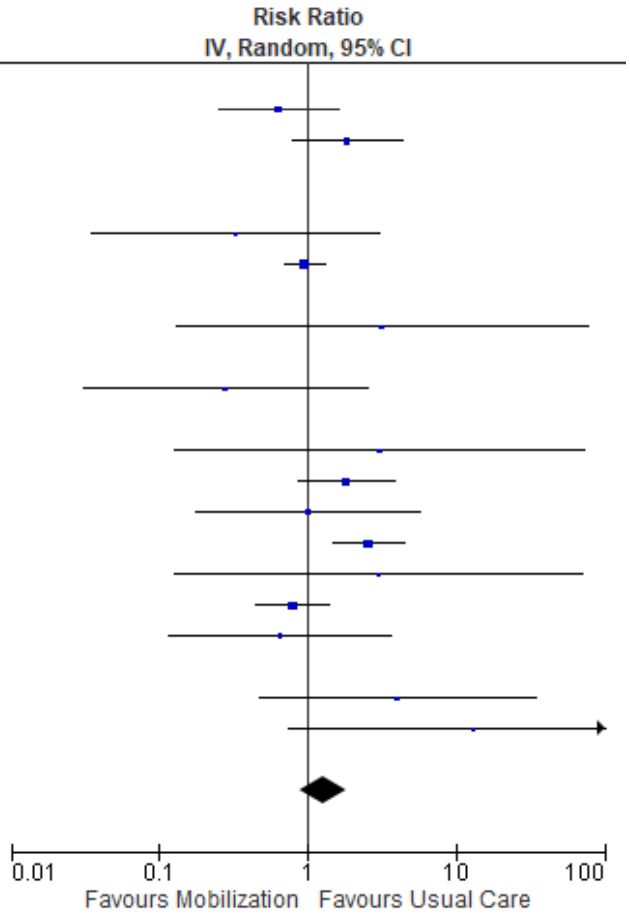


16. Adverse Events

Study or Subgroup	Enhanced Mobilization Events	Total	Usual Care Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Denhey 2013	0	74	0	76		Not estimable	2013
Morris 2016	7	150	11	150	9.3%	0.64 [0.25, 1.60]	2016
Schaller 2016	14	104	7	96	10.0%	1.85 [0.78, 4.38]	2016
Frazzitta 2016	0	15	0	16		Not estimable	2016
Machado 2017	0	22	0	16		Not estimable	2017
Eggmann 2018	1	58	3	57	2.4%	0.33 [0.04, 3.06]	2018
Fossat 2018	50	158	51	154	19.7%	0.96 [0.69, 1.32]	2018
Winkelman 2018	0	25	0	29		Not estimable	2018
Wright 2018	1	150	0	158	1.2%	3.16 [0.13, 76.94]	2018
Carvalho 2019	0	16	0	16		Not estimable	2019
Kho 2019	1	36	3	30	2.4%	0.28 [0.03, 2.53]	2019
Schujmann 2020	0	68	0	67		Not estimable	2020
Yu 2020	1	53	0	54	1.2%	3.06 [0.13, 73.37]	2020
Berney 2020	16	80	9	82	11.5%	1.82 [0.86, 3.88]	2020
Hodgson 2020	2	10	2	10	3.6%	1.00 [0.17, 5.77]	2020
Hodgson 2022	41	371	16	370	15.0%	2.56 [1.46, 4.47]	2022
McWilliams 2023	1	29	0	29	1.2%	3.00 [0.13, 70.74]	2023
Schweickert 2023	23	1069	23	846	14.7%	0.79 [0.45, 1.40]	2023
Lin 2023	2	39	3	38	3.7%	0.65 [0.11, 3.67]	2023
Wu 2023	0	28	0	28		Not estimable	2023
de Paula 2023	4	40	1	40	2.5%	4.00 [0.47, 34.24]	2023
Patel 2023	6	99	0	99	1.5%	13.00 [0.74, 227.69]	2023
Total (95% CI)		**2694**		**2461**	**100.0%**	**1.26 [0.87, 1.80]**	
Total events	170		129				

Heterogeneity: Tau² = 0.15; Chi² = 23.28, df = 14 (P = 0.06); I² = 40%

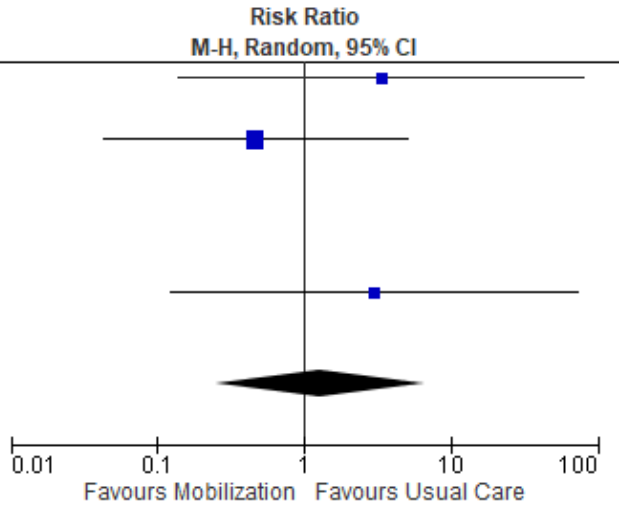
Test for overall effect: Z = 1.23 (P = 0.22)



17. Accidental Line Removal

Study or Subgroup	Enhanced Mobilization Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Schweickert 2009	1	49	0	55	26.5%	3.36 [0.14, 80.62]	2009
Morris 2016	0	150	0	150		Not estimable	2016
Schaller 2016	1	104	2	96	47.1%	0.46 [0.04, 5.01]	2016
Winkelman 2018	0	25	0	29		Not estimable	2018
Kho 2019	0	36	0	30		Not estimable	2019
Schujmann 2020	0	68	0	67		Not estimable	2020
Hodgson 2022	0	371	0	370		Not estimable	2022
Patel 2023	1	99	0	99	26.3%	3.00 [0.12, 72.76]	2023
de Paula 2023	0	40	0	45		Not estimable	2023
Total (95% CI)		**942**		**941**	**100.0%**	**1.28 [0.25, 6.58]**	
Total events	3		2				

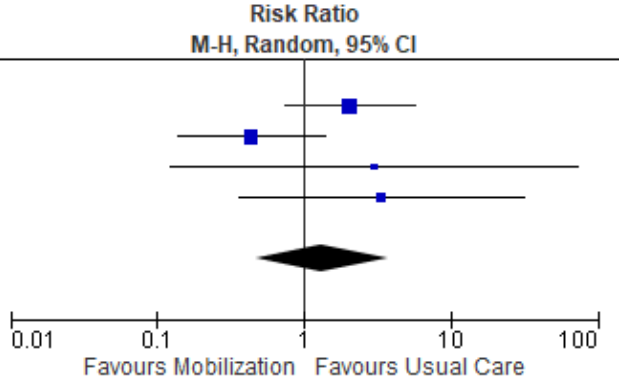
Heterogeneity: Tau² = 0.00; Chi² = 1.33, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.77)



18. Hypotension

Study or Subgroup	Enhanced Mobilization Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Schweickert 2009	0	49	0	55		Not estimable	2009
Schaller 2016	11	104	5	96	39.2%	2.03 [0.73, 5.63]	2016
Fossat 2018	4	158	9	154	35.4%	0.43 [0.14, 1.38]	2018
Patel 2023	1	99	0	99	9.1%	3.00 [0.12, 72.76]	2023
de Paula 2023	3	40	1	45	16.3%	3.38 [0.37, 31.16]	2023
Total (95% CI)		**450**		**449**	**100.0%**	**1.32 [0.47, 3.75]**	
Total events	19		15				

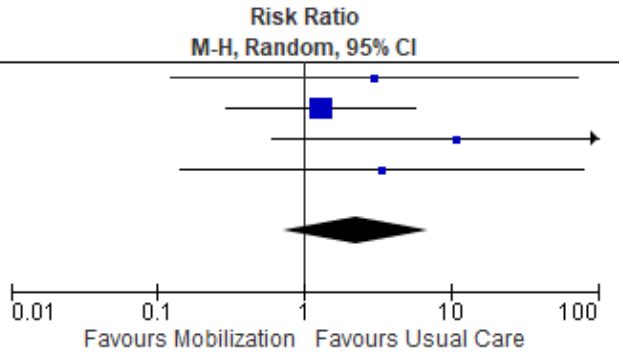
Heterogeneity: Tau² = 0.45; Chi² = 5.15, df = 3 (P = 0.16); I² = 42%
Test for overall effect: Z = 0.53 (P = 0.60)



19. Arrhythmia

Study or Subgroup	Enhanced Mobilization Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Morris 2016	1	150	0	150	12.7%	3.00 [0.12, 73.06]	2016
Fossat 2018	4	158	3	154	59.0%	1.30 [0.30, 5.71]	2018
Hodgson 2022	5	371	0	370	15.5%	10.97 [0.61, 197.69]	2022
de Paula 2023	1	40	0	45	12.8%	3.37 [0.14, 80.36]	2023
Total (95% CI)		**719**		**719**	**100.0%**	**2.27 [0.73, 7.08]**	
Total events	11		3				

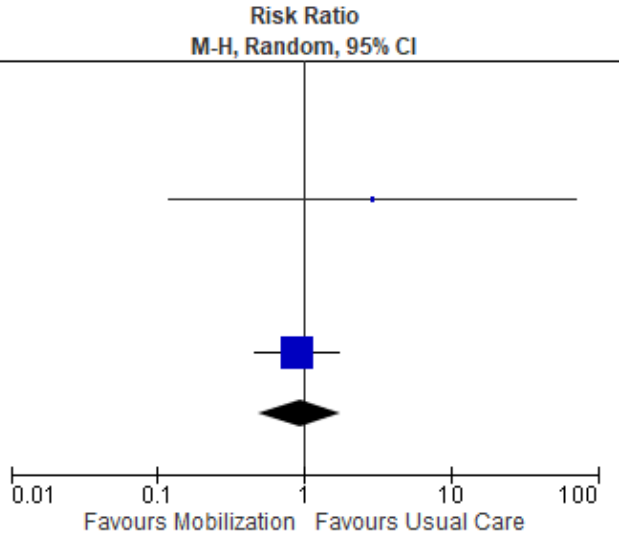
Heterogeneity: Tau² = 0.00; Chi² = 1.89, df = 3 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.41 (P = 0.16)



20. Unplanned Extubation

Study or Subgroup	Enhanced Mobilization Events	Total	Usual Care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Schweickert 2009	0	49	0	55		Not estimable	2009
Morris 2016	0	150	0	150		Not estimable	2016
Schaller 2016	0	104	0	96		Not estimable	2016
Winkelman 2018	0	25	0	29		Not estimable	2018
Fossat 2018	1	158	0	154	4.0%	2.92 [0.12, 71.24]	2018
Kho 2019	0	36	0	30		Not estimable	2019
Yu 2020	0	53	0	54		Not estimable	2020
Hodgson 2022	0	371	0	370		Not estimable	2022
de Paula 2023	0	40	0	45		Not estimable	2023
Schweickert 2023	19	1069	17	848	96.0%	0.89 [0.46, 1.70]	2023
Total (95% CI)		**2055**		**1831**	**100.0%**	**0.93 [0.49, 1.75]**	
Total events	20		17				

Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)



3. Risk Of Bias

Trial	Random Sequence Generation	Randomized Concealment	Blinding-Clinical Team/Patient	Blinding-Outcome Assessors	Incomplete Data	Selection bias	Other	Overall
Amundadottir 2019	Low	Possibly high	Possibly low	Low	Low	Low	Low	High
Berney 2020	Low	Low	Low	Low	Possibly Low	Low	Low	Low
Brummel 2014	Low	Low	Low	Low	Low	Low	Low	Low
Burtin 2009	Low	Low	Low	Low	Low	Low	Low	Low
Carvalho 2019	Low	Possibly Low	Possibly low	Low	|Low	Low	Low	Low
Carvalho 2023	Low	Possibly Low	Possibly low	Low	|Low	Possibly Low	Low	Low
Chen 2011	Unclear	Unclear	Unclear	High	Low	Possibly Low	Possibly Low	High
Coutinho 2016	Possibly low	Low	Possibly Low	Possibly Low	Low	Possibly High	Low	High
Dantas 2012	Possibly high	Possibly High	Possibly Low	Possibly Low	Low	Possibly High	Possibly High	High
De Azevedo 2021	Low	Possibly High	Possibly Low	Possibly Low	Possibly Low	Low	Low	Low
de Paula 2023	Low	Low	Low	Low	Low	Low	Low	Low
Denhey 2013	Low	Possibly High	Possibly ow	Low	Low	Low	Low	High
Deng 2022	Low	Low	Low	Low	Low	Low	Low	Low
Dos Santos 2018	Low	Low	Low	Low	Low	Low	Low	Low
Eggman 2018	Low	Low	Low	Low	Low	Low	Low	Low
Farzammanesh 2020	Possibly High	High	Possibly High	Possibly High	Low	Low	Possibly High	High
Fossat 2018	Low	Low	Possibly Low	Low	Low	Low	Low	Low
Frazzitta 2016	Low	Low	Possibly Low	Low	Low	Low	Low	Low
Hickmann 2018	Possibly High	Possibly High	Low	Low	Low	Low	Low	High
Hodgson 2016	Possibly High	Possibly High	Low	Low	Low	Low	Low	High
Hodgson 2020	Low	Possibly High	Low	Low	Low	Possibly High	Possibly High	High
Hodgson 2022	Low	Low	Low	Low	Low	Low	Low	Low
Kagan 2022	Low	Possibly High	Low	Low	High	Low	Possibly High	High
Kayambu 2015	Low	Low	Low	Low	Low	Low	Low	Low
Kho 2019	Low	Low	Low	Low	Low	Low	Low	Low
Kim 2014	Low	Low	Low	Possibly Low	Possibly Low	Possibly High	Possibly High	High
Kwakman 2022	Low	Low	Low	Low	Low	Low	Low	Low
Lin 2023	Low	Low	Low	Low	Low	Low	Low	Low
Lorenz 2024	Possibly Low	Possibly Low	Low	Low	Low	Low	Possibly Low	Low
Maca 2023	Possibly High	Possibly High	Low	Low	Low	Low	Low	High
Machado 2017	Low	Low	Low	Low	Low	Low	Low	Low
Maffei 2017	Low	Low	Low	Low	Low	Possibly High	Possibly High	High
McWilliams 2018	Low	Low	Low	Low	High	Low	Possibly Low	High

