# Fluoxetine Delivery for Wound Treatment Through an Integrated Bioelectronic Device – Pharmacokinetic Parameters and Safety Profile in Swine

Anthony Gallegos[1], Hsin-Ya Yang[1], Guillermo Villa-Martinez[1], Houpu Li[2], Ksenia Zlobina[3], Itidal Bazzi[1], Samhitha Sathyanarayanan[1], Moyasar Alhamo[1], Wan-Shen Hee[2], Prabhat Baniya[2], Narges Asefifeyzabadi[2], Tiffany Nguyen[2], Maryam Tebyani[2], Alexie Barbee[2], Kaelan Schorger[2], Sydnie Figuerres[2], Gordon Keller[2], Marcella Gomez[3], Athena Soulika[1,4], Min Zhao[5], Mircea Teodorescu[2], Marco Rolandi[2], Roslyn Rivkah Isseroff[1,6]

1. Dept. of Dermatology, UC Davis; 2. Dept. of Electrical and Computer Engineering, UC Santa Cruz; 3. Dept. of Applied Mathematics, UC Santa Cruz; 4. Pediatric Regenerative Medicine, Shriner's Hospitals for Children; 5. Dept. of Ophthalmology and Vision Science, UC Davis; 6. Dermatology Section, VA Northern California Health Care System

## Background

Wound infections are a significant medical challenge, complicating healing and often leading to wound chronicity or systemic infection. The rise of microbial resistance to antibiotics has exacerbated this problem, rendering many traditional treatments ineffective and creating a need for alternative strategies. Repurposing of existing non-antibiotic drugs is a promising avenue to mitigate wound infections. Selective serotonin reuptake inhibitors (SSRIs) have emerged as potential non-antibiotic candidates; studies have demonstrated their ability to limit growth and biofilm formation in Gram-negative bacteria, in addition to demonstrated pro-healing activity. However, the pharmacokinetics of fluoxetine in skin wounds has so far not been studied, and it is unclear if bolus topical application will produce tissue concentrations sufficient to mitigate infection in wounds; furthermore, the potential for unwanted systemic effects following topical treatment has not been evaluated.

Recently, we developed a wearable, programmable iontophoretic device which delivers fluoxetine topically to skin wounds. We hypothesized that topical application would produce tissue levels sufficient to help mitigate infection, without causing systemic effects, and that fluoxetine would be better absorbed into tissues with metered dosing from the device compared to bolus dosing.

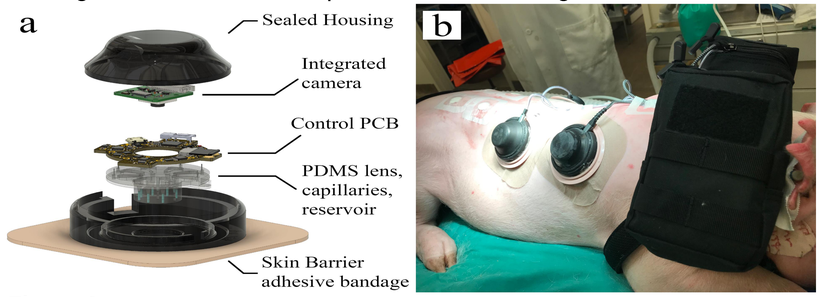


**Figure 1:** (a) An exploded view of the experimental device. (b) The device applied to pig dorsal wounds during a wound healing experiment.

## Methods

- Full-thickness 20 mm diameter circular wounds were created on the backs of Yorkshire pigs
- Fluoxetine was delivered to the wound surface using the experimental device, or daily using a pipette.
- Wound tissues and blood were harvested afterwards for analysis of fluoxetine, norfluoxetine, and serotonin by HPLC.

