

# The Impact of Serotonin Reuptake Inhibitors on Infection and Nonunion Rates in Operatively Managed Tibial Shaft & Femoral Shaft Fractures: A 1-Year Propensity-Matched Analysis

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**INTRODUCTION:** The impact of serotonin reuptake inhibitors (SSRIs) on bone healing remains under-investigated within the orthopaedic literature. Although previous *in vivo* and *in vitro* murine studies have suggested that SSRIs may attenuate osteoblastic activity, no studies have posited SSRIs to affect nonunion rates in operatively treated tibial or femoral shaft fractures. Therefore, this study aims to compare postoperative infection, nonunion, and delayed union rates in patients prescribed SSRIs with operatively treated femoral and tibial shaft fractures versus a propensity-matched cohort of patients with operatively treated femoral and tibial shaft fractures who do not take SSRIs.

**METHODS:** The TriNetX Database was queried to identify patients prescribed SSRIs who sustained tibial or femoral shaft fractures and subsequently underwent operative intervention with either intramedullary nailing or open reduction internal fixation using plate fixation. Patient identification was performed using a combination of International Classification of Disease-10 (ICD-10), Current Procedural Terminology (CPT), and Veterans Administration Drug Classification codes. Patients were propensity-matched in a 1:1 ratio based on eight preoperative characteristics including: age at surgery, female sex, BMI, nutritional deficiency, nicotine dependence, cannabis-related disorders, diabetes, and race. Rates of infection, nonunion diagnosis, and repeat operative intervention for nonunion were analyzed at the 1-year mark.

## RESULTS:

A total of 36,013 patients with femoral shaft fractures and 32,705 patients with tibial shaft fractures who underwent operative treatment were initially identified. Amongst these cohorts, 3,515 patients with femoral shaft fractures prescribed SSRIs (FSSRIs) were matched with 3,515 patients not prescribed SSRIs (FnSSRIs). Similarly, 3,125 patients with tibial shaft fractures prescribed SSRIs (TSSRIs) were matched with 3,125 patients not prescribed SSRIs (TnSSRIs). At the 1-year mark, the FSSRIs group demonstrated a higher rate of reported infections compared to the FnSSRIs group ( $p < 0.0001$ ), but showed no significant difference in nonunion rates or procedures for nonunions ( $p = 0.083$  and  $p = 0.081$ , respectively). The TSSRIs group exhibited higher rates of nonunion ( $p = 0.0084$ ) and infections ( $p = 0.0051$ ) compared to the TnSSRIs group, but no significant difference in procedures for nonunions ( $p = 0.636$ ).

**DISCUSSION AND CONCLUSION:** Herein, we demonstrate that patients prescribed SSRIs may have an increased risk of infections following the operative treatment of femoral and tibial shaft fractures at 1 year. Additionally, patients with tibial shaft fractures prescribed SSRIs may have an increased risk of nonunion compared to those who do not take SSRIs. These findings suggest that SSRI use may be associated with increased infection rates and tibial shaft nonunion. Overall, our results underscore the potential adverse influence of SSRI therapy in orthopaedic fracture care, warranting further investigation and consideration of SSRI usage in the perioperative period

| Femoral Shafts Only      | Procedure for Nonunion | Nonunion Diagnosis | Delayed Union | Infection   |
|--------------------------|------------------------|--------------------|---------------|-------------|
| Plate w/o SSRI n = 1225  | 27 = 2.20%             | 34 = 2.78%         | 26 = 2.12%    | 52 = 4.25%  |
| Plate w SSRI n = 1225    | 47 = 3.84%             | 39 = 3.18%         | 22 = 1.80%    | 87 = 7.10%  |
| p                        |                        | 0.0182             | 0.5524        | 0.0022      |
| IMN w/o SSRI n = 2362    | 46 = 1.95%             | 70 = 2.96%         | 57 = 2.41%    | 74 = 3.13%  |
| IMN w SSRI n = 2362      | 65 = 2.75%             | 87 = 3.68%         | 51 = 2.16%    | 106 = 4.49% |
| p                        | 0.068                  | 0.1676             | 0.5592        | 0.015       |
| Combined w/o SSRI n=3515 | 85 = 2.42%             | 95 = 2.70%         | 76 = 2.16%    | 107 = 3.04% |
| Combined w SSRI n=3515   | 109 = 3.10%            | 120 = 3.41%        | 71 = 2.02%    | 184 = 5.24% |
| p                        | 0.0806                 | 0.0833             | 0.6768        | <.0001      |

| Tibia only               | Procedure for Nonunion | Nonunion Diagnosis | Delayed Union | Infection    |
|--------------------------|------------------------|--------------------|---------------|--------------|
| Plate w/o SSRI n = 944   | 55 = 5.83%             | 56 = 5.93%         | 38 = 4.03%    | 82 = 8.69%   |
| Plate w SSRI n = 944     | 51 = 5.40%             | 75 = 7.95%         | 51 = 5.40%    | 102 = 10.81% |
| p                        | 0.6892                 | 0.0853             | 0.158         | 0.1207       |
| IMN w/o SSRI n = 2286    | 78 = 3.41%             | 122 = 5.34%        | 95 = 4.16%    | 121 = 5.29%  |
| IMN w SSRI n = 2286      | 76 = 3.33%             | 167 = 7.31%        | 130 = 5.69%   | 155 = 6.78%  |
| p                        | 0.8698                 | 0.0062             | 0.0167        | 0.0347       |
| Combined w/o SSRI n=3125 | 110 = 3.52%            | 167 = 5.34%        | 153 = 4.90%   | 187 = 5.98%  |
| Combined w SSRI n=3125   | 117 = 3.74%            | 217 = 6.94%        | 166 = 5.31%   | 243 = 7.78%  |
| p                        | 0.636                  | 0.0084             | 0.455         | 0.0051       |