# Antidepressant Use Is Linked to 4–6x Higher Opioid Abuse After Total Knee Arthroplasty

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INTRODUCTION:

Antidepressant medications—spanning selective serotonin reuptake inhibitors (SSRIs), tricyclics, monoamine oxidase inhibitors, and other agents—are widely prescribed in the aging population, including many patients undergoing total knee arthroplasty (TKA). While these medications are essential for managing psychiatric conditions, their physiologic effects—including platelet dysfunction, altered pain perception, and systemic immune modulation—may influence perioperative recovery and complications. Additionally, there is growing concern over pain management in this population. Patients on chronic antidepressants may experience heightened or prolonged postoperative pain, often leading to increased opioid analgesic prescriptions, which in turn may elevate the risk of opioid dependence or misuse after surgery.

Despite their prevalence, the effects of antidepressants on surgical outcomes remain poorly defined in the orthopedic literature. This study aimed to evaluate whether perioperative antidepressant use is associated with increased short- and long-term complications following TKA, including infection, thromboembolic events, prosthetic failure, pain-related interventions, and mortality.

METHODS:

We conducted a retrospective cohort study using the TriNetX Research Network, a federated database of deidentified electronic health records from U.S. healthcare systems. Adult patients undergoing primary TKA between 2005 and 2025 were identified using ICD-10 and CPT codes. Patients were grouped based on exposure to antidepressant medications (classified under ATC code N06AA), including SSRIs, monoamine reuptake inhibitors, monoamine oxidase inhibitors, and other antidepressants. Active prescription within 3 months before or after surgery defined perioperative exposure.

Propensity score matching (1:1) was performed to adjust for confounders, including age, sex, race, BMI, comorbidities, and concurrent medications. Outcomes were assessed at two time points: 90 days (short-term) and 5 years (long-term) postoperatively.

Short-term outcomes included opioid-related outcomes (prescription and abuse).sepsis, wound disruption, surgical site infection (SSI), infection, transfusion, thromboembolic events (DVT, PE, VTE), myocardial infarction (MI), liver failure, stroke, ED visits, readmission, and opioid-related outcomes (prescription and abuse).

Long-term outcomes included prosthetic joint infection (PJI), periprosthetic fracture (PPFx), revision TKA, mechanical loosening, osteolysis, articular wear, arthrofibrosis/stiffness, manipulation under anesthesia (MUA), lysis of adhesions (LOA), and mortality.

Statistical analyses included chi-square tests and independent t-tests. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. A two-sided P-value < 0.01 was considered significant.

RESULTS:

After matching, 106,516 patients were included in each cohort for short-term analysis and 44,251 for long-term analysis. Baseline characteristics were well balanced between groups (mean age 65.5–65.8 years, 69% female, BMI ~33; P > 0.05).

At 90 days, patients on antidepressants were significantly more likely to receive opioid prescriptions (85% vs. 80.5%; OR 1.05; P < 0.001) and to be diagnosed with opioid abuse (0.10% vs. 0.02%; OR 4.3; P < 0.001). These patients had a higher rate of emergency department visits (10.5% vs. 7.2%; OR 1.5; P < 0.001), but interestingly, there was no significant difference in readmission rates. They also had a significantly lower mortality rate (0.38% vs. 0.55%; OR 0.69; P < 0.001). Antidepressant users exhibited higher rates of multiple complications, as shown in Table 1.

At 5-year follow-up, antidepressant users were more likely to receive opioid prescriptions (96.1% vs. 89.6%; OR 1.07; P < 0.001) and to be diagnosed with opioid abuse (0.74% vs. 0.12%; OR 6.0; P < 0.001).

They also had significantly higher rates of periprosthetic fracture (PPFx) (2.4% vs. 1.2%; OR 1.9; P < 0.001), prosthetic joint infection (PJI) (4.5% vs. 2.5%; OR 1.8; P < 0.001), mechanical loosening (1.5% vs. 0.8%; OR 1.9; P < 0.001), and revision TKA (4.7% vs. 2.9%; OR 1.6; P < 0.001). Despite these complications, long-term mortality was still lower among antidepressant users (1.9% vs. 2.7%; OR 0.74; P < 0.001).

Notably, while the increase in opioid prescription rates among antidepressant users was relatively modest at both 90 days and 5 years (OR ≈ 1.0), the rate of opioid abuse was disproportionately elevated—ranging from four- to six-fold higher than non-users. This discrepancy suggests a heightened vulnerability to opioid misuse in this population, independent of baseline prescription volume.

DISCUSSION AND CONCLUSION:

Antidepressant use around the time of TKA is associated with significantly increased rates of opioid abuse—4 to 6 times higher than in non-users—despite only modest differences in opioid prescribing. These patients also experience higher rates of systemic and prosthetic complications yet exhibit lower mortality. This highlights the need for targeted

perioperative pain management and monitoring strategies in patients on chronic antidepressants. Future prospective studies are warranted to investigate the mechanisms underlying these associations and to identify modifiable risk factors that can optimize surgical outcomes for this vulnerable population.

**Table 1. 90 days outcomes**

| OUTCOME | ANTIDEPRESSANT GROUP (%) | CONTROL GROUP (%) | ODDS RATIO (95% CI)* |
|---|---|---|---|
| DVT | 1.4% | 1.1% | 1.3 |
| PE | 1.1% | 0.76% | 1.5 |
| IFP + | 1.2% | 0.7% | 1.76 |
| TRANSFUSION | 2.0% | 1.5% | 1.24 |
| SEPSIS | 0.78% | 0.44% | 1.8 |
| MI | 0.52% | 0.39% | 1.3 |
| STROKE | 0.75% | 0.43% | 1.7 |
| I&D | 0.4% | 0.2% | 2.2 |
| RENAL FAILURE | 2.3% | 1.5% | 1.5 |
| SSI | 0.3% | 0.16% | 1.8 |

*All P values < 0.001

+ IFP; Infection Following Procedure, I&D; Irrigation & Debridement