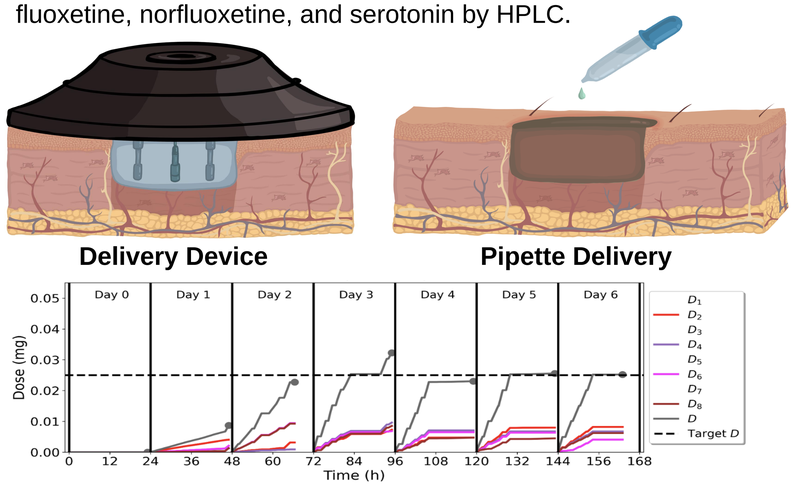


**Figure 2:** Fluoxetine amounts delivered by the device during successive daily treatment cycles

## Results

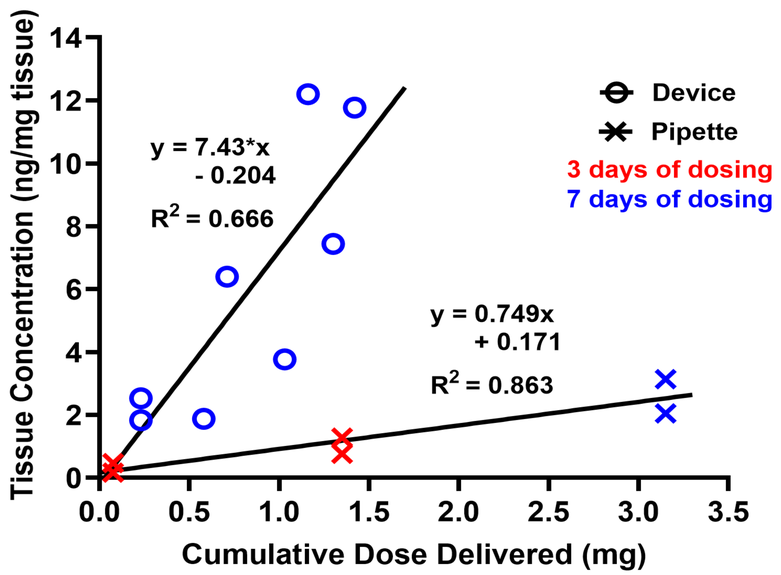


**Figure 3: Fluoxetine tissue concentrations were higher after application using the experimental device compared to daily bolus dosing (p=0.0041).** Wound tissue levels of fluoxetine measured by HPLC. Each data point represents one wound. Device, n=8 wounds; pipette, n=6 wounds.

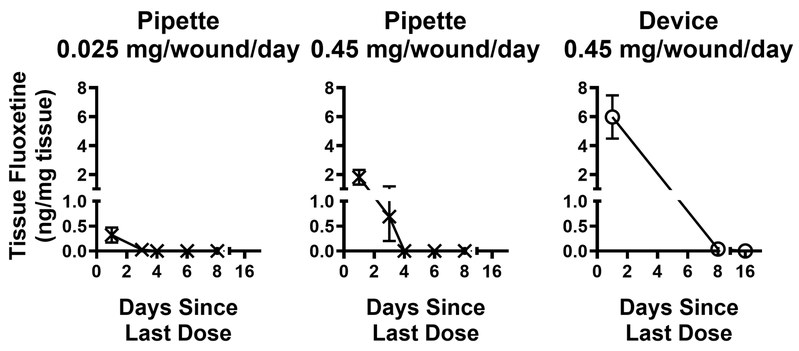


**Figure 4: Fluoxetine has a half-life of 0.988 ± 0.256 days in wound tissue.** Fluoxetine concentrations in wound tissues collected on differing days post-treatment, measured by HPLC. Plots show mean ± standard error, n=2 to 8 wounds per point.

