

Preoperative anxiolytic and antidepressant medications as risk factors for increased opioid use after total knee arthroplasty: a matched retrospective cohort analysis

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Abstract

Background: Previous literature has suggested that the presence of anxiety or depression may be linked to increased postoperative pain. The objective of this retrospective analysis was to assess whether patients who use anxiolytics or antidepressants preoperatively were associated with worse acute pain outcomes after elective total knee arthroplasty (TKA).

Methods: A chart review of patients who underwent TKA at our institution was conducted. The primary outcome was mean opioid use in oral morphine equivalents (OME) on the day of surgery (POD 0) through postoperative day 1 (POD1). Secondary outcomes included median pain scores during hospitalization, the need for an acute pain service (APS) consultation, and mean length of stay. Patients were matched (1 : 1) according to multiple factors including age, surgical anaesthesia type, preoperative pain scores, and placement of a single-injection adductor canal block.

Results: 83 patients were successfully matched in each group. During POD0-1, patients with anxiolytic or antidepressant prescriptions required a mean of 101.36 mg OME (SD = 66.89), compared to 86.78 mg (SD = 62.66) among patients without use of these medications ($P = 0.011$) (estimate of average treatment effect of +22.86). Similarly, these patients were more likely to report a slightly higher median pain score than patients not taking anxiolytics or antidepressants (4.00 [SD 1.95] vs. 3.77 [SD 2.01], $P = 0.031$) (estimate of average treatment effect of +0.55). However, there were no differences in hospital length of stay, acute pain service consultation, visit to an Emergency Department within one week of discharge, and readmission within one week of discharge. There were also no differences in outcomes when comparing patients with a history of anxiety or depression to those without this history.

Conclusions: The use of chronic anxiolytics or antidepressants was associated with increased opioid use and slightly higher pain scores in patients undergoing TKA. These associations were independent of a medical diagnosis of anxiety or depression. The moderate increase in perioperative opioid consumption and pain scores was not associated with an increase in APS consultations or length of stay.

Key words: anxiolytics, antidepressants, pain, knee arthroplasty.

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Approximately 10–20% of patients undergoing knee replacement surgery can present with a history of anxiety or depression [1]. Studies suggest that the presence of a mood disorder can influence recovery after surgery [2–4] and may be associated with increased cost and length of stay after arthroplasty [5]. Patients with anxiety may have an increased risk of poor pain control and worse physical performance after orthopaedic surgery [6–9]. Likewise, patients with a diagnosis of depression may be at increased risk of higher pain scores [10–12]. However, other studies have found no association

between the presence of these mood disorders and adverse postoperative outcomes [1, 13–15], or have found that disease severity influences outcomes [16, 17]. Given the variability in study methodology in identifying patients who have been classified as having either or both of these mood disorders, some authors have instead utilized anxiolytic or antidepressant medication prescription as a surrogate marker for the diagnoses as well as independent risk factors for negative outcomes. Several studies have suggested that patients who consume anxiolytics and/or antidepressants may be at increased

risk of persistent/chronic postoperative pain, long-term opioid use, or worse, or prolonged recovery compared to patients not using these medications preoperatively [12, 18–24]. However, the effect of these medications on acute postoperative pain has not been well-defined, and some studies have provided conflicting results [25]. In this study, we sought to assess whether preoperative use of anxiolytics or antidepressants was associated with acute pain outcomes after total knee arthroplasty (TKA). Our hypothesis was that patients who use chronic anxiolytics or antidepressants prior to TKA would have higher perioperative opioid consumption compared to patients who did not use these medications.

METHODS

Institutional review board (IRB) approval was obtained for this study (Mayo Clinic IRB #20-001163); the requirement for written and informed consent was waived by the IRB. Because this trial was a retrospective cohort study, clinical trial registration was not required. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies were followed. All records of patients who underwent total knee arthroplasty at Mayo Clinic Florida starting in 2019 were reviewed until the required number of patients specified by our power analysis were reached. Records were excluded if any of the following exclusion criteria existed: age less than 18 years; incomplete documentation for the primary or secondary outcome variables; enrolment in any other clinical study; revision surgery; bilateral TKA; unicompartement surgery; or patients who had any other procedure performed concurrently. Patients with chronic preoperative opioid use (defined as daily intake of any opioid medication for at least 4 weeks prior to surgery) or chronic pain conditions such as fibromyalgia were excluded.