McWilliams 2023	Low	Possibly High	Low	Low	Low	Low	Low	High
Morris 2016	Low	Low	Low	Low	Low	Low	Low	Low
Moss 2016	Unclear	Unclear	Low	Low	low	Low	Low	High
Nava 1998	Possibly Low	Unclear	Probably High	Probably High	Low	Unclear	Unclear	High
Nickels 2020	Low	Low	Low	Low	Low	Low	Low	Low
Nydal 2019	Low	Low	Low	Low	Low	Low	Low	Low
Nydal 2021	Low	Low	Low	Low	Low	Low	Low	Low
Patel 2023	Low	Low	Low	Low	Possibly High	Low	Possibly High	High
Pinkaew 2020	Unclear	Unclear	Possibly High	Possibly High	Possibly Low	Possibly Low	Unclear	High
Qie 2022	Low	Low	Low	Low	Low	Low	Low	Low
Rahiminezhad 2022	Low	Possibly Low	Low	Low	Low	Low	Low	Low
Rezvani 2022	Low	Low	Low	Possibly High	High	Low	Low	High
Schaller 2016	Low	Low	Low	Low	Low	Low	Low	Low
Schujmann 2020	Low	Low	Low	Low	Low	Low	Low	Low
Schweickert 2009	Low	Low	Low	Low	Low	Low	Low	Low
Schweickert 2023	Low	Low	Low	Low	Low	Low	Low	Low
Waldauf 2021	Low	Low	Low	Low	Low	Low	Low	Low
Winkelman 2018	Low	Low	Low	Low	Low	Low	Low	Low
Wright 2018	Low	Low	Low	High	High	Low	Low	High
Wu 2022	Low	Possibly High	Possibly High	High	Low	Low	Possibly Low	High
Wu 2023	Low	Low	Low	Low	Low	Low	Low	Low
Yousef-Brauner 2015	Possibly High	Possibly High	Low	Low	Low	Low	Possibly High	High
Yu 2020	Possibly Low	Possibly High	Possibly Low	Possibly Low	Possibly High	Possibly High	Possibly High	High
Yu 2022	Possibly Low	Possibly High	Possibly Low	Possibly High	Possibly high	Possibly High	Possibly High	High
Zhou 2022	Low	Low	Low	Low	Low	Low	Low	Low

4. Summary Of Findings Table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enhanced Mobilization	Usual Care	Relative (95% CI)	Absolute (95% CI)		
ICU Mortality												
27	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	547/2480 (22.1%)	474/2251 (21.1%)	**RR 0.98** (0.85 to 1.13)	**0 fewer per 100** (from 3 fewer to 3 more)	⨁◯◯◯ Very low	Important
Hospital Mortality												
23	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	267/1469 (18.2%)	263/1459 (18.0%)	**RR 1.01** (0.84 to 1.22)	**0 fewer per 100** (from 3 fewer to 4 more)	⨁◯◯◯ Very low	Important
Mortality at Longest Follow-Up												
43	randomised trials	not serious	not serious	not serious	very serious[b]	none	810/3597 (22.5%)	730/3325 (22.0%)	**RR 1.01** (0.93 to 1.10)	**0 fewer per 100** (from 2 fewer to 2 more)	⨁⨁◯◯ Low	Important
Incident Delirium												
8	randomised trials	not serious	serious[c]	not serious	very serious[d]	none	165/562 (29.4%)	193/585 (33.0%)	**RR 0.85** (0.65 to 1.11)	**5 fewer per 100** (from 12 fewer to 4 more)	⨁◯◯◯ Very low	Critical
Duration of Delirium (days)												
7	randomised trials	not serious	serious[c]	not serious	serious[e]	none	431	430	-	MD **1.34 lower** (1.85 lower to 0.83 lower)	⨁⨁◯◯ Low	Critical
ICU Acquired Weakness												
14	randomised trials	not serious	not serious	not serious	not serious	none	210/717 (29.3%)	267/710 (37.6%)	**RR 0.77** (0.64 to 0.93)	**9 fewer per 100** (from 14 fewer to 3 fewer)	⨁⨁⨁⨁ High	Critical
Medical Research Council Score												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enhanced Mobilization	Usual Care	Relative (95% CI)	Absolute (95% CI)		
18	randomised trials	not serious	serious[c]	not serious	serious[f]	none	657	637	-	MD **1.74 higher** (0.03 lower to 3.52 higher)	⨁⨁◯◯ Low	Critical
Duration of Invasive Mechanical Ventilation (days)												
34	randomised trials	not serious	serious[c]	not serious	not serious	none	2438	2172	-	MD **1.1 lower** (1.69 lower to 0.51 lower)	⨁⨁⨁◯ Moderate	Critical
Hospital Anxiety and Depression Scale												
4	randomised trials	not serious	not serious	not serious	serious[g]	none	63	59	-	MD **1.7 lower** (3.62 lower to 0.22 higher)	⨁⨁⨁◯ Moderate	Important
ICU Length of Stay (days)												
45	randomised trials	not serious	serious[c]	not serious	serious[h]	none	3269	2986	-	MD **1.01 lower** (1.75 lower to 0.27 lower)	⨁⨁◯◯ Low	Important
Hospital Length of Stay (days)												
32	randomised trials	not serious	serious[c]	not serious	serious[i]	none	2603	2361	-	MD **1.16 lower** (2.94 lower to 0.62 higher)	⨁⨁◯◯ Low	Important
6 Minute Walk Test (meters)												
9	randomised trials	not serious	serious[c]	not serious	not serious	none	379	376	-	MD **28.62 higher** (4.18 higher to 53.06 higher)	⨁⨁⨁◯ Moderate	Critical
Combined Functional Indices												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enhanced Mobilization	Usual Care	Relative (95% CI)	Absolute (95% CI)		
26	randomised trials	not serious	serious[c]	not serious	not serious	none	1342	1302	-	SMD **0.31 SD higher** (0.1 higher to 0.52 higher)	⨁⨁⨁◯ Moderate	Critical
Discharge to Home												
12	randomised trials	serious[j]	not serious	not serious	serious[k]	none	421/727 (57.9%)	362/719 (50.3%)	**RR 1.15** (1.00 to 1.33)	**8 more per 100** (from 0 fewer to 17 more)	⨁⨁◯◯ Low	Important
Quality of Life												
21	randomised trials	not serious	serious[c]	not serious	not serious	none	1279	1243	-	SMD **0.3 SD higher** (0.08 higher to 0.51 higher)	⨁⨁⨁◯ Moderate	Critical
Number of Patients with Adverse Events												
22	randomised trials	not serious	serious[c]	not serious	serious[l]	none	170/2694 (6.3%)	129/2461 (5.2%)	**RR 1.26** (0.87 to 1.80)	**1 more per 100** (from 1 fewer to 4 more)	⨁⨁◯◯ Low	Critical
Unplanned Extubation												
10	randomised trials	not serious	not serious	not serious	serious[l]	none	20/2055 (1.0%)	17/1831 (0.9%)	**RR 0.93** (0.49 to 1.75)	**0 fewer per 100** (from 0 fewer to 1 more)	⨁⨁⨁◯ Moderate	Critical
Accidental Line Removal												
9	randomised trials	not serious	not serious	not serious	serious[l]	none	3/942 (0.3%)	2/941 (0.2%)	**RR 1.28** (0.25 to 6.58)	**0 fewer per 100** (from 0 fewer to 1 more)	⨁⨁⨁◯ Moderate	Critical
Arrhythmia												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Enhanced Mobilization	Usual Care	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	not serious	not serious	not serious	serious[l]	none	11/719 (1.5%)	3/719 (0.4%)	**RR 2.27** (0.73 to 7.08)	**1 more per 100** (from 0 fewer to 3 more)	⨁⨁⨁◯ Moderate	Critical
Hypotension												
5	randomised trials	not serious	not serious	not serious	serious[m]	none	19/450 (4.2%)	15/449 (3.3%)	**RR 1.32** (0.47 to 3.75)	**1 more per 100** (from 2 fewer to 9 more)	⨁⨁⨁◯ Moderate	Critical

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference

Explanations

a. When the high ROB trials were excluded, the effect estimate changed and thus we elected to rate down for ROB
b. We elected to rate down as the MCID of 1 fewer deaths was crossed as well as the MCID of harm (1 more death)
c. We elected to rate down for high I2, low p-value, and lack of overlap in point estimates
d. We elected to rate down twice for low event rate and threshold for MCID is crossed both from a benefit and harm threshold
e. We elected to rate down as the MCID of 1 day was crossed
f. We elected to rate down as the MCID of 1 is crossed
g. We elected to rate down for low participant rate
h. We elected to rate down as the MCID of 1 day was crossed
i. We elected to rate down as the upper limit of the confidence interval crossed the MCID of 1 day
j. 6/12 studies were deemed to have high risk of bias for randomization, allocation concealment, loss to follow-up, and selective reporting. When the high ROB trials were removed, the effect estimate was lost and thus we rated down
k. We elected to rate down as threshold for MCID of 2 was crossed
l. We elected to rate down for low event rate
m. We elected to rate down as the upper end of the confidence interval crossed the MCID for harm of 5

5. Evidence-To-Decision Framework

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	ICU-acquired muscle weakness (ICUAW) is a common occurrence in critically ill patients, occurring in up to 50% of those who experience critical illness. ICUAW is associated with impairments in patients' long-term survival, physical functioning, and quality of life. While rehabilitation and mobilization delivered in the ICU setting are employed as a means to mitigate this, the appropriate volume, intensity, or method of delivery of this rehabilitation is an evolving area that merits close examination.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	The evidence used to answer this question comes from a meta-analysis of 55 randomized controlled trials. According to the evidence generated in this review, enhanced mobilization activitities (e.g. early mobilization, cycling, twice daily physio) compared to usual care resulted in 5 fewer patients per 100 developing delirium, and 1.3 days shorter duration of delirium. Enhanced mobilization resulted in 9 fewer patients per 100 developing ICU acquired weakness, and a medical research council score 1.54 points higher compared to usual care. Finally, patients who received enhanced mobilization had a 6 minute walk test that was 28.6 meters farther, and were more likely to be discharged home instead of to an alternative living environment (8 more patients per 100).	

Outcomes	With Usual Care	With Enhanced Mobilization	Difference	Relative effect (95% CI)
ICU Mortality	21 per 100	**21 per 100** (18 to 24)	**0 fewer per 100** (3 fewer to 3 more)	**RR 0.98** (0.85 to 1.13)
Incident Delirium	33 per 100	**28 per 100** (21 to 37)	**5 fewer per 100** (12 fewer to 4 more)	**RR 0.85** (0.65 to 1.11)
Duration of Delirium (days)	The mean duration of Delirium (days) was **0**	The mean duration of Delirium (days) in the intervention group was 1.34 lower (1.85 lower to 0.83 lower)	MD **1.34 lower** (1.85 lower to 0.83 lower)	-
ICU Acquired Weakness	376 per 100	**100 per 100** (100 to 100)	**86 fewer per 100** (135 fewer to 26 fewer)	**RR 0.77** (0.64 to 0.93)
Medical Research Council Score	The mean medical Research Council Score was **0**	The mean medical Research Council Score in the intervention group was 1.74 higher (0.03 lower to 3.52 higher)	MD **1.74 higher** (0.03 lower to 3.52 higher)	-
ICU Length of Stay (days)	The mean ICU Length of Stay (days) was **0**	The mean ICU Length of Stay (days) in the intervention group was 1.01 lower (1.75 lower to 0.27 lower)	MD **1.01 lower** (1.75 lower to 0.27 lower)	-

	6 Minute Walk Test (meters)	The mean 6 Minute Walk Test (meters) was **0**	The mean 6 Minute Walk Test (meters) in the intervention group was 28.62 undefined higher (4.18 higher to 53.06 higher)	MD **28.62 higher** (4.18 higher to 53.06 higher)	-	
	Combined Functional Indices	The mean combined Functional Indices was **0** SD	The mean combined Functional Indices in the intervention group was 0.31 standard deviations SD higher (0.1 higher to 0.52 higher)	SMD **0.31 SD higher** (0.1 higher to 0.52 higher)	-	
	Discharge to Home	50 per 100	**58 per 100** (50 to 67)	**8 more per 100** (0 fewer to 17 more)	**RR 1.15** (1.00 to 1.33)	
	Quality of Life	The mean quality of Life was **0** SD	The mean quality of Life in the intervention group was 0.3 standard deviations SD higher (0.08 higher to 0.51 higher)	SMD **0.3 SD higher** (0.08 higher to 0.51 higher)	-	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	The evidence for this question was drawn from 19 RCTs captured in the systematic review. Adverse events included unplanned extubation, accidental line removal, arrhythmia, and hypotension, in addition to any adverse event felt to be attributable to the physiotherapy intervention. Enhanced mobilization was associated with 1 more adverse event per 100 patients, with no difference in unplanned extubation, line removal, or hypotension.	

