

# Medication at risk of inducing delirium: development of a comprehensive pocket guide for clinical practice.

## Background and Objective:

Delirium is one of the most common causes of acute end-organ dysfunctions across all hospital settings. Patients who develop delirium are more likely to experience increased short- and long-term mortality, decreases in long-term cognitive function, longer hospital stay and increased complications of hospital care. Based on an existing list of medications at risk of inducing delirium developed by clinical experts at the University Hospital Innsbruck this study aimed to comprehensively review all available literature to date to develop the most comprehensive pocket guide detailing medication, mechanism of action and therapeutic alternatives for use in clinical practice.

## Design

A total of 17 scientific databases and 96 websites of professional medical organisations worldwide were searched to identify all original, peer-reviewed studies, literature reviews, grey literature and published guidelines. In addition, the Pharmacovigilance databases EUDRAVIGILANCE and FAERS were hand searched for any reported incidents and product characteristics using the EMA website and Medicines Complete. Both narrative and Systematic Review (SR) methodology were followed across three separate projects (PROSPERO:

CRC42022366025 & CRD42022366020). The SRs were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and reported in line with the Equator Network guidelines for systematic reviews. All titles, abstracts and full texts were considered against the inclusion and exclusion criteria by two researchers independently (RM/GBP), with discrepancies resolved by discussion or consideration by a third researcher (AEV). Quality assessment of all included studies was carried out using evaluated tools.

## Results

A total of 3600 records were identified across 17 scientific databases as well as 143 guidelines, frameworks or pocket guides. In addition, 26955 cases associated with delirium were identified in FEARS and 14,228 in EUDRAVIGILANZ. The product characteristics of 137 drugs across 29 drug classes were included in the study.

Antipsychotics, opioids and benzodiazepines carry the highest risk of inducing delirium; however, this study identified many more drugs, drug classes and drug combinations that put patients at risk.

## Conclusion

This research has allowed the development of the most comprehensive pocket guide on medication at risk of causing delirium available to practice to date, with further studies focusing on the systematic review of all literature relating to the risk in the peri-operative setting.

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## Strengths & Limitations

Strengths	Limitations
Rigorous quality standards & methodology followed (PROSPERO, PRISMA, EQUATOR).	Only literature published in English (and Icelandic) language included.
Careful development of search string using research librarian specialist. <sup>3,4</sup>	Evidence not available in full text is excluded.
Use of 17 databases with comprehensive focus on grey literature.	SR in Psychiatric & Delirium organisations is outstanding.
Product characteristics for generic medication and ALL branded products are included.	Pharmakovigilanz data is never complete - many cases remain unreported.
Use of Pharmakovigilanz databases FEARS/ EUDRAVIGILANZ to include all practice reports.	Medication licenses for use may be different in Europe vs. USA.

## Implications for Practice

- Antipsychotics, opioids and benzodiazepines carry the highest risk of inducing a delirium.
- Antibiotics, Analgesics (non-opioids), Anti-dementia/ Antiparkinsonian medication also carry a considerable risk.
- Symptoms such as Hallucinations and confusion are most commonly associated with a diagnosis of delirium (compared with disorientation, encephalopathy, malignant neuroleptic syndrome & serotonin syndrome).
- Identified drug combinations at risk further support prescribing decisions and patient safety.
- Sedatives and the risk of medications used in the peri-operative setting need further investigation.
- The relative risk of all identified drugs needs to be determined using a comprehensive real-world data analysis and expert consensus.

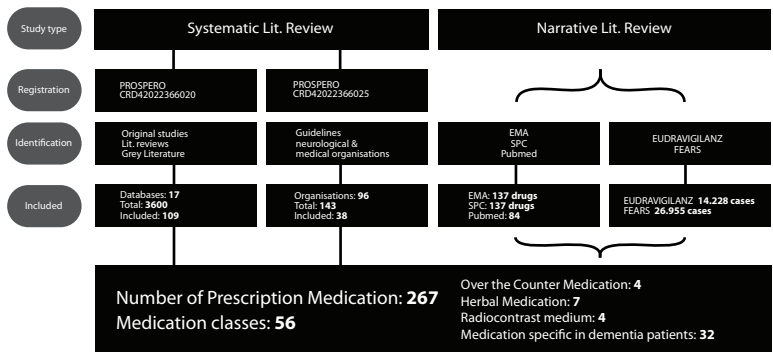


Figure 1: Literature search strategies & results to identify medication at risk of inducing a delirium to aid the development of a comprehensive pocket guide for clinical practice.

1. Puelle MR, Kosar CM, Xu G, Schmitt E, Jones RN, Marcantonio ER, Cooper Z, Inouye SK, Saczynski JS. The Language of Delirium: Keywords for Identifying Delirium from Medical Records. *J Gerontol Nurs.* 2015 Aug;41(8):34-42. doi: 10.3928/00989134-20150723-01. PMID: 26248142; PMCID: PMC4551393.
2. Slooter AJC, Otte WM, Devlin JW, Arora RC, Bleck TP, Claassen J, Duprey MS, Ely EW, Kaplan PW, Latronico N, Morandi A, Neufeld KJ, Sharshar T, MacLulich AMJ, Stevens RD. Updated nomenclature of delirium and acute encephalopathy: statement of ten Societies. *Intensive Care Med.* 2020 May;46(5):1020-1022. doi: 10.1007/s00134-019-05907-4. Epub 2020 Feb 13. PMID: 32055887; PMCID: PMC7210231.

