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ORIGINAL RESEARCH ARTICLE

The Risk of Preoperative Central Nervous System-Acting Medications on Delirium Following Hip or Knee Surgery: A Matched Case-Control Study

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Abstract

Introduction Medicines acting on the central nervous system can increase the risk of postoperative delirium, but the specific medicines associated with greatest risk remain unclear.

Objectives We aimed to examine the risk of individual central nervous system-acting medicines used preoperatively on delirium after hip or knee surgery.

Methods A matched case-control study was conducted using data from the Australian Government Department of Veterans' Affairs. We included people aged 65 years or older who had knee or hip surgery between 2000 and 2019. People with hip or knee surgery who developed postoperative delirium were cases and controls were people with hip or knee surgery but who did not develop postoperative delirium. Use of medicines including anxiolytics, sedatives, and hypnotics, opioid analgesics and antidepressants prior to surgery was compared between cases and controls.

Results A total of 2614 patient cases with postoperative delirium were matched by same sex, age (±2 years), and year of admission (±2 years) with 7842 controls without postoperative delirium. Cases were more likely to be exposed to nitrazepam (odds ratio [OR] = 1.81, 95% confidence interval [CI] 1.24–2.64), sertraline (OR = 1.50, 95% CI 1.20–1.87), mirtazapine (OR = 1.38, 95% CI 1.11–1.74), venlafaxine (OR = 1.42, 95% CI 1.02–1.98), citalopram (OR = 1.54, 95% CI 1.19–1.99), escitalopram (OR = 1.42, 95% CI 1.06–1.89) or fluvoxamine (OR = 5.01, 95% CI 2.15–11.68) prior to surgery than controls. At the class level, exposure to benzodiazepines (OR = 1.20, 95% CI 1.05–1.37) and antidepressants (OR = 1.64, 95% CI 1.47–1.83) prior to surgery was significantly higher in cases than in controls. The numbers needed to treat to harm for one additional delirium case were 43 for sertraline, 40 for citalopram, 57 for mirtazapine and 26 for nitrazepam. Whereas, the numbers needed to treat to harm were found to be 20 for sertraline, 17 for citalopram, 19 for mirtazapine and 10 for nitrazepam in the 85 years or older age group, indicating that the harmful effect of these medicines is pronounced as age advances.

Conclusions People who developed delirium following hip or knee surgery were more likely to be exposed to nitrazepam, sertraline, mirtazapine, venlafaxine, citalopram, escitalopram or fluvoxamine at the time of admission for surgery. Planning to reduce use of these medicines well prior to surgery may decrease the risk of postoperative delirium.

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Key Points

This study determined the risk of postoperative delirium associated with individual central nervous system medicines and reveals that medicines' risk for delirium differs by type of medicine within the class.

The study shows that a smaller number of people are needed to be treated for one additional postoperative delirium case in people aged 85 years or older compared with younger age groups, indicating that the risk of medicines for delirium increases with age.

Reducing the use of medicines with greatest risk prior to the surgery could decrease delirium risk in older people, especially for those having planned surgery.

1 Introduction

Delirium is one of the most common complications following major surgical procedures in older people with incidence rates reaching up to 55% in hip fracture surgery [1–6]. It is associated with an increased risk of death, prolonged hospital stay, discharge to institutional care and a decline in functional status [7]. An Australian retrospective study showed that older people who developed delirium following hip surgery had a higher mortality rate within 1 year than people who did not develop delirium (35% vs 24%) [8]. A prospective cohort study of older patients who underwent orthopaedic surgery in Taiwan found that postoperative delirium was significantly associated with a deterioration in functional status at 6 and 12 months postoperatively [9]. Another retrospective study in South Korea showed that people who developed delirium after hip fracture surgery had a higher mortality rate at 24 months of follow-up than those who did not develop delirium (36% vs 12%, $p = 0.032$) [6].

