

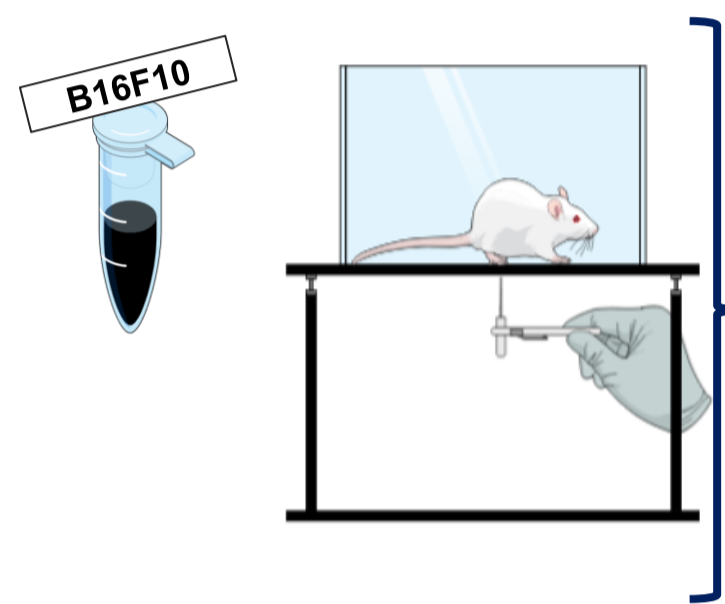
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Introduction and Goals

One strategy to improve the therapeutic utility of opioids is to co-administer with other analgesic agents, such as $\text{Ph}\alpha 1\beta$ toxin, looking for reducing side effects and improving analgesy. This work aims to test whether the in vivo antinociceptive interaction of methadone and $\text{Ph}\alpha 1\beta$ is sub-additive, additive or synergistic.