Patient data including age, gender, body mass index (BMI), surgical anaesthesia type (spinal vs. general), preoperative pain scores (numerical rating scale of 0–10), placement of a single-injection adductor canal block, perioperative midazolam use, and perioperative ketamine use were collected. Additionally, preoperative anxiolytic or antidepressant use was recorded. Use was defined as a documented active prescription for either medication class for at least 4 weeks prior to surgery in the electronic medical record. At our institution, all surgical patients visit our preoperative anaesthesia clinic prior to surgery. During this visit, staff verify all prescriptions and confirm the patient's current use of medications. If a prescription is no longer valid or if the patient does not take the prescribed medication for any rea-

son, said medication is classified as inactive. Thus, only active anxiolytic and antidepressant prescriptions were used for this study. These included benzodiazepines, tricyclic antidepressants, antipsychotic drugs (in the absence of a history of psychosis), norepinephrine/dopamine reuptake inhibitors, serotonin partial agonists, selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), antiepileptics (in the absence of a history of seizures), tetracyclic antidepressants, and monoamine oxidase inhibitors. A similar approach was utilized in the recording of a medical history of anxiety or depression in the electronic medical record.

Outcomes

The primary outcome of this study was mean postoperative opioid use (in oral morphine equivalents, OME) from entry into the hospital ward on postoperative day 0 (POD0) to 07:00 on postoperative day 2 or hospital discharge, whichever occurred sooner. Secondary outcomes included median pain scores with activity during entire hospitalization (as measured on a 0–10 numerical scale), the need for acute pain service consultation during hospital stay, mean length of stay (LOS) in days, incidence of emergency department (ED) visit within one week of discharge, and readmission within one week of discharge.

Perioperative course

All included patients underwent the usual total knee arthroplasty protocol at our institution. This included the use of systemic analgesia consisting of oral acetaminophen 1000 mg and celecoxib 400 mg (barring contraindications), intravenous dexamethasone 10 mg, and a spinal anaesthetic if not contraindicated or refused by the patient. Three of the 6 total joint surgeons request single injection adductor canal peripheral nerve blockade for TKA. Spinal anaesthetic, when utilized, consisted of 10 to 12.5 mg of preservative-free isobaric bupivacaine. No intrathecal opioid was administered in any anaesthetic. In the recovery area, patients were administered hydromorphone at the discretion of the anaesthesia team based on numerical pain score ratings. The perioperative period was defined as the time from anaesthesia start (or placement of preoperative nerve block, if applicable) to time of exit from the post-anaesthesia care unit (PACU). Patients were discharged from the PACU per usual criteria. After exit from the PACU, analgesic management followed a TKA protocol that included scheduled oral acetaminophen 1000 mg every 6 hours and celecoxib 200 mg every 12 hours, along with on-demand oxycodone as needed. Escalation of analgesia to include oral or intravenous hydro-

morphone or other analgesics was at the discretion of the surgical team. All postoperative opioids were counted for the purposes of this study. Postoperative days were defined as follows: POD0 was defined as starting at time of entry into the wards to 06:59 on the first morning after surgery; POD1 was defined as 07:00 on the first morning after surgery until 06:59 on the second morning after surgery; POD2 was defined as 07:00 on the second morning after surgery until 06:59 on the third morning after surgery, and so on.

Statistical analysis

Based on opioid use patterns in other studies utilizing similar analgesic methods as our practice [26], we assumed a mean opioid intake of 90 OME during the first 48 hours after surgery. We aimed to detect a difference of 30 mg of OME between our 2 study groups. We assumed a standard deviation (SD) of 70, a probability of type I error (alpha) of 0.05, and power of 75%. Given these values and assumptions, we calculated that a minimal sample size of 76 patients per group would be required to detect a 30 mg difference in OME. We calculated propensity scores to match (1 : 1) patients for 1) those that had preoperative anxiolytic or antidepressant prescriptions with those who did not, and 2) for those who had a history of anxiety or depression vs. those who did not. In both cases, a calliper of 0.06 was used [27–29]. Variables used for the match included age, sex, surgical anaesthesia type (spinal vs. general), preoperative pain scores (numerical rating scale 0–10), presence of chronic pain conditions, placement of a single-injection adductor canal block, perioperative midazolam use, and perioperative ketamine use. Additionally, a post-match analysis of BMI was conducted to ensure no significant differences in body mass index between the 2 groups. To assess the balance between the groups, standardized mean differences were calculated. For the analysis comparing patients with a history of anxiety or depression to those without that history, we controlled for use of anxiolytic or antidepressant prescriptions. Differences in outcomes were reported as means (for continuous outcomes) and odds ratios (OR) (for binary outcomes); standard deviations, 95% confidence intervals, and *P*-values were also reported. Estimates of average treatment effect were calculated. An estimate and 95% CI exclusive of 0, or an OR and 95% CI exclusive of 1 were considered statistically significant. All analyses were conducted using Stata/MP 17.0.