There are several risk factors for postoperative delirium; including older age, smoking, alcohol use, multiple comorbidities, medications, and impaired preoperative cognitive and functional status [10]. Many of these factors are not modifiable; however, medications are potentially modifiable [11]. One systematic review reported that the risk of developing delirium was increased by three-fold with the use of benzodiazepines (odds ratio [OR] = 3.0, 95% confidence interval [CI] 1.3–6.8) compared to people who were not taking these medicines [12]. A retrospective cohort study found that polypharmacy, defined as using five or more long-term medicines, was significantly associated with delirium (OR = 2.33, 95% CI 1.23–4.41) [13]. A systematic review that assessed the association between preoperative medication use and postoperative delirium showed that the use of psychoactive medicines as a group generally increased the risk of developing delirium by two-fold to seven-fold [14]. Evidence regarding the association between preoperative opioids and postoperative delirium showed mixed results [14], with some studies showing an increased risk of postoperative delirium associated with opioid use [15] and others showing no association [16].

The systematic review, which summarised results on the effect of preoperative medicines on postoperative delirium, revealed that most of the evidence was derived from studies that considered medicines as one of many potential predicators of delirium [14]. The majority of previous studies were not designed to investigate the effects of preoperative use of a specific medication or medication class on postoperative delirium. The studies lacked specificity in terms of medicine types, making it difficult to develop evidence-based recommendations about which individual medicines are associated with greatest delirium risk in clinical practice. This study was designed to address this research gap and examine the association between preoperative medication use and postoperative delirium so that delirium risk by medicine type could be determined for three classes of medicines acting on the central nervous system (CNS); benzodiazepines, opioids and antidepressants. The aim of this study was to determine the risk of individual classes of medicines used preoperatively on delirium following hip or knee surgery.

2 Methods

A matched case-control study was conducted using data from the Australian Government Department of Veterans' Affairs (DVA) healthcare claims database. The DVA claims database contains details of all prescription medicines, medical and allied health services, and hospitalisations provided to veterans for which DVA pays a subsidy. In 2019, the data file contained records for a treatment population of approximately 207,000 members of the veteran community [17]. Medicines are coded in the DVA claims dataset according to the World Health Organization Anatomical Therapeutic Chemical classification [18] and the Schedule of Pharmaceutical Benefits item codes [19], and hospitalisations are coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) [20].

The source population for this study was people aged 65 years or older who were admitted to hospital between 2000 and 2019 for hip or knee surgery. Patients who underwent arthroplasty or revision of arthroplasty of hip or knee were identified by ICD-10-AM procedure codes (4931800, 4931900, 4932100, 4951800, 4952100, 4951900, 4952400,

4953400, 4955400, 4932400, 4932700, 4933000, 4933300, 4933600, 4933900, 4934200, 4934500, 4934600, 4952700, 4953000, 4953300, 4954500, 4954800, 4955100, 4955400) [20]. The cases were all people in the source population who developed delirium within 7 days as recorded in the hospital coding record following knee or hip surgery and people in the same population without delirium served as controls. Delirium was identified using the 2016 ICD-10-AM code for delirium (F05) [20]. Each case was matched with three controls of the same sex, age at date of admission (± 2 years) and year of admission (± 2 years). Ethics approval was obtained from the Departments of Defence and Veterans' Affairs Human Research Ethics Committee (Ethics Approval Reference Number E015/013) and the University of South Australia Human Research Ethics Committee.

Exposure to medicines from three medication classes at the time of admission for hip or knee surgery was assessed for the cases and controls. The three medication classes were: benzodiazepines (N05B, N05C), opioid analgesics (N02A, R05DA04) and antidepressants (N06A). Prescription duration for dispensed medicines is not recorded in the DVA database. The exposure duration for each medicine was estimated by identifying the time period within which 75% of people returned for a repeat dispensing. This method to determine exposure has been used in pharmacoepidemiology research where duration of supply is not available in a dataset [21, 22]. Exposure of patients to medicines at the time of hospital admission was determined based on their date of hospital admission and the exposure duration estimate for the last date of medicine supply prior to admission. That is, if the time between the hospital admission date and the last dispensing date prior to admission was less than or equal to the exposure duration estimate, then the patient was considered to be exposed to the medicine at the time of hospital admission.

