The Effect of Fluoxetine and Duloxetine on Lumbar Spine Fusion in a Rodent Model

Yunsoo Lee MD[1], Jeremy C. Heard BS[2], Teeto Ezeonu BA[1], Rajkishen Narayanan MD[1], Sebastian Fras BS[2], Evan Bradley BS[2], Goutham R. Yalla BS[2], Dessislava Z. Markova PhD[2], Alexander R. Vaccaro MD PhD MBA[1], Christopher K. Kepler MD MBA[1]
[1]Rothman Orthopaedic Institute at Thomas Jefferson University, Philadelphia, PA, United States
[2]Department of Orthopaedic Surgery, Thomas Jefferson University, Philadelphia, PA, United States
yunsoo.a.lee@gmail.com
Disclosures: YL (N), JCH (N), TE (N), RN (N), DZM (N), SF (N), EB (N), GRY (N), ARV (4, 6, 7a, 7b, 9), CKK (7a, 8)

INTRODUCTION: Pseudarthrosis after lumbar fusion has an incidence as high as 10% and is often a source of increased health care cost and patient morbidity, especially if revision surgery is warranted. Identifying factors that may contribute to pseudarthrosis thus can improve quality of care. Antidepressant use in spine surgery patients can be as high as 11-26% and emerging clinical data has demonstrated that certain types, specifically selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), may lead to increased rates of pseudarthrosis after spine surgery. While the impact of these medications on spinal fusion has not been established in an animal model, a mouse fracture model has demonstrated that SSRIs hindered osteogenic differentiation and mineralization during ossification. In contrast, some literature has suggested that SNRIs may improve bone mineral density and reduce pain in osteoporotic patients with low back pain. Hence, there is no clear consensus on the impact of SSRIs or SNRIs on spinal fusion. Given the prevalence of serotonergic antidepressant medications and their potential to affect fusion rates, there is a need to establish whether a relationship exists between these medications and pseudarthrosis after spine surgery.

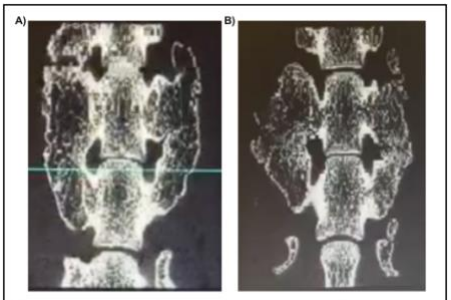

Figure 1. A) L4-5 bilaterally fused spine from the control group. Fusion score = 4. B) L4-5 bilaterally fused spine from the duloxetine group. Fusion score = 4.

METHODS: Experiments were conducted in accordance with the Institutional Animal Care and Use Committee. Drug Concentration: 10 mg/kg/day fluoxetine (SSRI) or 8 mg/kg/day duloxetine (SNRI) were delivered subcutaneously based on dose-effect relationships established by prior studies,[6,7] Experimental Model: 36 four-week-old male Sprague Dawley rats were divided into control (n=12), fluoxetine (n=12), and duloxetine (n=12) groups and underwent L4-L5 posterolateral lumbar non-instrumented fusion. Fluoxetine group rats were subcutaneously administered 10 mg/kg daily fluoxetine diluted in 0.9% normal saline, duloxetine group rats 8 mg/kg daily diluted in 0.9% normal saline and the control group rats 0.9% normal saline. Administration of these solutions was performed via subcutaneous injections, which began three weeks before surgery to simulate chronic use, as done in prior animal models[7], occurred daily, and continued until sacrifice at six weeks following surgery. Blood samples were obtained from the gingival vein before surgery, at 3 days after surgery, at 7 days after surgery, and at 14 days after surgery. V-PLEX assays were used to quantify cytokine levels in rat serum. Two independent observers assessed L4-L5 motion in flexion, extension, and lateral bending via manual palpation, where a score of 2 = no motion, 1 = restricted motion, and 0 = unrestricted motion was recorded. Rat spines were imaged via microtomography to determine bone volume fraction (BV/TV), bone mineral density (BMD), tissue mineral density (TMD), and fusion score. (**Figure 1**) A five point (0-4) scoring system was used: 4 = bilateral fusion, with radiographic density with connection at four points; 3 = unilateral fusion, with radiographic density at three points; 2 = not fused, with density present; 1 = not fused, with minimal density present on both sides; 0 = not fused, with density showing bone absorbed. IL-6 levels, BT/TV, BMD, and TMD were compared between groups with an ANOVA test for parametric data or a Friedman test for non-parametric data, with Bonferroni post-hoc comparison. Manual palpation and fusion scores were compared between groups using Fischer's exact test.