RESULTS

The initial dataset contained 308 patients who underwent a TKA starting in 2019. Of these 308 pa-

TABLE 1. Statistical matching model assessing preoperative anxiolytic or antidepressant prescription use vs. not, among patients undergoing primary total knee arthroplasty

Variable	Not matched				Matched			
	Preoperative anxiolytic or antidepressant prescription (<i>n</i> = 85)	No anxiolytic or antidepressant prescription (<i>n</i> = 223)	% bias	<i>P</i> -value	Preoperative anxiolytic or antidepressant prescription (<i>n</i> = 83)	No anxiolytic or antidepressant prescription (<i>n</i> = 83)	% bias	<i>P</i> -value
Age								
≤ 55	0.07	0.08	-3.50	0.788	0.07	0.09	-4.60	0.774
> 55 and ≤ 65	0.38	0.33	10.20	0.421	0.38	0.39	-2.50	0.873
> 65 and ≤ 75	0.45	0.35	20.00	0.115	0.45	0.39	12.40	0.432
> 75	0.10	0.23	-37.80	0.006	0.10	0.13	-10.00	0.467
Gender								
	0.24	0.46	-47.10	< 0.001	0.23	0.22	2.60	0.853
Anaesthesia type (spinal)	0.94	0.94	1.40	0.916	0.95	0.94	5.10	0.734
Nerve block placed in preop or PACU	0.10	0.07	8.50	0.496	0.10	0.06	13.20	0.389
Preoperative pain score	0.17	0.15	5.60	0.657	0.16	0.16	0.00	1.000
Perioperative midazolam administered	0.70	0.60	22.30	0.088	0.71	0.73	-5.10	0.730
Perioperative ketamine administered	0.02	0.01	7.60	0.524	0.01	0.00	9.00	0.319

PACU – post-anaesthesia care unit

TABLE 2. Primary and secondary outcomes based on exposure to preoperative anxiolytic or antidepressant prescription use among matched patients. Estimate of average treatment effect comparing exposure to anxiolytic or antidepressant prescriptions versus no exposure. Primary outcome presented as oral morphine equivalent (OME)

	Estimate of average treatment effect	Preoperative anxiolytic or antidepressant prescription (n = 83)	No anxiolytic or antidepressant prescription (n = 83)	P-value
Primary outcome		Mean (SD)	Mean (SD)	
Opioid use POD0-1, OME	(+) 22.86	101.36 (66.89)	86.78 (62.66)	0.011*
Secondary outcomes		Mean (SD)	Mean (SD)	
Median pain score during hospitalization	(+) 0.55	4.00 (1.95)	3.77 (2.01)	0.031*
Length of hospital stay, days	(+) 0.09	2.08 (0.81)	2.17 (0.87)	0.514
	OR	95% CI LCL	95% CI UCL	
Acute pain service consulted postoperatively	1.04	0.98	1.11	0.167
Emergency department visit within one week of discharge	1.00	0.95	1.04	0.854
Readmission to hospital within one week of discharge	1.00	0.97	1.03	0.944

SD – standard deviation, CI – confidence interval, LCL – lower confidence interval, UCL – upper confidence interval, POD0-1 – postoperative day 0 through 1, OR – odds ratio. Asterisks denote significant P-value.

tients, 85 (27.6%) had an active anxiolytic or antidepressant prescription prior to surgery. Eighty-three of these patients were successfully matched according to variables identified in Table 1, as described by Garrido *et al.* [28]. Body mass index was not statistically different between the 2 groups (31.9 vs. 32.4, $P = 0.70$). During POD0-1, patients with anxiolytic or antidepressant prescriptions required a mean of 101.36 mg OME (SD = 66.89), compared to 86.78 mg (SD = 62.66) among patients without use of these medications ($P = 0.011$, Table 2). Similarly, these patients were more likely to report a slightly higher median pain score than those patients not taking anxiolytics or antidepressants (4.00 [SD = 1.95] vs. 3.77 [SD = 2.01], $P = 0.031$). However, there were no other differences in evaluated outcomes (Table 2). Specifically, hospital length of stay (2.08 [SD = 0.81] vs. 2.17 [SD = 0.87], $P = 0.514$), acute pain service consulted (OR = 1.04, 95% CI: 0.98–1.11, $P = 0.167$), ED visit within one week of discharge (OR = 1.00, 95% CI: 0.95–1.04, $P = 0.854$), and readmission within one week of discharge (OR = 1.00, 95% CI: 0.97–1.03, $P = 0.944$) were not significantly different between the 2 groups.