Patient characteristics assessed at the time of hospital admission included age, sex, residential status (living in the community or an aged care facility), dementia status and socioeconomic status based on Australian Bureau of Statistics' socioeconomic indexes for areas [23]. Dementia status was determined by using supply of cholinesterase inhibitors (donepezil [Anatomical Therapeutic Chemical code N06DA02], rivastigmine [N06DA03] galantamine [N06DA04], memantine [Anatomical Therapeutic Chemical code N06DX01]) or risperidone for behavioural and psychological symptoms of dementia (Pharmaceutical Benefits item codes 08789N, 09293D, 01842Y, 08787L, 08788M, 08790P, 08791Q) as a proxy for dementia [24]. We also used hospitalisation records with a primary or secondary diagnosis of dementia in Alzheimer disease (ICD code F00), vascular dementia (F01), dementia in other diseases (F02), unspecified dementia (F03), delirium superimposed on dementia (F051) or Alzheimer disease (G30) to identify people with dementia. Hospitalisations for psychoses (F204, F313–15, F341, F412, F432), diabetes (E102–E108, E112–E118, E122–E128, E132–E138, E142–E148, E890) and alcohol abuse (F11–F16, F18, F19) in the 2 years period prior to surgery were identified.

The proportions of patients exposed to medicines of interest at the time of admission for surgery were compared in cases and controls. We used conditional logistic regression to determine the association between preoperative medicine use and postoperative delirium. Crude ORs and 95% CIs were first calculated for the medicines investigated both at a medication class and at an individual medicine level. The conditional logistic models were then adjusted for covariates including age, sex, type of surgery, residence, dementia status at admission, hospitalisation histories for psychoses, alcohol abuse, diabetes and comorbidity as measured by the Elixhauser Comorbidity Index [25]. The number needed to treat to harm was calculated for the overall population and for the age groups 85 years or older, based on the ORs and delirium rates in patients unexposed to individual medicines using the formula by Bjerre and LeLorier [26]. We used SAS version 9.4 to analyse the data (SAS Institute, Cary, NC, USA).

3 Results

A total of 2614 patient cases with postoperative delirium were matched by sex, age (±2 years) and year of admission (± 2 years) with 7842 controls without postoperative delirium. The median age for cases and controls was 88 years and people aged 85 years or older comprised 71.8% of cases and 71.0% of controls. More cases than controls were living in a residential aged care facility prior to admission ($p < 0.001$) and had dementia at the time of admission ($p < 0.001$) (Table 1).

The prevalence of exposure to benzodiazepines (odds ratio [OR] = 1.20, 95% CI 1.05–1.37) and antidepressants (OR = 1.64, 95% CI 1.47–1.83) prior to surgery was significantly higher in cases than in controls. Cases were less likely to be taking opioids (OR = 0.83, 95% CI 0.72–0.96) compared with controls. Exposure to any of these three classes of medications preoperatively was significantly higher in cases compared with controls (OR = 1.34, 95% CI 1.21–1.47, $p < 0.001$) at admission for hip or knee surgery.

When individual medicines were considered, cases were nearly twice as likely to be exposed to nitrazepam at the time of admission than controls (OR = 1.88, 95% CI 1.30–2.73, $p = 0.023$). Cases were also significantly more likely than controls to be exposed to nitrazepam (OR = 1.81, 95% CI 1.24–2.64), sertraline (OR = 1.50, 95% CI 1.20–1.87), mirtazapine (OR = 1.38, 95% CI 1.11–1.74), venlafaxine (OR = 1.42, 95% CI 1.02–1.98), citalopram (OR = 1.54, 95% CI