Table 1. Fusion Outcome Measures

	Control	Fluoxetine	Duloxetine
Fusion Rate (%)	83.3	88.9	66.7
Manual Palpation Score	1.75	1.67	1.33
Fusion Score	3.50	3.67	3.33
BV/TV	0.348	0.312	0.339
BMD (mg Ha/cm^3)	318.90	292.48	313.93
TMD (mg Ha/cm^3)	752.35	754.25	745.20

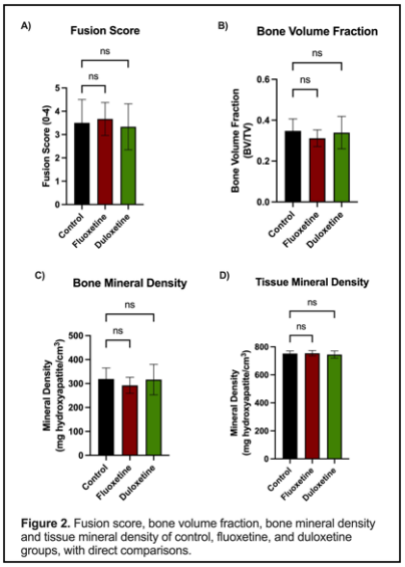

Figure 2. Fusion score, bone volume fraction, bone mineral density and tissue mineral density of control, fluoxetine, and duloxetine groups, with direct comparisons.

RESULTS: Outcomes were collected for control, fluoxetine, and duloxetine rats. (**Table 1**) There was no difference in fusion rates between groups (p=0.568). Manual palpation scores were not significantly different between the control and fluoxetine group (p=0.272), the control and duloxetine group (p=0.461), or the fluoxetine and duloxetine group (p=0.314). Fusion scores were not significantly different between the control and fluoxetine group (p=1.000), the control and duloxetine group (p=0.317), or the fluoxetine and duloxetine group (p=0.441). There was no significant difference in BV/TV (p=0.430), BMD (p=0.461), or TMD (p=0.589) between groups. (**Figure 2**) IL-6 levels in fluoxetine and duloxetine groups were significantly increased compared to the control group 3 days after surgery. IL-6 levels remained elevated compared to the control group in the duloxetine group at 7 days and at 14 days after surgery.

DISCUSSION: In this analysis, we found no difference in fusion rates between rats that received antidepressants and those that received a control solution, as well as between rats exposed to different antidepressants. Furthermore, there was no difference in bone quality metrics between groups. These findings contradict some clinical evidence that suggested an association between fluoxetine and pseudoarthrosis. Of the limited animal data in the literature, a mouse fracture model has demonstrated decreased bony trabecular thickness and bone mineral density after fluoxetine exposure. This raises the possibility that serotonin modulation may act through complex and distinct pathways to regulate bone formation in the context of fracture healing versus spine fusion. As in previous research, IL-6 levels were elevated in both antidepressant groups after surgery and remained high in the duloxetine group. Nevertheless, given the lack of difference in fusion rates and bone quality metrics, these results suggest that SSRIs and SNRI's may act on an IL-6 pathway that does not interact with the fusion process. Additional research is necessary to understand the mechanistic interaction between antidepressants and bone remodeling. Given the potential for multiple mechanisms of action, it would be valuable to have both in vitro and animal model data to elucidate whether these antidepressants are directly or indirectly affecting osteoblast and osteoclasts. Human clinical trials are needed to translate the results observed in this rodent model.

CLINICAL SIGNIFICANCE: Given that the prevalence of antidepressant usage is steadily rising in the United States, especially in spine surgery patients, it is important to understand their potential effects on fusion outcomes. While further prospective research is needed to comprehensively elucidate the long-term interactions between serotonergic agents and bone remodeling, these results optimistically suggest that antidepressants may not hinder spinal fusion and patients that take these medications are not at a higher rate of pseudarthrosis.