Outcomes	With Usual Care	With Enhanced Mobilization	Difference	Relative effect (95% CI)
Number of Patients with Adverse Events	5 per 100	**7 per 100** (5 to 9)	**1 more per 100** (1 fewer to 4 more)	**RR 1.26** (0.87 to 1.80)
Unplanned Extubation	1 per 100	**1 per 100** (0 to 2)	**0 fewer per 100** (0 fewer to 1 more)	**RR 0.93** (0.49 to 1.75)
Accidental Line Removal	0 per 100	**0 per 100** (0 to 1)	**0 fewer per 100** (0 fewer to 1 more)	**RR 1.28** (0.25 to 6.58)
Arrhythmia	0 per 100	**1 per 100** (0 to 3)	**1 more per 100** (0 fewer to 3 more)	**RR 2.27** (0.73 to 7.08)
Hypotension	3 per 100	**4 per 100** (2 to 13)	**1 more per 100** (2 fewer to 9 more)	**RR 1.32** (0.47 to 3.75)

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT

- ○ Very low
- ○ Low
- ● Moderate
- ○ High
- ○ No included studies

RESEARCH EVIDENCE

Outcomes	Importance	Certainty of the evidence (GRADE)
ICU Mortality		⨁◯◯◯ Very low[a,b]
Hospital Mortality		⨁◯◯◯ Very low[a,b]
Mortality at Longest Follow-Up		⨁⨁◯◯ Low[b]
Incident Delirium		⨁◯◯◯ Very low[c,d]
Duration of Delirium (days)		⨁⨁◯◯ Low[c,e]
ICU Acquired Weakness		⨁⨁⨁⨁ High
Medical Research Council Score		⨁⨁◯◯ Low[c,f]
Duration of Invasive Mechanical Ventilation (days)		⨁⨁⨁◯ Moderate[c]
Hospital Anxiety and Depression Scale		⨁⨁⨁◯ Moderate[g]
ICU Length of Stay (days)		⨁⨁◯◯ Low[c,h]
Hospital Length of Stay (days)		⨁⨁◯◯ Low[c,i]

ADDITIONAL CONSIDERATIONS

6 Minute Walk Test (meters)		⨁⨁⨁◯ Moderate[c]	
Combined Functional Indices		⨁⨁⨁◯ Moderate[c]	
Discharge to Home		⨁⨁◯◯ Low[j,k]	
Quality of Life		⨁⨁⨁◯ Moderate[c]	
Number of Patients with Adverse Events		⨁⨁◯◯ Low[c,l]	

a. When the high ROB trials were excluded, the effect estimate changed and thus we elected to rate down for ROB
b. We elected to rate down as the MCID of 1 fewer deaths was crossed as well as the MCID of harm (1 more death)
c. We elected to rate down for high I2, low p-value, and lack of overlap in point estimates
d. We elected to rate down twice for low event rate and threshold for MCID is crossed both from a benefit and harm threshold
e. We elected not to rate down as the MCID of 1 day was crossed
f. We elected to rate down as the MCID of 1 is crossed
g. We elected to rate down for low participant rate
h. We elected to rate down as the MCID of 1 day was crossed
i. We elected to rate down as the upper limit of the confidence interval crossed the MCID of 1 day
j. 6/12 studies were deemed to have high risk of bias for randomization, allocation concealment, loss to follow-up, and selective reporting. When the high ROB trials

	were removed, the effect estimate was lost and thus we rated down k. We elected to rate down as threshold for MCID of 2 was crossed l. We elected to rate down for low event rate	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	The MCID for mortality of 1 per 100 patients and duration of delirium of 2 days were driven by evidence generated from reviews on patients values and preferences.	While not driven by research evidence, the selected outcomes were voted on by a diverse panel of healthcare providers and patient/family representatives and deemed to be of high or critical importance. As such, the panel felt that there was no important uncertainty or variability in the value placed on these outcomes.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	There is moderate certainty evidence that enhanced mobilization decreases duration of delirium, incidence of ICU acquired weakness, and ICU length of stay. The evidence also supports that enhanced mobilization improves functional outcomes and quality of life. The panel weighed this against low quality evidence supporting that there was only 1 more adverse event per 100 patients, recognizing that several included trials did not have any adverse events in either trial arm. As a result, it was felt that on balance the net benefit appeared to outweigh the harms.	

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		While there was no research data captured on the cost of enhanced mobilization, the panel considered that enhanced mobilization likely requires increased person-power for implementation, even in the absence of additional equipment, and as such represented a moderate cost to implementation.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		While no studies were captured examining the required resources, the panel considered that the cost of required resources may depend upon who delivers the intervention and the expertise of the personnel required, in addition to any additional equipment.

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		No included studies assessed cost effectiveness, however, the panel considered the hospital, personal, and societal cost of resources required for increased mobilization activities compared to cost of delirum, increased home supports, or functional dependence.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No identified research evidence.	The panel considered that physiotherapy resources may be limited in certain ICU environments, but mobilization activities can potentially be delivered by nursing or other members of the allied healthcare team.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		The panel felt that there may be some hesitation on the part of key stakeholders around specific interventions included in the review, however, overall feel most would agree that movement and mobility is acceptable and beneficial.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		The panel felt that given that mobilization has become standard of care for critically ill patients, some degre of enhancement to this standard is likely feasible to implement.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation
We suggest providing enhanced mobilization over usual care rehabilitation/mobilization to adult patients admitted to the intensive care units(Conditional recommendation; For intervention; Moderate certainty of evidence)

6. Subgroup Analyses

Category	Group	No. of trials	Estimate of Effect and 95% CI	I^2	P-interaction
ICU Mortality					
	Twice Daily	4	0.71 (0.48, 1.06)	0%	0.19
	Cycling	10	0.92 (0.67, 1.26)	35%	
	Early Mobilization	8	1.08 (0.95, 1.24)	0%	
	Other	5	1.18 (0.76, 1.85)	0%	
Mortality at Longest Follow-Up					
	Twice Daily	6	0.83 (0.60, 1.15)	0%	0.49
	Cycling	12	0.94 (0.73, 1.20)	35%	
	Early Mobilization	15	1.08 (0.88, 1.32)	0%	
	Other	10	1.05 (0.93, 1.19)	0%	
Incidence of Delirium					
	Twice Daily	2	0.87 (0.47, 1.61)	0%	0.006
	Cycling	3	1.00 (0.81, 1.24)	0%	
	Early Mobilization	2	**0.54 (0.39, 0.75)**	0%	
	Other	1	1.42 (0.82, 2.46)	NA	
Duration of Delirium (days)					
	Twice Daily	2	-1.34 (-1.85, -0.83)	0%	0.59
	Cycling	1	-1.00 (-1.92, -0.08)	NA	
	Early Mobilization	4	-1.31 (-2.16, -0.46)	90%	
	Other	0	NA	NA	
ICU Acquired Weakness					
	Twice Daily	1	1.06 (0.62, 1.81)	NA	0.27
	Cycling	4	0.76 (0.46, 1.25)	57%	
	Early Mobilization	6	**0.67 (0.50, 0.90)**	35%	
	Other	3	0.97 (0.72, 1.29)	0%	
MRC Score					
	Twice Daily	3	0.58 (-3.71, 4.87)	70%	0.04
	Cycling	5	-0.25 (-3.29, 2.79)	65%	
	Early Mobilization	5	**7.04 (2.57, 11.51)**	65%	

	Other	4	0.05 (-2.91, 3.01)	39%	
Duration of Mechanical Ventilation (days)					
	Twice Daily	6	-1.31(-3.62, 0.99)	77%	0.09
	Cycling	10	-0.55 (-1.66, 0.55)	53%	
	Early Mobilization	10	**-2.00 (-2.99, -1.00)**	76%	
	Other	8	-0.40 (-1.23, 0.44)	46%	
ICU Length of Stay (days)					
	Twice Daily	9	-1.13 (-3.18, 0.91)	50%	0.39
	Cycling	11	**-1.04 (-1.75, -0.33)**	0%	
	Early Mobilization	13	**-1.75 (-3.06, -0.43)**	85%	
	Other	12	-0.28 (-1.34, 0.78)	69%	
6 Minute Walk Test (meters)					
	Twice Daily	3	**29.46 (7.90, 51.01)**	0%	0.98
	Cycling	3	26.65 (-12.41, 65.70)	0%	
	Early Mobilization	0	NA	NA	
	Other	3	23.29 (-46.77, 93.36)	86%	
Combined Functional Indices (standard mean difference)					
	Twice Daily	3	-0.10 (-0.59, 0.39)	69%	0.22
	Cycling	6	0.17 (-0.19, 0.53)	68%	
	Early Mobilization	12	**0.53 (0.17, 0.90)**	90%	
	Other	5	0.23 (-0.24, 0.70)	85%	
Discharge to Home					
	Twice Daily	1	1.03 (0.47, 2.27)	NA	0.12
	Cycling	2	1.11 (0.92, 1.34)	0%	
	Early Mobilization	5	**1.43 (1.07, 1.91)**	54%	
	Other	4	1.00 (0.90, 1.10)	0%	
Quality of Life Measures (standard mean difference)					
	Twice Daily	2	0.03 (-0.28, 0.34)	0%	0.28
	Cycling	7	**0.37 (0.06, 0.68)**	72%	
	Early Mobilization	9	0.39 (-0.06, 0.84)	91%	

	Other	3	0.03 (-0.32, 0.38)	56%	
Adverse Events					
	Twice Daily	3	3.08 (0.33, 20.09)	0%	0.006
	Cycling	6	1.12 (0.66, 1.90)	28%	
	Early Mobilization	8	**2.17 (1.42, 3.32)**	0%	
	Other	5	0.72 (0.45, 1.15)	0%	

9.5 PICO 5-Melatonin for Sleep

Pico 5: In adults admitted to the ICU, does melatonin vs no melatonin impact patient outcomes?

Population: Adults admitted to the ICU
Intervention: Melatonin at any dose, duration or frequency
Comparison: No melatonin
Outcomes: 1)Incidence of delirium; 2)Duration of delirium; 3)Sleep quality/quantity; 4)Incidence of anxiety; 5)Incidence of agitation; 6)ICU LOS; 7)Duration of mechanical ventilation; 8)Cognitive abilities-post ICU; 9)Incidence of post-ICU PTSD; 10)Mortality; ~~11)Quality of life~~ and; 12)Functional status post-ICU

1. Characteristics Of Included Trials

Name year	Patient Characteristics	Inclusion and exclusion	Intervention	Control	Primary outcome
Abbasi 2017 -RCT -Iran -Single center -Medical-surgical ICU n=137	Age: 51.2 (18.7) Male: 56.9% APACHE II: 7.7 (4.45) Intubated: NR Delirious at start: NR Reason for admission -Medical: 24.8% -Surgical: 58.4% -Trauma: 16.8%	**Inclusion:** 1)Adults >18yo admitted to the ICU less than 24hours ago 2)Healthy gastrointestinal function (patients tolerated oral medications by gavage or mouth) 3) RASS >-4 and GCS >8 4)No basic delirium or mood changes before admission in ICU **Exclusion:** 1)Less than 5 days ICU stay 2)Sensitivity reaction to the melatonin supplement 3)Pregnancy. 4)Previous history of seizure 5)Severe heart failure (New York Heart Association classification III/IV).	Melatonin 3mg PO daily (administered at 9pm) x5days n=67	Matched placebo n=70	Frequency of delirium measured with a Persian version of the CAM-ICU
Abbasi 2023 -RCT -Iran -Single center -Medical-surgical ICU n=41	Age: 51.9 (20.3) Male: 70.7% APACHE II: NR Intubated: 56.1% Delirious at start: NR Reason for admission -Medical: 31.7% -Surgical: 36.6% -Trauma: 31.7%	**Inclusion:** 1)Adult patients >18yo admitted to the ICU who had received IV vancomycin in the previous 3 weeks **Exclusion:** 1)Acute and chronic kidney disease 2)Oral intolerance	Melatonin 3mg PO BID (administration times not recorded)x7-14days n=20	Matched placebo n=21	Nephrotoxicity defined based on RIFLE criteria and changes in NGAL (neutrophil gelatinase-associated lipocalin) concentration

Alizadeh 2022 -RCT -Iran -Single Center -Medical ICU n=67	Age: 63.3(18.7) Male: 64.2% APACHE II: NR Intubated: 100% Delirious at start: NR Reason for admission -Medical:100% (COVID) -Surgical: 0% -Trauma: 0%	**Inclusion criteria:** 1)Adults >18yo admitted to the ICU for IMV for COVID-19 2)Within fist 24h of ICU admission **Exclusion criteria:** 1)Hepatic failure 2)Intolerance of nasogastric feeding were all exclusion criteria	21 mg melatonin PO daily x5 days as long as patient was intubated (administered at night) n=33	Matched placebo n=34	No primary outcome identified
Ameri 2022 -RCT -Iran -Single center - Medical ICU n=226	Age: 54.6 (12.5) Male: 42.5% APACHE II: NR Intubated: 0% Delirious at start: NR Reason for admission -Medical:100% (COVID) -Surgical: 0% -Trauma: 0%	**Inclusion criteria:** 1) Patients age of ≥20 years (weight≥35 kg) with a confirmed diagnosis of COVID-19 based on the positive real-time polymerase chain reaction test and requirement of admission in ICU 2)Had an oxygen saturation <88%, or RR> 30, or PaO2/ FiO2≤300 mmHg, or/and lung involvement>50% in chest CT scan imaging. **Exclusion criteria:** 1)Convulsive disorders 2)Chronic hepatic and renal diseases, 3)Use of invasive mechanical ventilation 4)Allergy to melatonin 5)Pregnancy or breastfeeding	Melatonin 5mg PO BID x 7 days (administration times not reported) n=109	No melatonin n=117	1)Mortality at 28 days 2)Need for IMV
Bandyopadhyay 2021 (Abstract) - RCT -India -Single center - Unclear type of ICU n=108	Age: NR Male: NR APACHE II: NR Intubated: NR Delirious at start: NR Reason for admission -Medical: NR -Surgical: NR -Trauma: NR	**Inclusion:** 1)Adults admitted to the ICU **Exclusion:** NR	Melatonin 3 mg PO daily (administered at 9pm) n=54	No melatonin n=54	Delirium