Table 1 Distribution of patient characteristics among cases and controls

Patient characteristic variable	Cases (n = 2614)	Controls (n = 7842)	P-value
Age, median (interquartile range)	88 (84–91)	88 (84–91)	1.00
Male sex, n (%)	1187 (45.4)	3561 (45.4)	1.00
Type of surgery, n (%)			
Knee	400 (15.3)	2380 (30.4)	< 0.001
Hip	2214 (84.7)	5462 (69.7)	
Residence, n (%)			
Residential aged care facility	768 (29.4)	1520 (19.4)	< 0.001
Community	1846 (70.6)	6322 (80.6)	
Socioeconomic status			
Lower	314 (12.0)	1249 (15.9)	< 0.001
Lower-middle	469 (17.9)	1567 (20.0)	
Middle	490 (18.8)	1425 (18.2)	
Middle-upper	487 (18.6)	1365 (17.4)	
Upper	834 (31.9)	2169 (27.7)	
Unknown	20 (0.8)	67 (0.9)	
Elixhauser score, mean (± standard deviation)	0.83 (±1.48)	0.61 (±1.23)	< 0.001
Dementia, n (%)	342 (13.1)	471 (6.0)	< 0.001

1.19–1.99), escitalopram (OR = 1.42, 95% CI 1.06–1.89) or fluvoxamine (OR = 5.01, 95% CI 2.15–11.68) at the time of admission. There was no significant difference between cases and controls in exposure to other individual medicines in the three classes at the time of admission (Table 2).

The numbers needed to treat to harm one additional patient were generally smaller for people aged 85 years or older compared with younger people, indicating that the harmful effect of medicines is more pronounced in the oldest age group (Fig. 1). The numbers needed to be treated to harm in the 85 years or older age group for one additional delirium case was 20 for sertraline, 17 citalopram, 19 mirtazapine and 10 for nitrazepam (Fig. 1, Table 2).

4 Discussion

4.1 Key Results

This case-control study examined the effect of preoperative CNS medicine use on postoperative delirium both at the individual medicine and class levels for CNS medications potentially associated with delirium. A significant difference between cases and controls was found regarding exposure to benzodiazepines prior to hip or knee surgery when analysed as a class (OR = 1.20, 95% CI 1.05–1.37). Benzodiazepines are hypothesised to induce delirium through increasing the inhibitory effect on gamma-aminobutyric acid receptors, one of the mechanisms assumed to be responsible for delirium [27]. Several studies in surgical and medical patients reported that benzodiazepine use increases the risk of delirium [12, 28–30]. Our result was in line with the finding of a previous study that reported an increased risk of postoperative delirium (RR = 2.10, 95% CI 1.23–3.59) in older patients who were taking benzodiazepines for longer than 1 year prior to surgery [28]. A case-control study of patients undergoing total joint arthroplasty found that patients who were taking benzodiazepines had an approximately ten-times higher risk of developing postoperative delirium (OR = 9.68, 95% CI 4.30–21.79) [29]. This large difference between the two studies could be because our study considered only preoperative use, whereas, the previous study focused on use of benzodiazepines during hospital stay, from the day of surgery to the incidence of postoperative delirium.

4.2 Preoperative Benzodiazepine Use and Postoperative Delirium

Our study showed that cases were twice as likely to be exposed to nitrazepam prior to admission for hip or knee surgery than controls (OR = 1.81, 95% CI 1.24–2.64, p = 0.002) unlike other benzodiazepines where significant differences were not observed. This result is in agreement with a previous matched case-control study that reported a higher association between postoperative delirium and postoperative exposure to long-acting benzodiazepines than to shorter or intermediate-acting benzodiazepines [16]. The association between preoperative diazepam use and postoperative delirium was not found to be statistically significant despite being a long-acting benzodiazepine such as nitrazepam. A previous study found that nitrazepam exerts a greater degree of sedation compared with diazepam [31]. Our results

Table 2 Use of medicines prior to hospital admission for hip or knee surgery in cases and controls by type of medicine