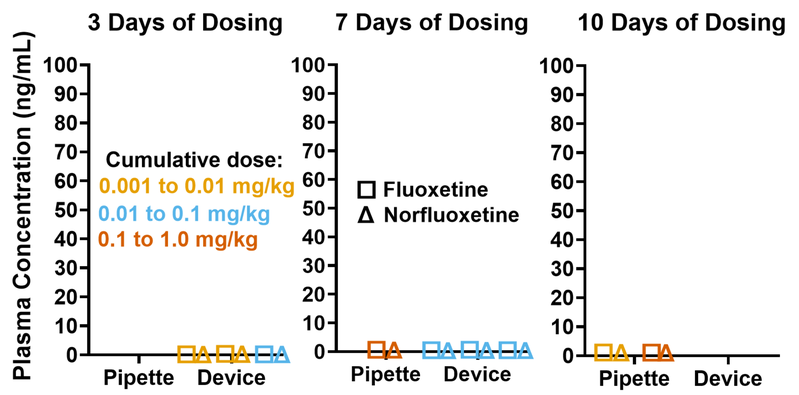


**Figure 5: Fluoxetine is not detected in the plasma after daily topical application.** Fluoxetine and norfluoxetine concentrations in pig plasma measured by HPLC (n=9 pigs). All results were below the limit of detection (LOD FLX: 7.4 ng/mL; NFLX: 6.9 ng/mL).

| | Dose Delivered (mg/wound/day) | Elimination constant ($days^{-1}$) | Half-life (days) | Tissue Concentration (max, ng/mg tissue) |
|---|---|---|---|---|
| Pipette | 0.025 | 1.245 | 0.5567 | 1.111 |
| Pipette | 0.45 | 0.4809 | 1.441 | 2.926 |
| FLX device | 0.45 | 0.7175 | 0.9661 | 12.25 |

**Table 1: Pharmacokinetic parameters of fluoxetine in the wound tissues**.

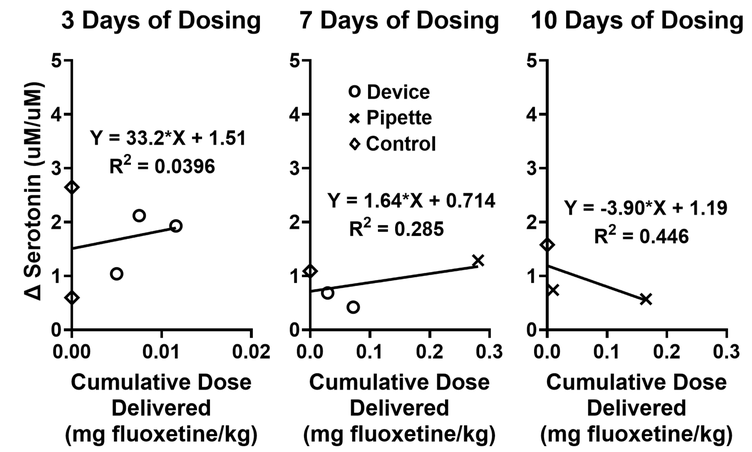


**Figure 6: Plasma serotonin levels are not affected by topical fluoxetine wound treatment.** Changes in plasma serotonin after topical fluoxetine wound application, plotted against the cumulative dose. Dose was normalized to the body weight of each pig. Each data point represents one pig. 3 days of dosing, n=5; 7 days, n=4; 10 days, n=3.

## Key Findings

1. **The experimental device, but not bolus dosing, produced tissue concentrations sufficient to mitigate infection by multi-drug resistant gram-positive and gram-negative bacteria.**
2. **Topical fluoxetine wound therapy is unlikely to produce systemic effects.**
3. **The half-life of fluoxetine in wound tissues was consistent with the elimination half-life of 1-4 days in blood after oral dosing.**

## References

1. Gallegos A, Li H, et al. Fluoxetine Delivery for Wound Treatment Through an Integrated Bioelectronic Device – Pharmacokinetic Parameters and Safety Profile in Swine. BioRxiv (2025).
2. Li H, Yang H, et al. Real-Time Diagnostics and Personalized Wound Therapy Powered by AI and Bioelectronics. MedRxiv (2025)

Email questions to Rivkah Isseroff (rrisseroff@ucdavis.edu) or Anthony Gallegos (ancgallegos@ucdavis.edu)
Illustrations created by Justine Arizabal (jgarizabal@formerstudents.ucdavis.edu)