Bellapart 2020 -RCT -Australia -Single center - Medsurg ICU n=33	Age: 55[#] (IQR 49-66) Male: NR APACHE II: 22 (14-29) Intubated: 100% Delirious at start: NR Reason for admission -Medical: NR -Surgical: NR -Trauma: NR	**Inclusion criteria:** 1)Patients admitted during their recovery phase of ICU defined as: -Weaning from mechanical ventilation -No further vasopressors -Weaning sedatives to increase awake during day-light hours 2)Expected to have a minimal length of 5 days of respiratory weaning 3)Preserved enteral absorption or the absence of ileus 4)No history of sleep disorders **Exclusion criteria:** 1)Factors interfering with the metabolism of melatonin or an enhanced adrenergic state, included (i) Beta-blockers, vasopressors, corticosteroids, nonsteroidal drugs, naloxone, or pre-intensive care prescription of antipsychotics (ii) Advanced liver disease (iii) Burns prior to debridement and grafts (iv) Ongoing sepsis (v) Neurocritical patients	Melatonin 3 mg PO -First administered at 9pm then every hour after the initial loading dose, a 0.5 mg melatonin dose or its equivalent in volume was administered until a last dose at 3am. -Total of 6mg PO n=21	Matched placebo n=12	Delirium
Bourne 2008 -RCT -United Kingdom -Single center -General ICU n=24	Age: 64.3(12.3) Male: 45.8% APACHE II: 17.1 (3.6) Intubated: 100% Delirious at start: NR Reason for admission -Medical: 100% -Surgical: 0% -Trauma: 0%	**Inclusion Criteria:** 1)Admitted to the ICU with acute respiratory failure requiring invasive mechanical ventilation and tracheostomy to assist weaning **Exclusion Criteria:** 1)Expected ICU length of stay of less than 5 days 2)Preadmission treatment of sleep disturbances 3)C/I to enteral feeding 4)Convulsions, psychiatric or neurological disease, alcohol consumption of greater than or equal to 50 units per week or drug use 5)Sleep apnoea 6)Severe heart failure 7)Low levels of consciousness, (i.e., SAS<4)	Melatonin 10 mg PO daily x4 days (administered at 9pm) N=12	Matched placebo N=12	Sleep efficiency index (SEI was defined as the ratio of a patient's total sleep time over the time available for 'nocturnal' sleep (9 hours, from 10 p.m. to 7 a.m., corresponding to nursing staff shift patterns)
Dianatkhah 2015 RCT -Iran -Single center -CV-surgical ICU n=137	Age: 60.9 (10.0) Male: 52.5% APACHE NR Intubated: 100% Delirious at start: NR Reason for admission -Medical: 0%	**Inclusion:** 1)Patients undergoing elective CABG **Exclusion:** 1)Subjects taking psychiatric medications 2)CNS depressants, and hypnotic drugs 3)History of suffering from any sleep disorder	Melatonin 3mg PO qhs (1 hour before bed) starting 3 days before the OR until discharge N=66	Oxazepam 10mg PO qhs (1 hour before bed) starting 3 days before the OR until discharge N=71	No primary outcome listed but discuss Sleep Quality

	-Surgical: 100% (CV-ICU) -Trauma: 0%				
Dianatkhah 2017 -RCT -Iran -Single center -Neurologic ICU n=40	Age: 55.3 (13.2) Male: 52.5% APACHE NR Intubated: NR Delirious at start: NR Reason for admission -Medical: (Neurological 100%) -Surgical: NR -Trauma: 0%	**Inclusion criteria:** 1)Adults admitted with a spontaneous ICH admitted to an ICU within 24hours **Exclusion criteria:** 1)Traumatic ICH 2)C/I to receiving oral medication 3)Brain tumor 4)Glasgow coma scale (GCS) score ≥8 5)Underlying respiratory disease 6)Renal impairment 7)Pregnancy or breastfeeding	Melatonin 30mg PO once daily (administered at night)	Matched placebo	No primary outcome
Escames 2021 (trial registry) -RCT -Spain -Single center -Medical ICU n=18	Age: 62.7 (10.4) Male: 61.1% APACHE NR Intubated: NR Delirious at start: NR Reason for admission -Medical: 100% (Covid) -Surgical: 0% -Trauma: 0%	**Inclusion:** 1)Adults with COVID-19 who were admitted to an ICU for less than 7 days **Exclusion:** 1)Included in another COVID-19 study 2)Liver transaminases >5 times the ULN 3)Stage IV kidney failure or requiring IHD 4)Pregnancy 5)Terminal illness 6)Autoimmune disease	Melatonin 5 mg/kg IV current weight/day divided into 4 doses a day with a maximum daily dose of 500 mg. -After the first 3 days of treatment, three intensive care physicians in charge of the patient decided whether to extend the treatment until day 6 of the study (total of 7 days of treatment) based on the patient's clinical evaluation N=12	Matched placebo N=6	Mortality at 1 week
Foreman 2015 -RCT -United States -Single center -Neurological ICU	Age: 57.5 (16.5) Male: 75% APACHE II:11.5 (6.5) Intubated: 58.3%	**Inclusion:** 1)Adults admitted to the neurologic ICU who were undergoing continuous EEG monitoring **Exclusion:**	Melatonin 3mg PO daily (administered at 8pm) x7 days -In addition: eye coverings, passive	Usual care (not including intervention)	Total sleep time

n=12	Delirious at start: NR Reason for admission -Medical: (Neurological 100%) -Surgical: NR -Trauma: 0%	1)Lack of reactivity on initial cEEG 2)Expected mortality ≤24h 3)General anesthesia ≤24h before study 4)Continuous infusions of benzodiazepines or opiates 4)History of sleep apnea or random SpO2 <85% during sleep	noise-cancelling headphones, option for soft foam ear plugs		
Gandolfi 2020 -RCT -Brazil -Multi-center -Medical surgical ICUs n=203	Age: 58.5 (15.1) Male: 60.1% APACHE II:NR Intubated: NR Delirious at start: NR Reason for admission -Medical: NR -Surgical: 46.3% -Trauma: 3.9%	**Inclusion:** 1)Adults >18yo admitted to the ICU for at least one night **Exclusion:** 1)Unable to answer questionnaires; 2)History of seizures, neurologic or psychiatric illnesses 3)Sleep apnea 4)Renal or hepatic impairment 5)Intestinal obstruction or other conditions that affected intestinal absorption 6)Autoimmune diseases 7)Patients who are deaf or mute 8)Pregnant or lactating	Melatonin 10mg PO daily (administered nightly at 8pm, 2h after dinner) x7days n=102	Matched placebo n=101	No identified primary outcome
Hakiminia 2022 -RCT -Iran -Unclear type of ICU but does involve neuro -Single center n=60	Age: 47.7 (21.9) Male: 80% APACHE II:NR Intubated: NR Delirious at start: NR Reason for admission -Medical: NR -Surgical: NR -Trauma: 55%	**Inclusion:** 1)Age ≥18 years old, diagnosed with TBI (skull fracture; brain laceration, contusion, or hematoma; SAH; ICH; intra-ventricular hemorrhage; or traumatic axonal injury) or non-TBI (due to strokes, infections, hypoxia, or brain tumors) 2)Identified within the first 72 hours of brain injury onset in the intensive care unit (ICU) or neurology ward 3)Proper function of the gastrointestinal tract (patients tolerated oral medications by gavage or mouth). **Exclusion:** 1)Less than five days stay in the ICU or neurology Ward 2)Sensitivity reaction to the melatonin tablet 3)Pregnancy 4)Hepatic failure (class C according to Child-Pugh score), 5)Renal failure (need dialysis), 6)Severe heart failure (New York Heart Association (NYHA) classification III/ IV)	Melatonin total 21mg PO daily (administered as 12mg PO qam and 9mg PO qhs) x5days n=30	Matched placebo n=30	Serum levels of malondialdehyde, S100B and C-reactive protein (CRP) were compared at baseline, and after five days' intervention

		7)Sepsis within first five days of admission 8)Previous history of any of brain injury			
Ibrahim 2016 -RCT -Australia -Single center -Unclear type of ICU n=32	Age:60[#] Male: 59.4% APACHE II:18.5 Intubated: 100% Delirious at start: 25% Reason for admission -Medical: NR -Surgical: NR -Trauma: 55%	**Inclusion:** 1) Adults >16yo admitted to the ICU and have a tracheostomy in situ 2)Weaning from mechanical ventilation 3)GCS > 9 4)Sedative infusions or boluses stopped for > 12 h **Exclusion:** 1)Pregnancy or breastfeeding 2)Allergy to melatonin 3)Intestinal obstruction, ileus, gastroparesis or other conditions likely to affect enteral absorption of melatonin 4)Patient likely to die within 24 hours	Melatonin 3mg PO daily (administered at 10pm) x2 days or until ICU discharge n=14	Matched placebo n=18	Duration of nocturnal sleep compared to diurnal sleep
Jaiswal 2019 -RCT -United States -Single center -CV surgical ICU n=117	Age: 59.7 (9.93) Male: 76.3% APACHE II:NR Intubated: 100% Delirious at start: NR Reason for admission -Medical: 0% -Surgical: 100% (CV-ICU) -Trauma: 0%	**Inclusion:** 1)Age ≥18yo admitted to the ICU for an elective pulmonary thromboendarterectomy **Exclusion:** 1)Pregnant 2)Cirrhosis 3)Using fluvoxamine	Ramelteon 8mg PO daily (administered at 9pm) x6 nights while still in the ICU -The medication started the night before the procedure N=59	Matched placebo N=58	Delirium prevalence
Javaherforooshzadeh 2023 -RCT -Iran -Single center -CV surgical ICU n=80	Age: 57.1 (15) Male: 49.6% APACHE II:NR Intubated: 100% Delirious at start: NR Reason for admission -Medical: 0% -Surgical: 100% (CV-ICU) -Trauma: 0%	**Inclusion:** 1)Patients ≥35y admitted to CVICU for an elective CABG **Exclusion:** 1)Emergency procedures 2)Mental illnesses 3)Ejection fraction < 30% 4)Chronic renal and liver dysfunctions 5)Prolonged mechanical ventilation 6)Allergy to melatonin or dexmedetomidine	Dexmedetomidine 0.5mcg/kg bolus, followed by an infusion 0.3-0.5mcg/kg/h for 24h -Dexmedetomidine was titrated to Riker Sedation-agitation Scale score or ≥3 -Also administered melatonin 3mg PO the night before the operation at 10pm, and repeated every	Dexmedetomidine 0.5mcg/kg bolus, followed by an infusion 0.3-0.5mcg/kg/h for 24h - Dexmedetomidine was titrated to Riker Sedation-agitation Scale score or ≥3 N=40	Delirium prevalence

			night at 10pm x5days N=40		
Jouybar 2023 -RCT -Iran -Single center -CV surgical ICU n=59	Age: 62.2 (6.4) Male: 59% APACHE II:NR Intubated: 100% Delirious at start: 0% Reason for admission -Medical: 0% -Surgical: 100% -Trauma: 0%	**Inclusion:** Patients aged 40–75yo admitted for an on-pump CABG, then to the CV-surgical ICU post-operatively **Exclusion:** 1)Recent myocardial infarction (<3 months), 2)Emergency operation 3)Re-operation 4)Renal insufficiency 5)Immunologic disorders 6)Cerebrovascular disease or prior stroke by computerized tomography of the brain or patient history, 7)Severe pulmonary disease 8)Ejection fraction below 40%, 9)Current anticoagulation with warfarin 10)Any concomitant surgery (valvular, etc.) 11)Non-sinus rhythm 12)Hepatic insufficiency, 13)Alcohol abuse, regular use of benzodiazepines or opioids 14)Psychiatric disease 15)Dementia 16)Pregnancy, breastfeeding 17)Active infection 18)Graft count <2 and more than six, pump time >90 min, aortic and carotid atheromatous (more than 50%), 19)Experiencing adverse effects of melatonin such as daytime drowsiness, headache, or stomach pain.	Melatonin 10mg PO nightlyx4 weeks PRIOR to surgery then 2 days post-operatively in the ICU n=29	Matched placebo n=30	Cognitive function
Malhrose 2021 -RCT -Egypt -Single center -CV-ICU n=110	Age: 66.6 (6.5) Male: 75.5% APACHE II:NR Intubated: 0% Delirious at start: NR Reason for admission -Medical: 0% -Surgical: 100% -Trauma: 0% -Sepsis: 100%	**Inclusion:** 1) Patients ≥60yo undergoing elective coronary artery **Exclusion:** 1)Emergency procedures 2)Preoperative mental illness 3)Preoperative renal failure 4)Chronic liver disease (Child classification class B and C) 5)Patients diagnosed by carotid duplex to have carotid disease 6)Prolonged postoperative intubation and re-exploration	Dexmedetomidine IV (0.4 mcg/kg bolus followed by 0.2-0.7 mcg/kg/h continuous infusion x24h) and melatonin (5 mg at 10 PM the night before surgery and the same dose was repeated every 24 hours for 3 postoperative days) -Dexmedetomidine titrated to a Risker	Dexmedetomidine IV (0.4 mcg/kg bolus followed by 0.2-0.7 mcg/kg/h continuous infusion x24h) N=55	Prevalence of delirium