To assess the potential influence of a history of anxiety or depression within this cohort, 50 patients who had a history of either of these diagnoses were matched with 50 patients who did not (Table 3). For this comparison, none of the outcomes of interest were different between the 2 groups (Table 4). Specifically, opioid use, median pain score, length of stay, acute pain service consultation, ED visit within one week of discharge, and readmission within one week of discharge were not significantly different between the 2 groups.

DISCUSSION

The results of this study suggest an association between preoperative anxiolytic or antidepressant medication use and a modest increase in mean postoperative opioid consumption on POD0-1. Previous studies have suggested that chronic exposure to anxiolytics prior to surgery may be associated with increased postoperative opioid use. For example, a cohort study by Rishel *et al.* [30] suggested that patients exposed to chronic anxiolytics were more likely to use opioids more than 90 days after surgery and had a 44% increase in opioid dose during that same period. Similarly, some studies have shown that patients who routinely took antidepressants prior to surgery had worse pain in the first few days after surgery compared to patients who did not take these medications [31, 32]. Few studies have examined the influence of anxiolytics or antidepressants as a single exposure variable on acute pain. Our study uniquely focused on exposure to either anxiolytics or antidepressants rather than a history of anxiety and/or depression for 2 reasons. First, anxiety- and depression-related disorders are not isolated from one another but rather can exist on a continuous spectrum. As such, patients who suffer from anxiety may benefit from antidepressant therapy and vice-versa. For example, duloxetine, venlafaxine, and escitalopram are efficacious in the treatment of adults with generalized anxiety disorder [33]. Second, the presence of a history of anxiety or depression may not be associated with increased opioid use after surgery. A recent logistic regression study successfully utilized exposure to either anxiolytics or antidepressants (rather

than medical history) as one of the predictive factors for prolonged opioid use after surgery [34]. Indeed, secondary analysis in our study suggested that the presence of a medical history of either anxiety or depression did not influence opioid use, pain scores, or risk of APS consultation.

The mechanism by which long-term use of anxiolytics or antidepressants could increase opioid use in the acute period after surgery is not clear. For benzodiazepines, a potential mechanism could be related to the neurotransmitter gamma-aminobutyric acid (GABA). Chronic benzodiazepine use has been associated with decreased postsynaptic GABA activity, which can result in increased excitatory neuron function and potentially decreased response to analgesic agents. Interestingly, a 2018 in vitro study suggested that opioids, through mu opioid receptor activation, may also cause changes in GABA receptor activity, which can lead to excitatory activity in the spinal dorsal horn [35]. Thus, an opioid – GABA receptor interaction may also be a potential pathway for altered response to analgesic agents among patients exposed to anxiolytics that function via GABA receptors. The potential mechanism by which chronic use of antidepressants could be associated with increased postoperative opioid use is more difficult to elucidate. The mechanism of action of SSRIs and SNRIs is complex and involves not only serotonin-related activity but also GABAergic and glutamatergic neurons [36]. Alterations in the levels of these neurotransmitters and/or their receptors may be a potential pathway for altered response to opioids. However, much research is needed in this area to postulate on potential mechanisms.

The estimate of average treatment effect of +22.86 mg OME on POD0-1 when patients were exposed to anxiolytics/antidepressants can be clinically significant, particularly in institutions and surgical centres that aim to decrease postoperative opioid use via the implementation of multimodal analgesia protocols. This increase in OME use could be associated with increased risk of postoperative nausea and vomiting and patient dissatisfaction, which can in turn affect critical post-arthroplasty outcome measures such as rapid postoperative ambulation. The authors also believe these results are worth reporting because of the potential increased risk of respiratory depression and sedation associated with increased opioid use, particularly in the setting of concurrent use of other medications such as benzodiazepines or gabapentinoids.