Medicine (ATC code)[b]	Cases ($n = 2614$)	Controls ($n = 7842$)	Crude OR (95% CI)	Adjusted OR[a]		NNTH
				(95% CI)	*P*-value	
Any benzodiazepine (N05CD, N05BA) [yes vs no]	400 (15.3%)	1015 (12.9%)	1.22 (1.07–1.38)	1.20 (1.05–1.37)	**0.007**	106
Temazepam (N05CD07)	210 (8.0%)	576 (7.4%)	1.10 (0.94–1.30)	1.03 (0.87–1.23)	0.720	–
Oxazepam (N05BA04)	98 (3.7%)	237 (3.0%)	1.25 (0.99–1.60)	1.22 (0.96–1.60)	0.105	–
Nitrazepam (N05CD02)	48 (1.8%)	90 (1.2%)	1.60 (1.13–2.28)	1.81 (1.24–2.64)	**0.002**	26
Diazepam (N05BA01)	40 (1.5%)	104 (1.3%)	1.12 (0.78–1.62)	1.30 (0.88–1.92)	0.181	–
Alprazolam (N05BA12)	15 (0.6%)	45 (0.6%)	0.96 (0.54–1.71)	0.94 (0.51–1.73)	0.843	–
Any opioid (N02A, R05DA04) [yes vs no]	338 (12.9%)	1007 (12.8%)	1.01 (0.88–1.15)	0.83 (0.72–0.96)	**0.014**	–
Oxycodone (N02AA05, N02AA55)	113 (4.3%)	299 (3.8%)	1.14 (0.91–1.43)	0.91 (0.71–1.15)	0.420	–
Codeine (N02AA59, R05DA04)	29 (1.1%)	134 (1.7%)	0.67 (0.47–1.021)	0.72 (0.47–1.11)	0.136	–
Buprenorphine (N02AE01, N07BC01, N07BC51)	130 (5.0%)	325 (4.1%)	1.19 (0.97–1.47)	1.00 (0.81–1.26)	0.954	–
Tramadol (N02AX02)	38 (1.5%)	173 (2.2%)	0.64 (0.45–0.91)	0.65 (0.45–0.94)	**0.021**	–
Fentanyl (N02AB03)	36 (1.4%)	99 (1.3%)	1.09 (0.75–1.60)	0.90 (0.60–1.36)	0.622	–
Morphine (N02AA01)	13 (0.5%)	27 (0.3%)	1.45 (0.75–.84)	1.19 (0.61–2.46)	0.638	–
Tapentadol (N02AX06)	14 (0.5%)	38 (0.5%)	1.11 (0.59–2.08)	1.00 (0.52–1.95)	0.993	–
Any antidepressant (N06A) [yes vs no]	798 (30.5%)	1553 (19.8%)	1.80 (1.62–1.99)	1.64 (1.47–1.83)	**< 0.001**	38
Amitriptyline (N06AA09)	103 (3.9%)	261 (3.3%)	1.16 (0.92–1.46)	1.17 (0.91–1.50)	0.128	–
Sertraline (N06AB06)	145 (5.5%)	250 (3.2%)	1.75 (1.42–2.16)	1.50 (1.20–1.87)	**< 0.001**	43
Mirtazapine (N06AX11)	140 (5.4%)	258 (3.3%)	1.68 (1.36–2.07)	1.38 (1.11–1.74)	**0.006**	57
Venlafaxine (N06AX16)	61 (2.3%)	120 (1.5%)	1.54 (1.13–2.10)	1.42 (1.02–1.98)	**0.039**	38
Citalopram (N06AB04)	117 (4.5%)	181 (2.3%)	2.00 (1.56–2.54)	1.54 (1.19–1.99)	**0.001**	40
Escitalopram (N06AB10)	82 (3.1%)	167 (2.1%)	1.50 (1.14–1.96)	1.42 (1.06–1.89)	**0.019**	51
Paroxetine (N06AB05)	34 (1.3%)	85 (1.1%)	1.20 (0.81–1.80)	1.02 (0.66–1.56)	0.939	-
Doxepine (N06AA12)	27 (1.0%)	69 (0.9%)	1.18 (0.75–1.85)	1.30 (0.81–2.09)	0.280	–
Dothiepin (N06AA16)	22 (0.8%)	45 (0.6%)	1.47 (0.88–2.46)	1.58 (0.90–2.77)	0.177	–
Desvenlafaxine (N06AX23)	20 (0.8%)	40 (0.5%)	1.52 (0.88–2.64)	1.37 (0.76–2.44)	0.282	–
Duloxetine (N06AX21)	20 (0.8%)	33 (0.4%)	1.82 (1.04–3.17)	1.74 (0.97–3.11)	0.067	–
Fluoxetine (N06AB03)	17 (0.7%)	38 (0.5%)	1.84 (1.05–3.21)	1.42 (0.76–2.64)	0.274	–
Fluvoxamine (N06AB08)	17 (0.7%)	13 (0.2%)	5.10 (2.34–11.14)	5.01 (2.15–11.68)	**< 0.001**	5
Moclobemide (N06AG02)	9 (0.3%)	18 (0.2%)	1.50 (0.67–3.34)	1.98 (0.86–4.57)	0.111	–
Nortriptyline (N06AA10)	7 (0.3%)	13 (0.2%)	1.62 (0.65–4.05)	0.84 (0.31–2.25)	0.725	–
Imipramine (N06AA02)	10 (0.4%)	30 (0.4%)	1.00 (0.49–2.05)	1.15 (0.53–2.49)	0.727	–
Mianserin (N06AX03)	5 (0.2%)	15 (0.2%)	1.00 (0.36–2.75)	1.02 (0.31–3.40)	0.970	–
Any of the above medicine groups (yes vs no)	1166 (44.6%)	2773 (35.4%)	1.48 (1.35–1.63)	1.34 (1.21–1.47)	**< 0.001**	74