			Sedation Agitation Scale score of 4 N=55		
Mansilla-Rosello 2022 -RCT -Spain -Single center -Medicalsurgical ICU n=29	Age: 68.6[#] Male: 62.1% APACHE II:NR Intubated: 0% Delirious at start: NR Reason for admission -Medical: 0% -Surgical: 100% -Trauma: 0% -Sepsis: 100%	**Inclusion:** 1)Adults ≥18yo admitted to the ICU with severe sepsis (infectious SIRS associated with organ dysfunction, hypoperfusion or hypotension due to a disease requiring surgical intervention by the General Surgery) **Exclusion criteria**: 1)Pregnancy, 2)Medical or surgical terminal illness (incurable advanced neoplasia, chronic diseases such as liver cirrhosis or chronic renal failure), 3)Impaired mental abilities, psychiatric illness under treatment 4)Melatonin hypersensitivity 5)Patients who took melatonin 2 days before surgery	Melatonin 60mg IV daily for 5 days. -Given 24h from the diagnosis of sepsis n=15	Matched placebo n=14	Incidence of Organ dysfunction
Mistraletti 2015 -RCT -Italy -Single center -Medical-surgical ICU n=82	Age: 66.5 (15) Male: 59.8% APACHE II:NR Intubated: 0% Delirious at start: NR Reason for admission -Medical: 11% -Surgical: 36.6% -Trauma: NR -Sepsis: 100%	**Inclusion:** High-risk patient: 1)Acute respiratory failure (requiring invasive or non-invasive respiratory assistance) 2)An expected length of stay longer than 2 days 3)Mortality predicted at ICU admission over 13% **Exclusion:** 1)Age < 18 years 2)GI track impracticability 3)Status asthmaticus 4)Intoxication 5)RRT for chronic renal failure 6)Child C hepatopathy 7)Home mechanical ventilation 8)HIV 9)Expected GCS score < 12 at discharge 10)Neuropsychiatry disability 11)Pregnancy/breast feeding 12)Too ill	On day 3 of the ICU admission, melatonin 6mg PO daily total (administered as 3mg at 8PM and 3mg at midnight) n=41	Matched placebo n=41	Dosing of hydroxyzine given
Naderi-Behdani 2022 -RCT -Iran -Single center -General ICU n=96	Age: 56 (24.7) Male: 64.6% APACHE II:12 Intubated: NR Delirious at start: NR Reason for admission	**Inclusion criteria**: 1)Adult surgical, medical, and traumatic patients (age≥18 years old) who were admitted to ICU with two blood sugar more than 140mg/dL within the first 24 hours of admission. **Exclusion:** 1)Diabetes mellitus	Melatonin 6mg PO BID (administered at 12am and 12pm)x3days N=48	Matched placebo N=48	Blood glucose, insulin, adiponectin and HbA1c levels on the 4th day.

	-Medical: 34.4% -Surgical: NR -Trauma: 36.5%	2)Hypersensitivity to different melatonin dosage forms 3)HbA1c >6.5 4)NPO 5)Receiving glucocorticoid therapy and dextrose serum at night 6)Pregnant women 7)Patients who died or had early ICU discharge before completing the study			
Nishikimi 2018 - RCT -Japan -Single center -Medsurg ICU n=88	Age: 68[#] Male: 64.8% APACHE II:24 Intubated: 43.2% Delirious at start: NR Reason for admission -Medical: 67% -Surgical: NR -Trauma: NR	**Inclusion:** 1)Adults (age ≥ 20 yr old) admitted to the ICU who could receive their medications orally or through a nasogastric tube during the first 48 hours of admission to the ICU. **Exclusion:** 1)Already receiving ramelteon or fluvoxamine maleate prior to their admission to the ICU 2)Allergy to ramelteon	Ramelteon 8mg PO daily (administered at 8pm) until ICU discharge. n=45	Matched placebo n=43	ICU LOS
Owens 2022 (Abstract) -RCT -United States -Single center -CV Surgical ICU n=97	Age: NR Male: NR APACHE II:NR Intubated: 0% Delirious at start: 0% (prevention study) Reason for admission -Medical: 0% -Surgical: 100% (CV-surgery) -Trauma: 0%	**Inclusion:** Patients admitted to the ICU post-operatively for a pulmonary thromboendarterectomy surgery **Exclusion:** 1)Patients who remained intubated and sedated for the duration of monitoring	Ramelteon 8mg PO daily (administered at 9pm), starting the night before surgery and continuing up to 5 days post-operatively n=50	Matched placebo n=47	ICU Delirium incidence
Sharifnia 2021 -RCT -Iran -Single center -Neuro ICU n=40	Age: 55.3 (13.2) Male: 52.5% APACHE II:NR Intubated: 100% Delirious at start: NR Reason for admission -Medical: NR -Surgical: NR -Trauma: NR	**Inclusion:** 1)Adult patients with confirmed acute ICH who were admitted to the ICU within 24 hours of stroke onset **Exclusion:** 1)Traumatic ICH 2)Brain neoplasm 3)C/I to receiving oral medication 4)GCS ≥8 5)Renal insufficiency 6)Pregnancy or breastfeeding	Melatonin 30mg PO daily (administered nightly) x5 nights n=20	No melatonin n=20	S100B neuronal injury biomarker

Shi 2021 -RCT -China -Single center -Cardiac ICU n=297	Age: 71.6 (6.7) Male: 61.3% APACHE II:NR Intubated: NR Delirious at start: NR Reason for admission -Medical: 100% (Post PCI) -Surgical: NR -Trauma: NR	**Inclusion:** 1)>60yo who underwent a percutaneous coronary intervention under general anesthesia and were admitted to the ICU post-procedure. 2)Able to receive either melatonin or placebo within 7 days of the procedure **Exclusion:** 1)Likely unsalvageable on admission 2)High cholesterol combined with diabetes 3)Brain injury or neurosurgery 4)Neurologic disease 5)Mental illness and epilepsy 6)Other reasons (identified by researchers)	Melatonin 3mg PO daily x7days starting after PCI (timing not indicated) n=148	Matched placebo n=149	Incidence of delirium
Soltani 2022 -RCT -Iran -Single center -General ICU N=52	Age: 36.7 (16.9) Male: 71.2% APACHE II: 7.8 (3.9) Intubated: 100% Delirious at start: NR Reason for admission -Medical: 0% -Surgical: NR -Trauma: 100% (Traumatic ICH)	**Inclusion:** 1)Adults ≥18yo admitted to an ICU with traumatic intracranial hemorrhage confirmed by CT, requiring surgery, initial GCS 4-8, average volume of ICH 30-35cc 2)Expected to live longer than 2 days **Exclusion:** 1)Liver disease 2)Renal insufficiency 3)Pregnant 4)Brain tumor 5)Allergy to melatonin	Melatonin 3mg PO daily (administered at 9pm). Given as long as was in ICU n=26	Matched placebo n=26	Dose of fentanyl and midazolam
Vijayakumar 2016 -RCT -India -Single center -Unclear type of ICU n=56	Age: 37.5 (12.4) Male: 67.2% APACHE II:9.4 (3.9) Intubated: 66.1% Delirious at start: NR Reason for admission -Medical: 100% (organophosphate OD) -Surgical: NR -Trauma: 0%	**Inclusion:** 1)Patients aged between 18 and 50 years, presenting with history and clinical syndrome suggestive of organophosphorus compound poisoning with low pseudocholinesterase levels (<5320 IU/L) **Exclusion** 1)APACHE II score>20 2)Postcardiac Arrest 3)Patients receiving any of the following medications chronically: opioids, opioid antagonists, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, central nervous system	Melatonin 3mg PO daily (administered at 9pm) N=26	Matching placebo N=30	Duration of delirium

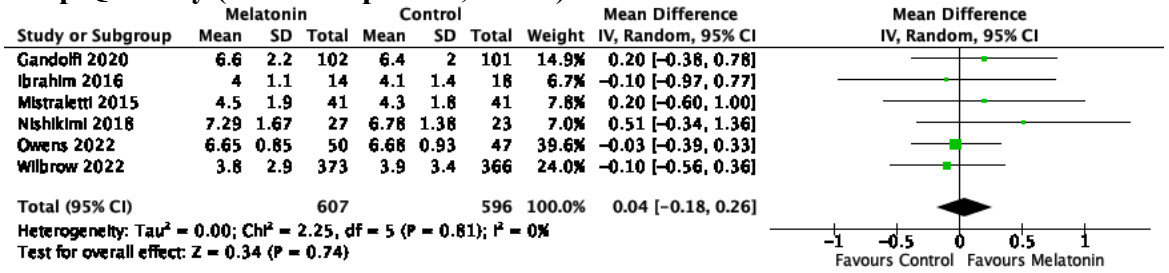
		depressants, warfarin, angiotensin converting enzyme inhibitors, or diuretics 4)Moderate to severe hepatic or renal dysfunction 5)Known psychiatric disorder 6)Cardiac disease			
Wibrow 2022 -RCT -Australia -Multi-center -Unclear types of ICU n=841	Age: 61.9 (15.2) Male: 62.7% APACHE II: 17.4 (6.7) Intubated: NR Delirious at start: 8.9% Reason for admission -Medical: 46.1% -Surgical: 25.3% -Trauma: 7.8%	**Inclusion:** Adults ≥18yo admitted to an ICU who were enrolled within 48h of their admission, and expected to have a LOS>72h **Exclusion:** 1)Hypersensitivity to melatonin 2)Expected death within 48h 3)Pregnant, breastfeeding 4)Non-English speaker 5)Neurologic impairment that would prevent a delirium assessment 6)Not enteral route 7)Hepatic impairment	Melatonin 4mg PO daily (administered at 9pm) x14nights or until ICU discharge n=419	Matching placebo n=422	Delirium prevalence
Yin 2022 -RCT -Iran -Single-center -Post CV-surgery ICU n=497	Age: 68.8 (7.3) Male: 59.4% APACHE II: NR Intubated: NR Delirious at start: NR Reason for admission -Medical: NR -Surgical: NR -Trauma: NR	**Inclusion:** 1)Age≥ 60yo who could be randomized and able to take IP within 7 days (it says after surgery-but I think this is an error) 2)Admitted to the ICU with acute heart failure **Exclusion:** 1) Unsalvageable patients likely on admission 2) High cholesterol combined with diabetes 3) Combined with brain injury or neurosurgery history 4) Neurologic disease 5) Patients with a history of mental illness and epilepsy 6) Researchers found other reasons	Melatonin 3mg PO daily after acute heart failure (does not tell time of administration) x 7 days N=236	Placebo N=244	Delirium prevalence
Zadeh 2021 -RCT -Iran -Single-center -Post CV-surgery ICU n=60	Age: 61.6 (8.8) Male: 30% APACHE II: NR Intubated: NR Delirious at start: NR Reason for admission -Medical: 0% -Surgical: 100% (CV surgery) -Trauma: 0%	**Inclusion:** Age≥ 30yo, being a candidate for elective on-pump CABG, being in anesthesia class II–III anesthetic risk, having a minimum ejection fraction of 30% **Exclusion:** 1)Melatonin contraindications 2)Allergy to the drug or its compounds 3)Chronic or recent use of melatonin or hypnotic drugs 4)Receiving barbiturates or antipsychotics 5)History of liver or	Melatonin 3 mg PO the evening before the operation and 3 mg on the morning of surgery. -The treatment was continued	Matching placebo n=30	Delirium prevalence

		kidney disease or chronic pulmonary disease 6)History of neurological or psychological diseases 7)Alcohol consumption 8)Inability to communicate Verbally 9)Occurrence of serious and life-threatening events during or after	until second postoperative day with 3 mg of melatonin daily (does not say what time) n=30		

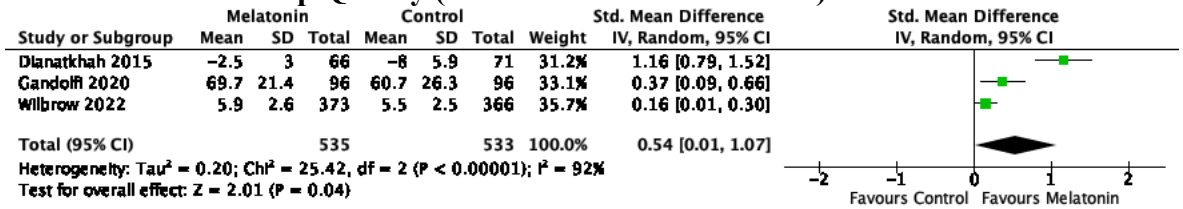
APACHE=Acute Physiology and Chronic Health Evaluation; BID=bis in die (i.e. twice a day); CAM-ICU=Confusion Assessment Method for ICU; CABG=Coronary artery bypass graft; CCU=Coronary care unit; C/I=Contraindication; CT= Computed tomography; CV=Cardiovascular; EEG=Electroencephalogram; ICU=Intensive care unit; IHD=Intermittent hemodialysis; IMV=Invasive mechanical ventilation; GCS=Glasgow coma scale; LOS=Length of stay; NR=Not recorded; RASS= Richmond Agitation Sedation Scale; RCT=Randomized clinical trial; SAS=Riker Sedation-Agitation Scale; SIRS=Systemic Inflammatory Response Syndrome; TBI=Traumatic brain injury; ULN=Upper limit of normal

2. Forest Plots

1. Sleep Quantity (Total Sleep Time; hours)



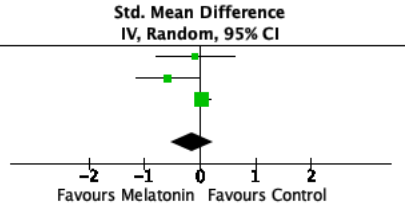
2. Perceived Sleep Quality (standard error of the mean)



