Selective Serotonin Re-Uptake Inhibitors Impair Fracture Healing

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Background/Purpose: Selective serotonin re-uptake inhibitors (SSRIs) are one of the most commonly prescribed antidepressants worldwide. Recent studies have linked chronic SSRI use to osteoporosis and an increased fracture risk. To date there are no studies investigating the effect of SSRIs on fracture healing. Here, we first examined the direct effect of SSRIs on osteoprogenitor cells (OPCs) in an in vitro setting followed by an in vivo analysis in a mouse model.

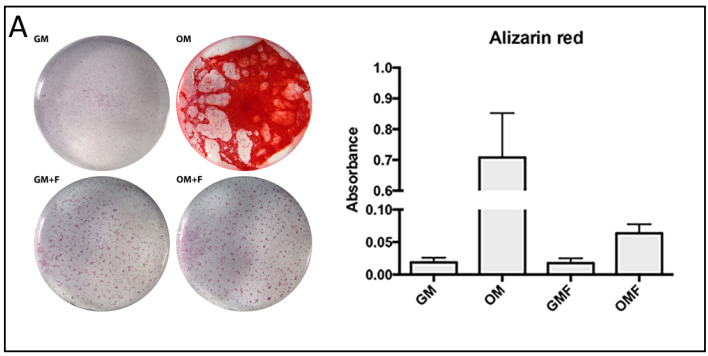
Methods: Bone marrow-derived OPCs were treated with 5, 10, 20, 50, or 100 μM of fluoxetine or control media. Cell proliferation and differentiation were assessed with standard tests including BrdU (bromodeoxyuridine), PCNA (proliferating cell nuclear antigen) staining, qPCR (quantitative polymerase chain reaction) for collagen type 1, runx2, osteocalcin, osteopontin, osterix, alkaline phosphatase (ALP), and Alizarin Red staining. For the in vivo experiments, adult C57/BL6 mice were treated with fluoxetine for 3 weeks prior to surgery. A 1-mm unicortical drill hole model was utilized to assess bone formation rate, callus volume, proliferation, differentiation, and remodeling in vivo. Mice were euthanized at 7 and 14 days postinjury.

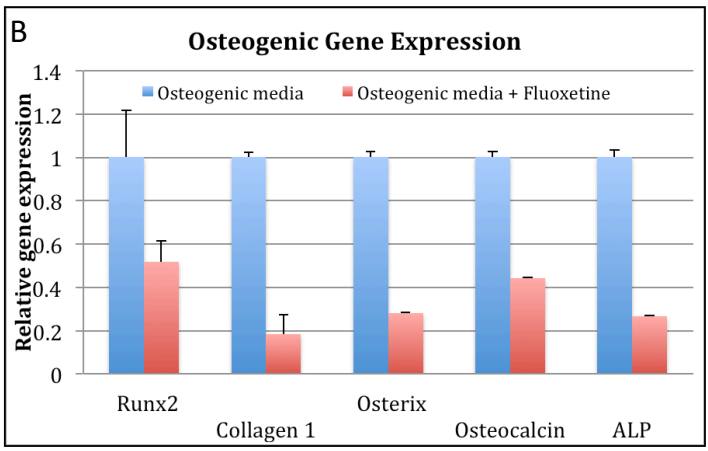
Results: Selective serotonin re-uptake inhibitors decrease osteoprogenitor cells proliferation and differentiation in vitro. In this study we sought to investigate if SSRIs had a direct effect on OPCs and primary osteoblasts. We harvested bone marrow-derived mesenchymal stem cells, using the well-accepted scrape and flush technique. Cells were plated on tissue culture plastic and split for the experiments once they had reached confluence. First, we tested whether treatment with fluoxetine affected the mitotic activity of these primary cell cultures. Treatment with fluoxetine resulted in a significant reduction of the proliferative activity compared to the control cells ($P = 0.032$). Next, we assessed whether differentiation was affected by fluoxetine treatment. We treated cells with osteogenic differentiation media ± fluoxetine for 7 days and then performed an alkaline phosphatase assay (Fig. 1A). After 7 days we found a significant reduction in alkaline phosphatase activity after fluoxetine treatment ($P = 0.009$). Quantitative PCR revealed that osteoblastic markers, such as runx2, collagen type 1, osterix, osteocalcin, and ALP were down-regulated in the fluoxetine-treated cells ($P < 0.002$) (Fig. 1B). Selective serotonin re-uptake inhibitors impede fracture healing in a murine fracture model. Finally, we examined the injured tibiae from control and SSRI-treated mice by microCT. Both at 7 and 14 days, cortical and trabecular BV/TV (bone volume/total volume)was significantly lower in mice treated with fluoxetine, confirming the in vitro findings in an in vivo model (Fig. 1C,D).

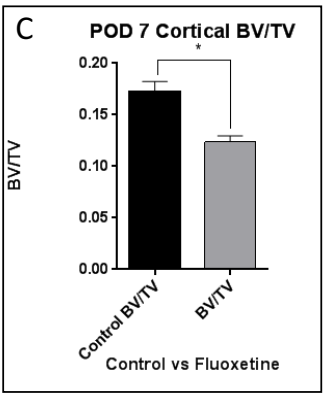
Conclusion: These experiments demonstrate that fluoxetine inhibits osteoprogenitor cell/osteoblast proliferation and impedes osteogenic differentiation both in vitro and in vivo. Animal research and human clinical data have unmistakably shown that chronic SSRI use leads

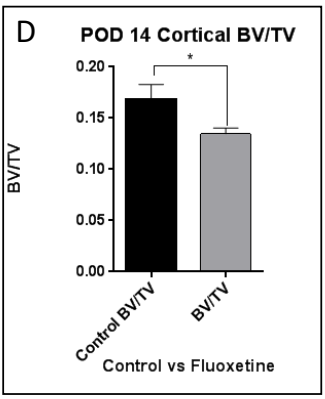
See pages 49 - 106 for financial disclosure information.

to osteoporosis, thus putting patients at risk for fragility fractures. If in fact SSRIs have a negative effect on bone regeneration after a fracture, then this patient cohort will be prone for delayed unions and nonunions. In addition, the discovery of the mechanism of action by which SSRIs inhibit bone formation may identify other, not yet identified therapeutic targets for future biomimetic approaches to enhance fracture healing.









The FDA has stated that it is the responsibility of the physician to determine the FDA clearance status of each drug or medical device he or she wishes to use in clinical practice.