ATC Anatomical Therapeutic Chemical, *CI* confidence interval, *NNTH* numbers needed to treat to harm, *OR* odds ratio, – indicates NNTH not calculated for non-significant differences

Bold indicates significant *p*-values

[a]Adjusted for age, sex, surgery type, residence, dementia, hospitalisation histories for diabetes mellitus, psychoses, alcohol abuse and Elixhauser Comorbidity Index

[b]Only medicines used by at least ten patients were included in the models for individual medicines

suggest that the degree of sedation caused by the specific benzodiazepine agent could also be a factor that determines the associated risk in inducing delirium.

Even though there are several studies that reported the effect of individual benzodiazepines on delirium [2, 16, 32, 33], none determined the effect of preoperative use of benzodiazepines on postoperative delirium. In one study involving patients undergoing hip fracture surgery, perioperative midazolam use was shown to increase the risk of postoperative delirium [2]. In medical patients admitted to the intensive care unit, use of lorazepam in the previous 24

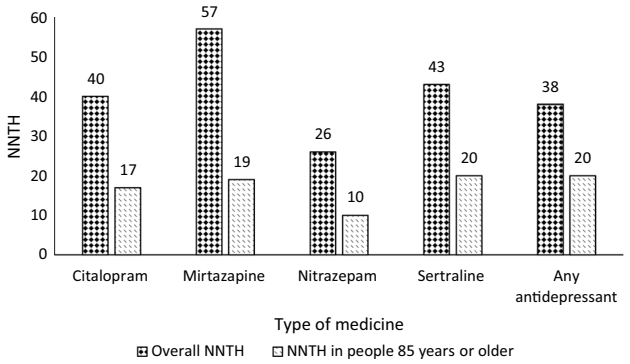

Fig. 1 Numbers needed to treat to harm (NNTH) with the central nervous system medicines preoperatively for one additional patient to develop delirium postoperatively

hours prior to assessment was associated with a higher risk of developing delirium (OR = 1.2, 95% CI 1.1–1.4) [32].

4.3 Preoperative Opioid Use and Postoperative Delirium

The current study also revealed that the prevalence of exposure to opioids prior to surgery was not associated with an increased risk of delirium, whether analysed as a group or by individual agents. This is similar to a finding from a study of 472 patients undergoing noncardiac surgery, which showed no association between long-term opioid use and postoperative delirium [34]. It was also reported in an earlier nested-case control study in patients undergoing various types of surgery including orthopaedic surgery that opioid use was not associated with delirium following the surgical procedures [16]. Untreated pain is a risk factor for postoperative delirium [35], thus appropriate pain management with opioids may explain the findings with no or lower association between postoperative delirium and the use of these medicines. However, there are several other studies that contradict our finding [14, 15, 36]. A retrospective study of 954 patients who underwent total knee arthroplasty found that the use of opioids for longer than 3 months prior to the procedure was significantly higher in patients who developed postoperative delirium (66.6%) compared with the non-delirium group (9%) [36]. Another cohort study involving 500 patients for elective surgery found that patients who took narcotic analgesics immediately before admission were more likely to develop postoperative delirium (OR = 2.7, 95% CI 1.37–5.3) compared with those who did not receive opioids [14].