3. Awakenings (Standard mean difference)

Study or Subgroup	Melatonin Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bellapart 2020	12.9	11.9	21	15.7	47.6	12	19.5%	−0.09 [−0.80, 0.62]
Nishikimi 2018	0.8	0.87	27	1.31	0.87	23	25.7%	−0.58 [−1.15, −0.01]
Wilbrow 2022	−5.6	2.6	373	−5.7	2.5	366	54.9%	0.04 [−0.11, 0.18]
Total (95% CI)			421			401	100.0%	−0.14 [−0.53, 0.24]

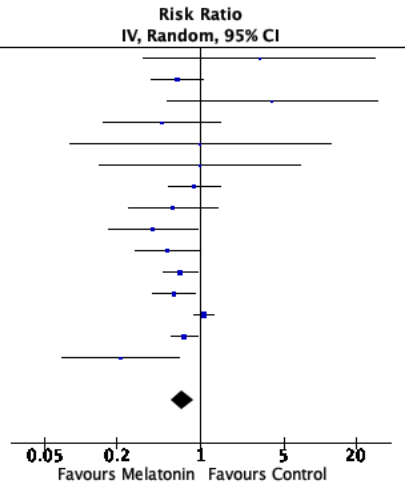
Heterogeneity: Tau² = 0.06; Chi² = 4.30, df = 2 (P = 0.12); I² = 54%
Test for overall effect: Z = 0.74 (P = 0.46)



4. Proportion with Delirium

Study or Subgroup	Melatonin Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Abbasi 2017	3	67	1	70	0.9%	3.13 [0.33, 29.39]
Bandyopadhyay 2021	16	54	25	54	9.3%	0.64 [0.39, 1.06]
Bourne 2008	4	12	1	12	1.0%	4.00 [0.52, 30.76]
Dianatkhah 2015	4	66	9	71	3.0%	0.48 [0.15, 1.48]
Foreman 2015	1	6	1	6	0.7%	1.00 [0.08, 12.56]
Gandolfi 2020	2	102	2	101	1.1%	0.99 [0.14, 6.89]
Jaiswal 2019	19	59	21	58	9.2%	0.89 [0.54, 1.47]
Javaherforooshzadeh 2023	6	34	12	40	4.6%	0.59 [0.25, 1.40]
Malhrose 2021	6	55	15	55	4.6%	0.40 [0.17, 0.95]
Nishikimi 2018	11	45	20	43	7.5%	0.53 [0.29, 0.96]
Shi 2021	40	148	59	149	13.0%	0.68 [0.49, 0.95]
Vijayakumar 2016	13	26	25	30	11.0%	0.60 [0.40, 0.91]
Wilbrow 2022	147	419	138	422	16.4%	1.07 [0.89, 1.30]
Yin 2022	67	248	92	249	14.7%	0.73 [0.56, 0.95]
Zadeh 2021	3	30	14	30	3.0%	0.21 [0.07, 0.67]
Total (95% CI)		1371		1390	100.0%	0.70 [0.57, 0.87]
Total events	342		435			

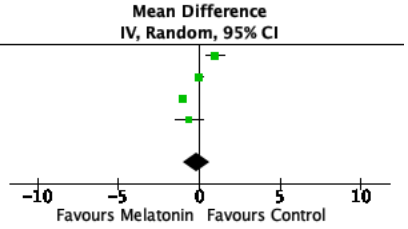
Heterogeneity: Tau² = 0.06; Chi² = 27.97, df = 14 (P = 0.01); I² = 50%
Test for overall effect: Z = 3.21 (P = 0.001)



5. Duration of Delirium (days)

Study or Subgroup	Melatonin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abbasi 2017	3	1.7	67	2	1.7	70	24.5%	1.00 [0.43, 1.57]
Jaiswal 2019	0	0.74	59	0	0.74	58	26.9%	0.00 [−0.27, 0.27]
Malhrose 2021	1	0.28	55	2	0.6	55	27.3%	−1.00 [−1.17, −0.83]
Nishikimi 2018	0.78	1.81	45	1.4	2.3	43	21.3%	−0.62 [−1.49, 0.25]
Total (95% CI)			226			226	100.0%	−0.16 [−1.00, 0.68]

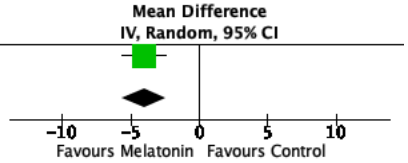
Heterogeneity: Tau² = 0.67; Chi² = 69.62, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 0.37 (P = 0.71)



6. Anxiety (Hamilton Anxiety Rating Scale)

Study or Subgroup	Melatonin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Dianatkhah 2015	5	3.33	66	9	5.93	71	100.0%	−4.00 [−5.60, −2.40]
Total (95% CI)			66			71	100.0%	−4.00 [−5.60, −2.40]

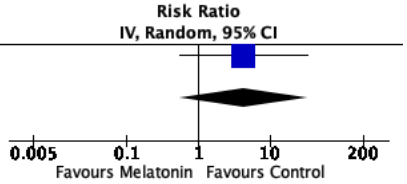
Heterogeneity: Not applicable
Test for overall effect: Z = 4.91 (P < 0.00001)



7. Proportion with Agitation

Study or Subgroup	Melatonin Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Ibrahim 2016	4	13	1	14	100.0%	4.31 [0.55, 33.70]
Total (95% CI)		13		14	100.0%	4.31 [0.55, 33.70]
Total events	4		1			

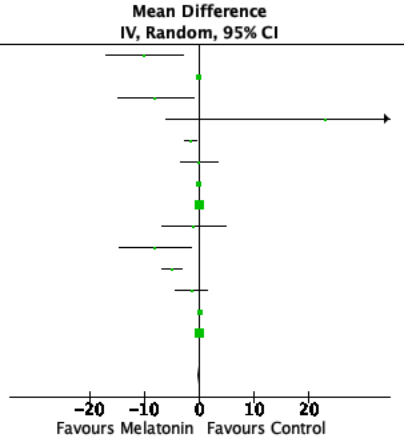
Heterogeneity: Not applicable
Test for overall effect: Z = 1.39 (P = 0.16)



8. Duration of Invasive Mechanical Ventilation (days)

Study or Subgroup	Melatonin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Alizadeh 2022	27	12.6	33	37	17.03	34	0.0%	−10.00 [−17.16, −2.84]
Dianatkhah 2015	0.958	0.722	66	1.021	0.747	71	14.4%	−0.06 [−0.31, 0.18]
Dianatkhah 2017	4	10.4	20	12	11.9	20	0.0%	−8.00 [−14.93, −1.07]
Escames 2021	41.2	44.8	12	18	18.38	6	0.0%	23.20 [−6.11, 52.51]
Gandolfi 2020	2	4.4	102	3.5	3.7	101	1.3%	−1.50 [−2.62, −0.38]
Hakiminia 2022	3	5.56	30	3	7.4	30	0.1%	0.00 [−3.31, 3.31]
Jaiswal 2019	2	0.741	59	2	0.741	58	13.1%	0.00 [−0.27, 0.27]
Malhrose 2021	0.22	0.1	55	0.25	0.1	55	29.8%	−0.03 [−0.07, 0.01]
Mistraletti 2015	11	8.1	41	12	17	41	0.0%	−1.00 [−6.76, 4.76]
Sharifnia 2021	4	10.4	26	12	11.8	20	0.0%	−8.00 [−14.54, −1.46]
Soltani 2022	7	3	26	12	4	26	0.4%	−5.00 [−6.92, −3.08]
Vijayakumar 2016	3.88	3.52	16	5.26	5.52	21	0.2%	−1.38 [−4.30, 1.54]
Wilbrow 2022	0.46	2.6	419	0.27	2	422	10.8%	0.19 [−0.12, 0.50]
Zadeh 2021	0.25	0.05	30	0.27	0.088	30	29.8%	−0.02 [−0.06, 0.02]
Total (95% CI)			935			935	100.0%	−0.06 [−0.18, 0.07]

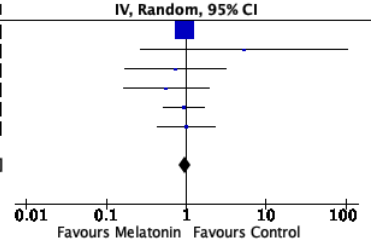
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 56.11$, df = 13 (P < 0.00001); $I^2 = 77\%$
Test for overall effect: Z = 0.86 (P = 0.39)



9. In Hospital Mortality

Study or Subgroup	Melatonin Events	Melatonin Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Alizadeh 2022	28	33	30	34	83.3%	0.96 [0.80, 1.16]
Hakiminia 2022	2	28	0	30	0.3%	5.34 [0.27, 106.70]
Jaiswal 2019	3	59	4	58	1.4%	0.74 [0.17, 3.15]
Mansilla-Rosello 2022	3	15	5	14	2.0%	0.56 [0.16, 1.92]
Mistraletti 2015	14	41	15	41	8.7%	0.93 [0.52, 1.68]
Naderi-Behdani 2022	9	48	9	48	4.3%	1.00 [0.43, 2.30]
Total (95% CI)		224		225	100.0%	0.95 [0.80, 1.13]
Total events	59		63			

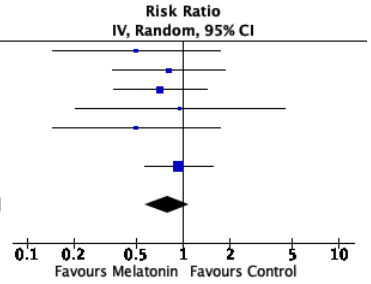
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.14$, $df = 5$ ($P = 0.83$); $I^2 = 0\%$
Test for overall effect: $Z = 0.55$ ($P = 0.58$)



10. ICU Mortality

Study or Subgroup	Melatonin Events	Melatonin Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Dianatkhah 2017	3	20	6	20	7.1%	0.50 [0.14, 1.73]
Gandolfi 2020	9	102	11	101	15.6%	0.81 [0.35, 1.87]
Mistraletti 2015	10	41	14	41	23.1%	0.71 [0.36, 1.42]
Nishikimi 2018	3	45	3	43	4.6%	0.96 [0.20, 4.48]
Sharifnia 2021	3	20	6	20	7.1%	0.50 [0.14, 1.73]
Vijayakumar 2016	0	26	0	30		Not estimable
Wilbrow 2022	27	419	29	422	42.5%	0.94 [0.57, 1.56]
Total (95% CI)		673		677	100.0%	0.79 [0.57, 1.10]
Total events	55		69			

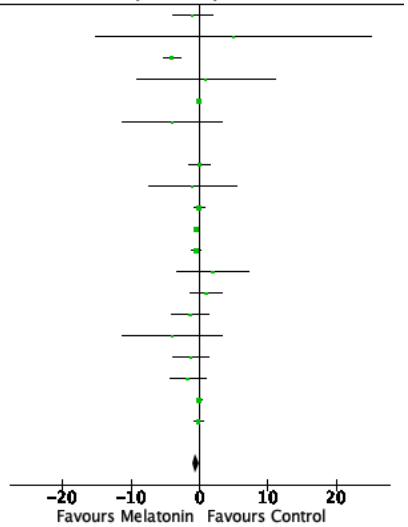
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.63$, $df = 5$ ($P = 0.90$); $I^2 = 0\%$
Test for overall effect: $Z = 1.42$ ($P = 0.16$)



11. ICU Length of Stay (days)

Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Abbasi 2017	8.8	5.9	67	9.8	10.6	70	1.7%	-1.00 [-3.86, 1.86]
Abbasi 2023	27	36.3	20	22	28.9	21	0.0%	5.00 [-15.15, 25.15]
Ameri 2022	9	2.96	109	13	5.92	117	6.5%	-4.00 [-5.21, -2.79]
Bellapart 2020	24	14.8	21	23	14.1	12	0.2%	1.00 [-9.18, 11.18]
Dianatkhah 2015	0.958	0.722	66	1.021	0.747	71	15.4%	-0.06 [-0.31, 0.18]
Dianatkhah 2017	8	11.1	20	12	12.6	20	0.3%	-4.00 [-11.36, 3.36]
Escames 2021	43.4	43.3	12	43	0	6		Not estimable
Gandolfi 2020	4	5.9	102	4	5.9	101	4.4%	0.00 [-1.62, 1.62]
Hakiminia 2022	13	9.6	30	14	15.2	30	0.4%	-1.00 [-7.43, 5.43]
Jaiswal 2019	4	2.22	59	4	1.48	58	11.0%	0.00 [-0.68, 0.68]
Javaherforooshzadeh 2023	2.33	0.5	40	2.72	0.75	40	15.1%	-0.39 [-0.67, -0.11]
Malhrose 2021	3.1	1.4	55	3.6	2	55	11.4%	-0.50 [-1.15, 0.15]
Mistraletti 2015	14	8.9	41	12	14.8	41	0.5%	2.00 [-3.29, 7.29]
Naderi-Behdani 2022	6	7.22	48	5	4.44	48	2.3%	1.00 [-1.40, 3.40]
Nishikimi 2018	4.56	3.68	45	5.86	8.29	43	1.9%	-1.30 [-4.00, 1.40]
Sharifnia 2021	8	11.1	20	12	12.6	20	0.3%	-4.00 [-11.36, 3.36]
Soltani 2022	13.31	5.17	26	14.55	4.72	26	1.9%	-1.24 [-3.93, 1.45]
Vijayakumar 2016	7.65	3.58	26	9.36	6.35	30	2.0%	-1.71 [-4.37, 0.95]
Wilbrow 2022	5	3	419	5	3	422	13.9%	0.00 [-0.41, 0.41]
Zadeh 2021	3.83	1	30	4	1.7	30	10.8%	-0.17 [-0.88, 0.54]
Total (95% CI)			1256			1261	100.0%	-0.49 [-0.89, -0.10]

