

Medication at risk of inducing delirium in dementia patients

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Background and Objective:

Acute states of confusion including symptoms such as hallucination, altered state of consciousness and awareness, disorientation, encephalopathy, serotonin syndrome and malignant neuroleptic syndrome. These are commonly recognised under the umbrella term delirium. Dementia patients have a fivefold higher chance of developing a delirium and an overlapping symptom profile making diagnosis particularly difficult. One known risk factor for the development of delirium in this patient group is medication. However, medication that carry a specific risk of delirium in Alzheimer and dementia patients are not extensively reported as any medication is considered to carry a potential risk for these patients. The aim of this study was to provide a narrative overview of the available evidence as reported by product and manufacturers characteristics (EMA website & Medicines Complete) and pharmacovigilance reports in EUDRAVIGILANCE and FEARS.

Design

A narrative literature review hand searched any incident reports on the Pharmacovigilance databases EUDRAVIGILANCE and FAERS as well as product characteristics of all generic and branded products using the EMA website and Medicines complete. A relative risk assessment based on the number of reported cases in EUDRAVIGILANCE and FAERS was additionally conducted using EXCEL 365. All information was

presented in a pocket guide format based on an existing list of medication at risk of inducing a delirium, developed by expert clinical practitioners at the University Hospital Innsbruck.

Results

26.955 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 in particular are associated with high numbers of cases of delirium, hallucinations, disorientation and confusion (Table 1). Among the active substances, olanzapine, clozapine, zolpidem, oxycodone and procyclidine are those that have been associated with a high delirium-inducing property (Table 2). Only 11 drugs were identified to increase the risk of delirium in dementia. These include transdermal buprenorphine, diphenhydramine, valproate, olanzapine, risperidone and its main metabolite paliperidone, mianserin, osetamivir, memantine, refecoxib and gatrifloxacin (Table 3).

Conclusion

This narrative review is the first to report on both pharmacovigilance sites and product characteristics. It's focus on medication at risk of inducing a delirium in dementia patients adds unique information to the treatment of this high-risk patient group.

Strengths & Limitations

Strengths	Limitations
Careful development of search string using research librarian specialist. ^{1,2}	FEARS & EUDRAVIGILANZ do not provide a comprehensive picture of practice observations.
Analysis of all branded product characteristics as well as the generic.	Medication licenses for use may be different in Europe vs. USA.
Comprehensive analysis of both international pharmacovigilance databases FEARS & EUDRAVIGILANZ.	A narrative methodology and not a quality assured systematic literature methodology was followed.
First study to focus on dementia.	

	Hallucination	Confusion	Altered mental state	Disorientation	Encephalopathy	Neuroleptic malignant syndrome	Serotonin
Anaesthetics (Opioids)	●						●
Anaesthetics (Non-opioids)	●	●					
Antibiotics	●	●		●	●		
Antidepressants	●	●				●	●
Antipsychotics	●	●					●
Anti-parkinsonian	●	●				●	
Benzodiazepines	●	●					

Table 1. Depiction of the most frequent delirium symptom reported across the drug classes identified to have the highest risk.

Risk	EUDRAVIGILANZ	FEARS
> 500 Cases	olanzapin	olanzapin lorazepam gabapenin
	clozapin	clozapin morphin pregabalin
	zolpidem	zolpidem risperidon paroxetin
	oxycodon	oxycodon tramadol sertraline
	clobazam	quetiapin haloperidol lithium fentanyl
5%	procyclidin	procyclidin tolperison
	biperiden	biperiden

Table 2. Drugs associated with the highest risk of inducing a delirium across all patient groups reported in the pharmacovigilance databases EUDRAVIGILANZ and FEARS.

Dementia
diphenhydramine osetamivir
gatrifloxacin risperidone and its main metabolite paliperidone
memantine transdermal buprenorphine
mianserin valproate
olanzapine

Table 3. Drugs specifically associated with delirium in dementia patients.

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.