4.4 Preoperative Antidepressant Use and Postoperative Delirium

Antidepressants as a class were twice as likely to be taken prior to hip or knee surgery by cases than by controls (OR = 1.64, 95% CI 1.47–1.83, $p < 0.001$). This finding is in agreement with results of previous studies showing significant associations between antidepressants and delirium [37–40]. At the individual medicine level, our study also revealed that a significantly higher proportion of cases were exposed to mirtazapine, sertraline, venlafaxine, escitalopram, citalopram or fluvoxamine prior to admission for surgery than controls.

There is opportunity to temporarily cease or stop medicines with a significant risk of inducing delirium including these antidepressants and nitrazepam or change to safer alternatives or non-pharmacological management options in older patients prior to surgery. However, this must be planned well in advance because these medicines need to be weaned gradually over time, with abrupt withdrawal having adverse effects including delirium [41, 42]. In people undergoing elective procedures, tapering may be practicable as clinicians and patients would have sufficient time to take actions before the date of surgery. Moreover, clinicians should make sure that the conditions that still require treatment are appropriately treated with alternative options. For instance, depression must be managed well while making regimen changes to antidepressants as evidence shows that depression itself is a predictor of postoperative delirium [43, 44].

4.5 Strengths and Limitations

Although this study produced evidence by type of individual medicines that could help clinicians to make informed decisions in their practice, it has some limitations that need to be taken into account while interpreting the results. First, the study did not consider the specific anaesthetic agents used for surgery, medications prescribed or discontinued during hospital admission and the length of surgery. This might underestimate the number of people exposed to the medicines investigated, especially benzodiazepines and opioid analgesics that are commonly used as premedication in surgery. Second, the doses and the duration of use of each medicine before the surgery and substance abuse were not assessed in this study. Previous studies have shown that the risk of postoperative delirium increases with dose [16] and with the duration of exposure [35, 45]. Even though we adjusted our results for dementia, we could not control for the presence of other forms of cognitive disability including mild cognitive impairment because of the unavailability of data in our dataset. Moreover, we were not able to evaluate

the use of all individual medicines in each class owing to the small number of people taking some of the medicines and some of our non-significant findings may be because the study had insufficient power to assess the effect. Further studies with a larger sample size are required to investigate the effects of the remaining medicines on postoperative delirium.

5 Conclusions

This study shows that the prevalence of preoperative exposure to benzodiazepines and antidepressants as a class was significantly different between people who developed delirium after hip or knee surgery and those who did not develop delirium following the procedures. Cases were twice as likely to be exposed to antidepressants prior to admission for surgery than controls. Cases were more likely to be exposed to nitrazepam, mirtazapine, sertraline, venlafaxine, escitalopram, citalopram or fluvoxamine than controls at the time of admission. This evidence suggests recommendations about medication use at the time of surgery are warranted. Future prospective studies with a bigger sample size should determine the risk of preoperative use of other medicines not investigated in this study and evaluate the effects of dose and duration of exposure.

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Declarations

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Conflicts of interest/Competing interests None of the authors has any conflicts of interest related to this study.

Ethical approval Ethics approval was obtained from the University of South Australia, and the Departments of Defence and Veterans' Affairs Human Research Ethics Committees.

Consent to participate This observational study was based on administrative claims data and did not require patient consent. Patients and/or the public were not involved.

Consent for publication Not applicable.

Availability of data and material Unpublished data related to this study can be requested from the corresponding author by e-mail.

Code availability Not applicable.

Author contributions GMK: study design, data analysis and interpretation and drafting of the manuscript. EER, TAN, NLP, and LMKE: study design, data interpretation and critical revision of the manuscript for important intellectual content. All authors read and approved the final version of this article.

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