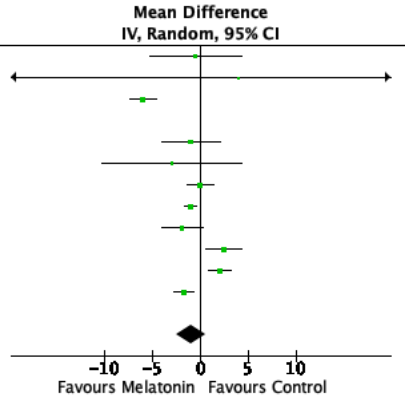
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 49.52$, $df = 18$ ($P < 0.0001$); $I^2 = 64\%$
Test for overall effect: $Z = 2.43$ ($P = 0.02$)



12. Hospital Length of Stay (days)

Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Abbasi 2017	18.1	13.5	67	18.6	15.6	70	5.7%	−0.50 [−5.38, 4.38]
Abbasi 2023	38	34.8	20	34	56.3	21	0.3%	4.00 [−24.50, 32.50]
Ameri 2022	15	2.96	109	21	7.41	117	11.7%	−6.00 [−7.45, −4.55]
Escames 2021	48.2	44.4	12	48	0	6		Not estimable
Gandolfi 2020	9	9.6	102	10	12.6	101	8.6%	−1.00 [−4.08, 2.08]
Hakiminia 2022	16	11.85	30	19	16.67	30	3.3%	−3.00 [−10.32, 4.32]
Jaiswal 2019	12	4.44	59	12	2.96	58	11.9%	0.00 [−1.37, 1.37]
Javaherforooshzadeh 2023	7.53	0.75	40	8.6	2	40	12.8%	−1.07 [−1.73, −0.41]
Malhrose 2021	11.9	5.3	55	13.8	6.2	55	10.4%	−1.90 [−4.06, 0.26]
Shi 2021	15.9	9.7	148	13.4	6.6	149	10.9%	2.50 [0.61, 4.39]
Wilbrow 2022	14	8.9	419	12	8.9	422	12.1%	2.00 [0.80, 3.20]
Yin 2022	18.1	5.7	248	19.8	6.1	249	12.4%	−1.70 [−2.74, −0.66]
Total (95% CI)			1309			1318	100.0%	−0.93 [−2.47, 0.61]

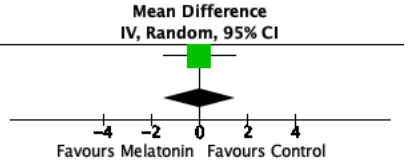
Heterogeneity: Tau² = 4.71; Chi² = 87.50, df = 10 (P < 0.00001); I² = 89%
Test for overall effect: Z = 1.19 (P = 0.23)



13. Functional Status Post-ICU

Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Hakiminia 2022	3	2.96	30	3	2.96	30	100.0%	0.00 [−1.50, 1.50]
Total (95% CI)			30			30	100.0%	0.00 [−1.50, 1.50]

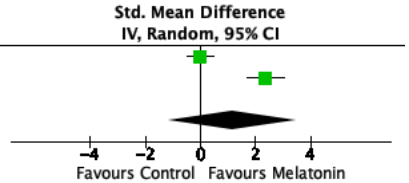
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



14. Post-ICU Cognitive Function

Study or Subgroup	Melatonin Mean	Melatonin SD	Melatonin Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hakiminia 2022	10	2.41	30	10	2.04	30	50.5%	0.00 [−0.51, 0.51]
Jouybar 2023	19.47	0.8	29	17.5	0.84	30	49.5%	2.37 [1.69, 3.04]
Total (95% CI)			59			60	100.0%	1.17 [−1.15, 3.49]

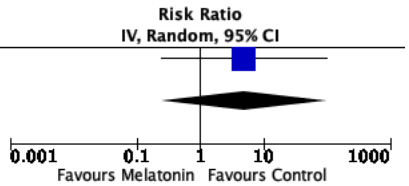
Heterogeneity: Tau² = 2.71; Chi² = 30.26, df = 1 (P < 0.00001); I² = 97%
Test for overall effect: Z = 0.99 (P = 0.32)



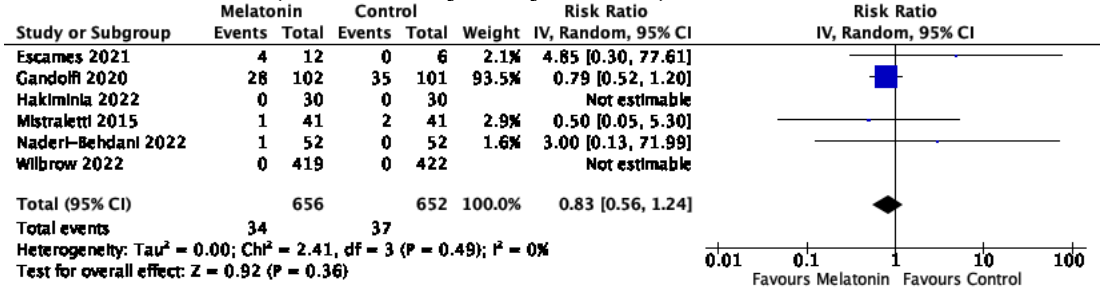
15. Post-ICU PTSD

Study or Subgroup	Melatonin Events	Melatonin Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Mistraletti 2015	2	41	0	41	100.0%	5.00 [0.25, 101.04]
Total (95% CI)		41		41	100.0%	5.00 [0.25, 101.04]
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)



16. Adverse Events (as defined by study authors)



3. Risk Of Bias

Trial	Random Sequence Generation	Randomized Concealment	Blinding-Clinical Team/Patient	Blinding-Outcome Assessors	Incomplete Data	Selection bias	Other	Overall
Abbasi 2017	Low	Low	Low	Low	Possibly Low	Low	Low	Low
Abbasi 2023	Low	Possibly Low	Low	Low	High	Low	Low	High
Alizadeh 2022	Low	Possibly Low	Possibly Low	Possibly Low	Low	Low	Low	Low
Ameri 2022	Low	Possibly High	Low	Possibly Low	High	Low	Low	High
Bandyopadhyay 2021	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Bellapart 2020	High	Low	Low	Low	High	Low	Low	High
Bourne 2008	Possibly High	Possibly Low	Possibly Low	Possibly Low	Low	Low	Low	Possibly High
Dianatkhah 2015	High	High	Possibly Low	Possibly Low	Low	Low	Possibly Low	High
Dianatkhah 2017	Possibly High	Possibly Low	Possibly Low	Possibly Low	Low	Low	Low	High
Escames 2021	Possibly High	Low	Low	Low	Low	Low	Possibly High	High
Foreman 2015	Low	Low	Low	Low	Low	Possibly High	Possibly High	High
Gandolfi 2020	Low	Low	Low	Low	Low	Low	Low	Low
Hakiminia 2022	Low	Possibly Low	Possibly Low	Low	Low	Low	Low	Low
Ibrahim 2016	Low	Low	Low	Low	Low	Possibly High	Possibly High	High
Jaiswal 2019	Low	Low	Low	Low	Low	Low	Low	Low
Javaherforoo-shzadeh 2023	Possibly High	Possibly High	Low	Low	Low	Low	Low	High
Jouybar 2023	Low	Low	Low	Low	Low	Low	Low	Low
Malhrose 2021	Possibly High	Possibly High	Possibly Low	Possibly Low	Low	High	Possibly High	High
Mansilla-Rosello 2022	Low	Possibly High	Low	Low	Low	Low	Low	High
Mistraletti 2015	Low	Possibly High	Low	Low	Low	Possibly High	Low	Possibly High
Naderi-Behdani 2022	Low	Low	Low	Low	Low	Low	Low	Low
Nishikimi 2018	Low	Possibly Low	Possibly Low	Possibly Low	Low	Low	Possibly Low	Low
Owens 2022	Unclear	Unclear	Unclear	Unclear	Low	Possibly High	Low	High

Sharifnia 2021	Possibly High	Possibly Low	High	High	Low	High	Low	High
Shi 2021	Low	Low	Low	Low	Low	Possibly High	Possibly High	High
Soltani 2022	Low	Possibly High	Possibly Low	Possibly Low	Low	High	Low	High
Vijayakumar 2016	Low	Possibly High	Low	Possibly High	Low	High	Low	High
Wibrow 2022	Low	Low	Low	Low	Low	Low	Low	Low
Yin 2022	Low	Low	Low	Low	Low	Low	Low	Low
Zadeh 2021	Low	Low	Low	Low	Low	Low	Low	Low

4. Summary Of Findings Table

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Melatonin	No melatonin	Relative (95% CI)	Absolute (95% CI)		
Sleep Quantity-Total Nocturnal Sleep Time (hours)												
6	randomised trials	serious[a]	not serious	not serious	not serious	none	607	596	-	MD **0.04 higher** (0.18 lower to 0.26 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Perceived Sleep Quality-SMD												
3	randomised trials	not serious	serious[b]	not serious	serious[c]	none	535	433	-	SMD **0.54 higher** (0.01 higher to 1.07 higher)	⨁⨁◯◯ Low	CRITICAL
Awakenings												
3	randomised trials	not serious	serious[b]	not serious	very serious[d]	none	421	401	-	SMD **0.14 lower** (0.53 lower to 0.24 higher)	⨁◯◯◯ Very low	CRITICAL
Delirium Prevalence												
15	randomised trials	not serious[e]	serious[f]	not serious	serious[g]	none	342/1371 (24.9%)	435/1390 (31.3%)	**RR 0.70** (0.57 to 0.87)	**9 fewer per 100** (from 13 fewer to 4 fewer)	⨁⨁◯◯ Low	CRITICAL
Duration of Delirium (days)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Melatonin	No melatonin	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	not serious	serious[b]	not serious	serious[h]	none	226	226	-	MD **0.16 lower** (1 lower to 0.68 higher)	⨁⨁◯◯ Low	CRITICAL
Anxiety												
1	randomised trials	serious[i]	not serious	not serious	very serious[j]	none	66	71	-	MD **4 lower** (5.6 lower to 2.4 lower)	⨁◯◯◯ Very low	IMPORTANT
Proportion with Agitation												
1	randomised trials	serious[k]	not serious	not serious	very serious[j]	none	4/13 (30.8%)	1/14 (7.1%)	**RR 4.31** (0.55 to 33.70)	**24 more per 100** (from 3 fewer to 100 more)	⨁◯◯◯ Very low	IMPORTANT
Duration Invasive Mechanical Ventilation (days)												
14	randomised trials	serious[m]	serious[b]	not serious	not serious	none	935	935	-	MD **0.06 lower** (0.18 lower to 0.07 higher)	⨁⨁◯◯ Low	IMPORTANT
Mortality in hospital												
6	randomised trials	not serious	not serious	not serious	extremely serious[n]	none	59/224 (26.3%)	63/225 (28.0%)	**RR 0.95** (0.80 to 1.13)	**1 fewer per 100** (from 6 fewer to 4 more)	⨁◯◯◯ Very low	IMPORTANT
ICU Mortality												
7	randomised trials	not serious	not serious	not serious	very serious[o]	none	55/673 (8.2%)	69/677 (10.2%)	**RR 0.79** (0.57 to 1.10)	**2 fewer per 100** (from 4 fewer to 1 more)	⨁⨁◯◯ Low	IMPORTANT
ICU Length of Stay (days)												
20	randomised trials	serious[p]	serious[b]	not serious	not serious	none	1256	1261	-	MD **0.49 lower** (0.89 lower to 0.1 lower)	⨁⨁◯◯ Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Melatonin	No melatonin	Relative (95% CI)	Absolute (95% CI)		
Hospital Length of Stay (days)												
12	randomised trials	not serious	serious[b]	not serious	serious[q]	none	1309	1318	-	MD **0.93 lower** (2.47 lower to 0.61 higher)	⨁⨁◯◯ Low	IMPORTANT
Functional Status Post-ICU												
1	randomised trials	not serious	not serious	not serious	very serious[r]	none	30	30	-	MD **0** (1.5 lower to 1.5 higher)	⨁⨁◯◯ Low	IMPORTANT
Post-ICU Cognitive Function												
2	randomised trials	not serious	serious[b]	not serious	very serious[s]	none	59	60	-	SMD **1.17 higher** (1.15 lower to 3.49 higher)	⨁◯◯◯ Very low	IMPORTANT
Post-ICU PTSD												
1	randomised trials	serious[t]	not serious	not serious	very serious[t]	none	2/41 (4.9%)	0/41 (0.0%)	**RR 5.00** (0.25 to 101.04)	**0 fewer per 100** (from 0 fewer to 0 fewer)	⨁◯◯◯ Very low	IMPORTANT
Adverse Events (defined by study author)												
6	randomised trials	serious[u]	not serious	not serious	serious[v]	none	34/656 (5.2%)	37/652 (6.4%)	**RR 0.83** (0.56 to 1.24)	**1 fewer per 100** (from 2 fewer to 1 more)	⨁⨁◯◯ Low	CRITICAL

Explanations

a. When high risk of bias trials are excluded, the point estimate changes from improved duration of sleep to less sleep
b. High I2, Pointe estimates do not overlap, Confidence intervals do not overlap
c. There is both benefit and harm
d. There is both benefit and harm
e. 8 trials have high risk of bias out of 17. When the high risk of bias trials are removed, the confidence interval remained in favour of melatonin reducing delirium
f. Although I2 is only 50%, the confidence intervals and point estimates do not overlap
g. The MID is crossed by the lower end of the CI
h. The confidence interval crossed the threshold for benefit
i. One trial at high risk of bias for possible issues with randomization and allocation
j. One trial, small number of participants, and with a minimally important clinical difference of 3.9 points , the lower end of the confidence interval crosses that threshold

k. One trial who with possible issues with selective reporting and did not disclose funding.
l. One trial, small number of events, and confidence interval demonstrates both important harm and benefit
m. When high risk of bias studies are excluded, although the point estimate remains consistent, the confidence interval will cross the line of no effect
n. Threshold for both important harm and benefit is demonstrated, in addition to crossing the threshold for large benefit (5 per 100).
o. With the minimally important difference of 1 patient per 100, the threshold for minimally important benefit and harm are both crossed
p. 12 trials have high risk of bias. When those trials are removed, the effect estimate is lost
q. The upper end of the confidence interval crosses the line of minimal clinical importance (2 days)
r. Only one trail with very small number of participants and point estimate shows harm and benefit
s. Only 2 small trails with low number of participants and point estimate demonstarting benefit and harm
t. Only one trial with issues of allocation and possible selective reporting bias
u. When low ROB trials are excluded the point estimate crosses the line of no effect
v. Low number of events not meeting OIS