LIMITATIONS

There are several limitations in this study. First, this is a retrospective analysis and thus subject to selection bias and omitted variable bias. Although we

TABLE 3. Statistical matching model assessing history of anxiety or depression vs. not, among patients undergoing primary total knee arthroplasty

Variable	Not matched				Matched			
	History of anxiety or depression (n = 51)	No history of anxiety or depression (n = 257)	% bias	P-value	History of anxiety or depression (n = 50)	No history of anxiety or depression (n = 50)	% bias	P-value
Age								
≤ 55	0.08	0.08	0.10	0.994	0.08	0.08	0.00	1.000
> 55 and ≤ 65	0.31	0.35	-8.00	0.605	0.32	0.30	4.20	0.831
> 65 and ≤ 75	0.53	0.35	36.20	0.017	0.52	0.52	0.00	1.000
> 75	0.08	0.22	-40.10	0.021	0.08	0.10	-5.70	0.730
Gender								
Female	0.27	0.42	-31.10	0.050	0.26	0.26	0.00	1.000
Male	0.91	0.95	-16.30	0.242	0.90	0.92	-7.50	0.730
Anaesthesia type (spinal)								
Spinal	0.12	0.07	16.20	0.252	0.12	0.12	0.00	1.000
General	0.18	0.15	8.50	0.573	0.18	0.12	16.10	0.406
Nerve block placed in preop or PACU								
Yes	0.69	0.61	15.30	0.327	0.70	0.76	-12.50	0.504
No	0.02	0.02	3.00	0.838	0.02	0.02	0.00	1.000
Perioperative midazolam administered								
Yes								
No								
Perioperative ketamine administered								
Yes								
No								

PACU – post-anaesthesia care unit

TABLE 4. Primary and secondary outcomes based on history of anxiety or depression among matched patients. Estimate of average treatment effect comparing history of anxiety or depression versus none. Primary outcome presented as oral morphine equivalent (OME)

	Estimate of average treatment effect	History of anxiety or depression (n = 50)	No history of anxiety or depression (n = 50)	
Primary outcome		Mean (SD)	Mean (SD)	P-value
Opioid use POD0-1, OME (mean)	(+) 6.44	89.43 (60.35)	101.81 (51.48)	0.540
Secondary outcomes		Mean (SD)	Mean (SD)	P-value
Median pain score during hospitalization	(+) 0.07	4.14 (1.54)	4.48 (1.74)	0.827
Length of hospital stay, days (mean)	(+) 0.25	1.82 (0.80)	1.82 (0.66)	0.126
	OR	95% CI LCL	95% CI UCL	P-value
Acute pain service consulted postoperatively	0.98	0.94	1.03	0.469
Emergency department visit within one week of discharge	1.04	0.97	1.12	0.242
Readmission to hospital within one week of discharge	1.04	0.98	1.10	0.219

SD – standard deviation, CI – confidence interval, LCL – lower confidence interval, UCL – upper confidence interval, POD0-1 – postoperative day 0 through 1, OR – odds ratio.

successfully matched our study populations based on multiple variables that could influence the results, our analysis may be influenced by a variable that has not been controlled in the matching process.

Second, while we defined “preoperative use of anxiolytics or antidepressants” as daily intake during the 4 weeks immediately prior to the surgery, we did not control for duration of exposure beyond that timeframe. Thus, we recognize that in our analysis some patients may have been exposed to anxiolytics or antidepressants for a much longer period than others. However, we believe that our study reflects a realistic cohort of patients that may present for TKA.

Third, our institution’s use of a standardized post-arthroplasty multimodal analgesic protocol, including the use of local infiltration analgesia in every patient, probably contributes to low overall pain scores as well as modest opioid intake amongst the majority of our TKA patients. The efficacy of this regimen may therefore impact the magnitude of the outcome measures in our study.

Lastly, this study did not seek, nor was powered to detect, safety outcomes such as respiratory depression, altered mental status, or patient falls. These are all important outcome metrics that can be a consequence of opioid or benzodiazepine administration postoperatively. Future studies could assess the risk of safety outcomes after preoperative exposure to anxiolytics or antidepressants.

CONCLUSIONS

In our study, the use of chronic anxiolytics or antidepressants was associated with increased opioid use in patients undergoing TKA. These findings could have an implication on the potential risks for

patients who are taking these medications and undergo knee arthroplasty surgery. Future research could address whether this increase in opioid use results in any changes in safety outcomes.

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