5. Evidence-To-Decision Framework

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Poor sleep often begins with the onset of an acute illness and will continue well beyond the initial insult. A lack of sleep is cited as being one of the major factors of stress in the ICU. Not only that, sleep may play an important role for recovery of a critical illness The need to improve sleep and strengthen the circadian rhythm of critically ill patients is an evolving field. Circadian rhythm abnormalities and reduced levels of melatonin have been documented in critical illness, therefore, exogenous replacement with melatonin is a warranted and appropriate question.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ● Small ○ Moderate ○ Large	Desirable effects: **1.** Improvement in perceived sleep quality- SMD 0.54, 95% CI 0.01 to 1.07 (low certainty)	

○ Varies ○ Don't know	**2.** Reduction in delirium RR 0.70, 95% CI 0.57 to 0.87; ARR 9 fewer per 100, 95% CI 13 fewer to 4 fewer (low certainty) **3.** Reduction in ICU length of stay, days-MD -0.5, 95% CI -0.89 to -0.10 (low certainty) Little to no difference **1.** Total Nocturnal sleep time, hours-MD 0.04 hours, 95% CI -0.18 to 0.26 hours (moderate certainty) **2.** Duration of delirium MD -0.16 days, 95% CI -1 to 0.68 days (low certainty) **3.** Duration of IMV, days-MD -0.06 days, 95% CI -0.18 to 0.07 days (low certainty) **4.** Hospital LOS, days-MD -0.93 days, 95% CI -2.47 to 0.61 days (low certainty) Uncertain effect **1.** Number of awakenings (SMD) -0.14, 95% CI -0.53 to 0.24 (very low certainty) **2.** Anxiety (HADS score), MD -4, 95% CI -5.6 to -2.4 (very low certainty) **3.** Proportion with agitation RR 4.31, 95% CI 0.55 to 33.7 (very low certainty) **4.** In hospital mortality RR 0.95, 95% CI 0.80 to 1.13 (very low certainty) **5.** ICU mortality RR 0.79, 95% CI 0.57 to 1.10 (low certainty) **6.** Functional status post ICU-MD 0, 95% CI -1.50 to 1.50 (low certainty) **7.** Post-ICU cognitive dysfunction-SMD 1.17, 95% CI-1.15 to 3.49 (very low certainty) **8.** Post-ICU PTSD RR 5, 95% CI 0.25 to 101.04 (very low certainty)	
Undesirable Effects How substantial are the undesirable anticipated effects?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	Possibly slight reduction in adverse events RR 0.83 95% CI 0.56 to 1.24 (low certainty)	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Desirable effects: **1.** Improvement in perceived sleep quality- SMD 0.54, 95% CI 0.01 to 1.07 (low certainty) **2.** Reduction in delirium RR 0.70, 95% CI 0.57 to 0.87; ARR 9 fewer per 100, 95% CI 13 fewer to 4 fewer (low certainty) **3.** Reduction in ICU length of stay, days-MD -0.5, 95% CI -0.89 to -0.10 (low certainty) Little to no difference **1.** Total Nocturnal sleep time, hours-MD 0.04 hours, 95% CI -0.18 to 0.26 hours (moderate certainty) **2.** Duration of delirium MD -0.16 days, 95% CI -1 to 0.68 days (low certainty) **3.** Duration of IMV, days-MD -0.06 days, 95% CI -0.18 to 0.07 days (low certainty) **4.** Hospital LOS, days-MD -0.93 days, 95% CI -2.47 to 0.61 days (low certainty) Uncertain effect	

	1. Number of awakenings (SMD) -0.14, 95% CI -0.53 to 0.24 (very low certainty) **2.** Anxiety (HADS score), MD -4, 95% CI -5.6 to -2.4 (very low certainty) **3.** Proportion with agitation RR 4.31, 95% CI 0.55 to 33.7 (very low certainty) **4.** In hospital mortality RR 0.95, 95% CI 0.80 to 1.13 (very low certainty) **5.** ICU mortality RR 0.79, 95% CI 0.57 to 1.10 (low certainty) **6.** Functional status post ICU-MD 0, 95% CI -1.50 to 1.50 (low certainty) **7.** Post-ICU cognitive dysfunction-SMD 1.17, 95% CI-1.15 to 3.49 (very low certainty) **8.** Post-ICU PTSD RR 5, 95% CI 0.25 to 101.04 (very low certainty) Possibly slight reduction in adverse events Possibly slight reduction in adverse events RR 0.83 95% CI 0.56 to 1.24 (low certainty)	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	1-Not all trials examined all sleep outcomes that may be significant (e.g. REM sleep) -We did capture important end-points of the outcomes (e.g. ICU LOS, delirium)	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Desirable effects: **1.** Improvement in perceived sleep quality- SMD 0.54, 95% CI 0.01 to 1.07 (low certainty) **2.** Reduction in delirium RR 0.70, 95% CI 0.57 to 0.87; ARR 9 fewer per 100, 95% CI 13 fewer to 4 fewer (low certainty) **3.** Reduction in ICU length of stay, days-MD -0.5, 95% CI -0.89 to -0.10 (low certainty) Little to no difference **1.** Total Nocturnal sleep time, hours-MD 0.04 hours, 95% CI -0.18 to 0.26 hours (moderate certainty) **2.** Duration of delirium MD -0.16 days, 95% CI -1 to 0.68 days (low certainty) **3.** Duration of IMV, days-MD -0.06 days, 95% CI -0.18 to 0.07 days (low certainty) **4.** Hospital LOS, days-MD -0.93 days, 95% CI -2.47 to 0.61 days (low certainty) Uncertain effect **1.** Number of awakenings (SMD) -0.14, 95% CI -0.53 to 0.24 (very low certainty) **2.** Anxiety (HADS score), MD -4, 95% CI -5.6 to -2.4 (very low certainty) **3.** Proportion with agitation RR 4.31, 95% CI 0.55 to 33.7 (very low certainty) **4.** In hospital mortality RR 0.95, 95% CI 0.80 to 1.13 (very low certainty) **5.** ICU mortality RR 0.79, 95% CI 0.57 to 1.10 (low certainty) **6.** Functional status post ICU-MD 0, 95% CI -1.50 to 1.50 (low certainty) **7.** Post-ICU cognitive dysfunction-SMD 1.17, 95% CI-1.15 to 3.49 (very low certainty) **8.** Post-ICU PTSD RR 5, 95% CI 0.25 to 101.04 (very low certainty) Possibly slight reduction in adverse events RR 0.83 95% CI 0.56 to 1.24 (low certainty)	-Impressive reduction in delirium with possible reduction in adverse events -Recall the certainty of events is low as to why we cannot say melatonin definitely should be favored

Resources required How large are the resource requirements (costs)?"		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● Don't know	There is likely variability in cost of approval, vs supplement -No data on the cost of melatonin internationally -The drug/supplement is not regulated depended on country -We don't always know what the dose is (in the US) In North America, it is a relatively cheap medication with possible benefits	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	The next large RCT, it would be very worthwhile to examine cost effectiveness	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	-Impossible to know access worldwide -Also, implications of drug recommendations in guidelines and profiting from companies -If there is an impact on delirium, is hyperactive delirium treated differently based on race-are there biases driving the intervention (an easy supplement)-may be a benefit to improve disparities (cheap, easy to administer) Covers access issues and bias for delirium interventions	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Trials performed in MANY countries around the world -Discussion on if supplements that are NOT FDA approved should be allowed -Most stakeholders would say is it ok, and most people would say it is reasonable -There is also access to Ramelteon for those that do not think that we should be recommending an unregulated supplement	

	-Also acceptable to many patients-commonly known substance	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	30 trials completed Just need oral access	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation
We suggest administering melatonin over no melatonin in adult patients admitted to the intensive care unit (Conditional recommendation; For intervention; Low certainty of evidence).

6. Subgroup Analysis

Category	Group	No. of trials	Estimate of effect and 95% CI	I^2	P-Interaction
SLEEP QUANTITY-TOTAL NOCTURNAL SLEEP (Hours)-Mean difference					
Medication	Melatonin	4	0.03 (-0.28, 0.33)	0%	0.80
	Ramelteon	2	0.10 (-0.35, 0.55)	25%	
Frequency of Dosing	Nightly	6	0.04 (-0.18, 0.26)	0%	N/A
	Multi-dose administration	0	N/A	N/A	
Dose of melatonin	≤10mg	4	0.03 (-0.28, 0.33)	0%	N/A
	>10mg	0	N/A	N/A	
Comparator agent	Placebo	6	0.04 (-0.18, 0.26)	0%	N/A
	Benzodiazepine	0	N/A	N/A	
	Dexmedetomidine	0	N/A	N/A	
Type of ICU	General Med/Surg	4	0.11 (-0.20, 0.41)	0%	0.57
	Neuro ICU	0	N/A	N/A	
	CV-Surg	1	-0.03 (-0.39, 0.33)	0%	
PERCEIVED SLEEP QUALITY-Standard Error of the Mean					
Medication	Melatonin	3	0.54 (0.01, 1.07)	92%	N/A
	Ramelteon	0	N/A	N/A	
Frequency of Dosing	Nightly	3	0.54 (0.01, 1.07)	92%	N/A
	Multi-dose administration	0	N/A	N/A	
Dose of melatonin	≤10mg	3	0.54 (0.01, 1.07)	92%	N/A
	>10mg	0	N/A	N/A	
Comparator agent	Placebo	2	0.23 (0.03, 0.43)	44%	<0.0001
	Benzodiazepine	1	1.16 (0.79, 1.52)	N/A	
	Dexmedetomidine	0	N/A	N/A	
Type of ICU	General Med/Surg	2	0.23 (0.03, 0.43)	44%	<0.0001
	Neuro ICU	0	N/A	N/A	
	CV-Surg	1	1.16 (0.79, 1.52)	N/A	
PROPORTION WITH DELIRIUM-Relative Risk					
Medication	Melatonin	13	0.70 (0.55, 0.89)	54%	0.99

	Ramelteon	2	0.70 (0.42, 1.17)	42%	
Frequency of Dosing	Nightly	12	0.74 (0.56, 0.96)	46%	0.04
	Multi-dose administration	1	0.21 (0.07, 0.67)	N/A	
Dose of melatonin	≤10mg	13	0.70 (0.55, 0.89)	54%	N/A
	>10mg	0	N/A	N/A	
Comparator agent	Placebo	12	0.74 (0.59, 0.93)	54%	0.36
	Benzodiazepine	1	0.48 (0.15, 1.48)	N/A	
	Dexmedetomidine	2	0.49 (0.26, 0.90)	0%	
Type of ICU	General Med/Surg	6	0.85 (0.54, 1.33)	61%	0.61
	Neuro ICU	1	1.00 (0.08, 12.56)	N/A	
	CV-Surg	7	0.66 (0.54, 0.83)	17%	
DURATION OF INVASIVE MECHANICAL VENTILATION (days)-Mean difference					
Medication	Melatonin	13	-0.07 (-0.21, 0.07)	79%	0.67
	Ramelteon	1	0.00 (-0.27, 0.27)	N/A	
Frequency of Dosing	Nightly	11	-0.34 (-0.70, 0.02)	81%	0.61
	Multi-dose administration	3	0.03 (-1.35, 1.41)	17%	
Dose of melatonin	≤10mg	8	-0.05 (-0.16, 0.07)	80%	0.1
	>10mg	5	-4.98 (-10.86, 0.90)	72%	
Comparator agent	Placebo	12	-0.56 (-1.06, -0.07)	80%	0.11
	Benzodiazepine	1	-0.06 (-0.31, 0.18)	N/A	
	Dexmedetomidine	1	-0.06 (-0.18, 0.07)	N/A	
Type of ICU	General Med/Surg	6	-1.16 (-2.88, 0.56)	74%	0.02
	Neuro ICU	4	-4.49 (-8.05, -0.93)	68%	
	CV-Surg	4	-0.03 (-0.05, 0.00)	0%	
ICU LENGTH OF STAY (days)-Mean Difference					
Medication	Melatonin	18	-0.55 (-0.99, -0.11)	67%	0.25
	Ramelteon	2	-0.08 (-0.74, 0.58)	0%	
Frequency of Dosing	Nightly	15	-0.20 (-0.35, -0.04)	0%	0.49
	Multi-dose administration	5	-1.14 (-3.80, 1.53)	91%	
Dose of melatonin	≤10mg	13	-0.57 (-1.03, -0.11)	74%	0.62
	>10mg	5	-0.03 (-2.13, 2.08)	1%	
Comparator agent	Placebo	17	-0.76 (-1.54, 0.01)	67%	0.07

	Benzodiazepine	1	-0.06 (-0.31, 0.18)	N/A	
	Dexmedetomidine	2	-0.41 (-0.66, -0.15)	0%	
Type of ICU	General Med/Surg	11	-0.81 (-2.23, 0.62)	79%	0.31
	Neuro ICU	4	-1.72 (-3.96, 0.52)	0%	
	CV-Surg	5	-0.21 (-0.38, -0.04)	3%	