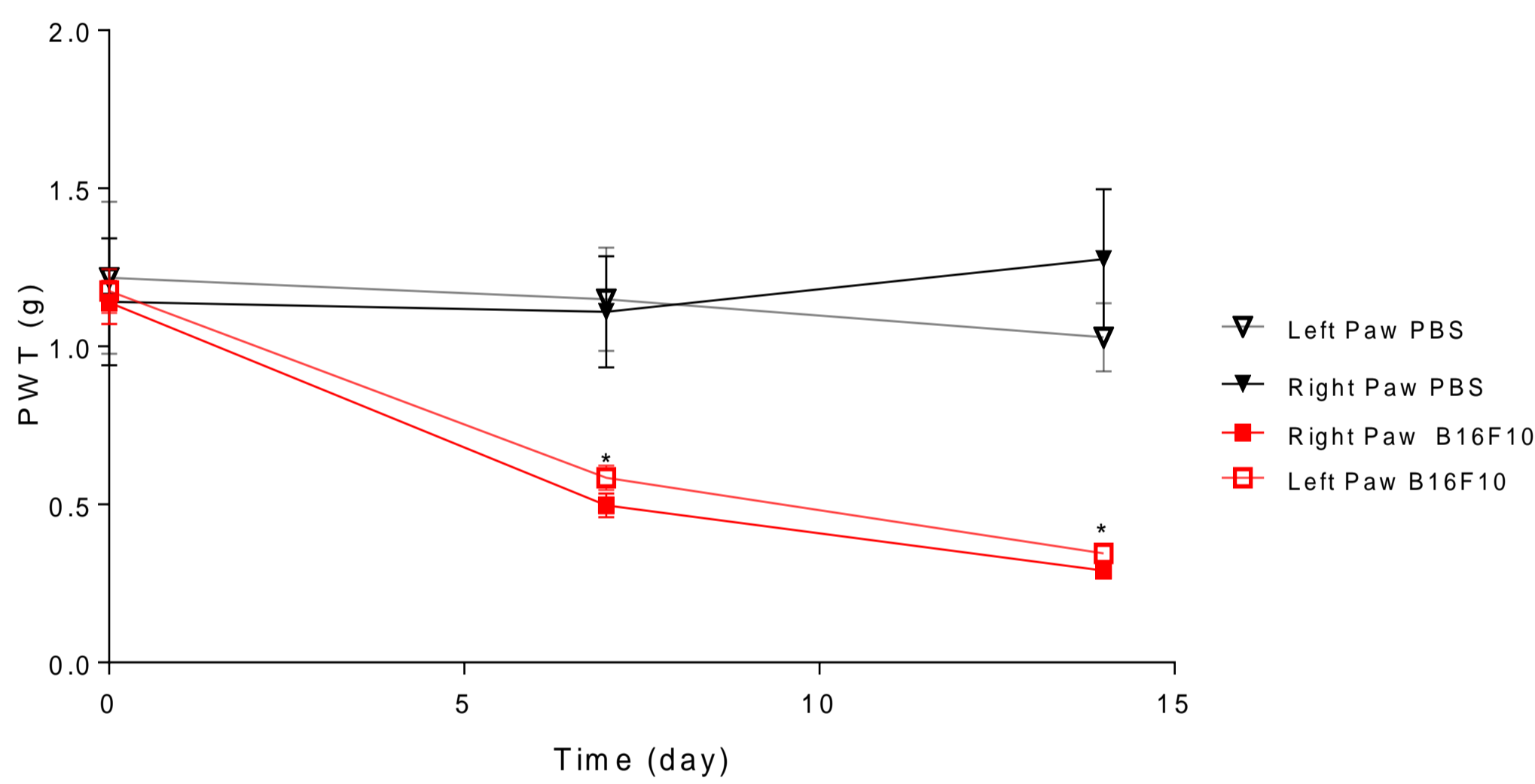
Methodology



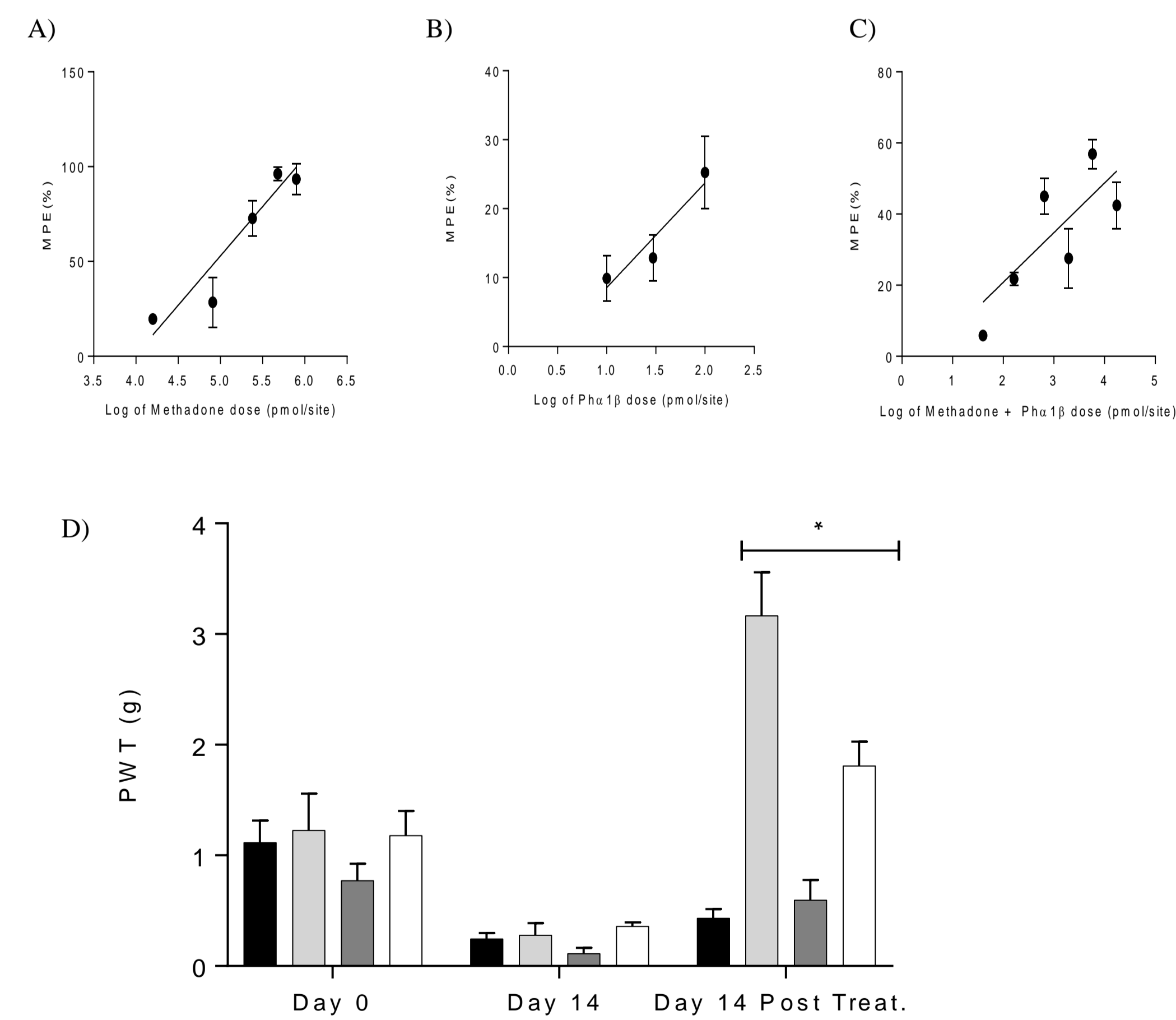
Von Frey Test (Measures)

- Basal – Day 1
- Day 7
- Day 14 (Before and After Treatment)

Melanoma Model - Results



Treatment - Results



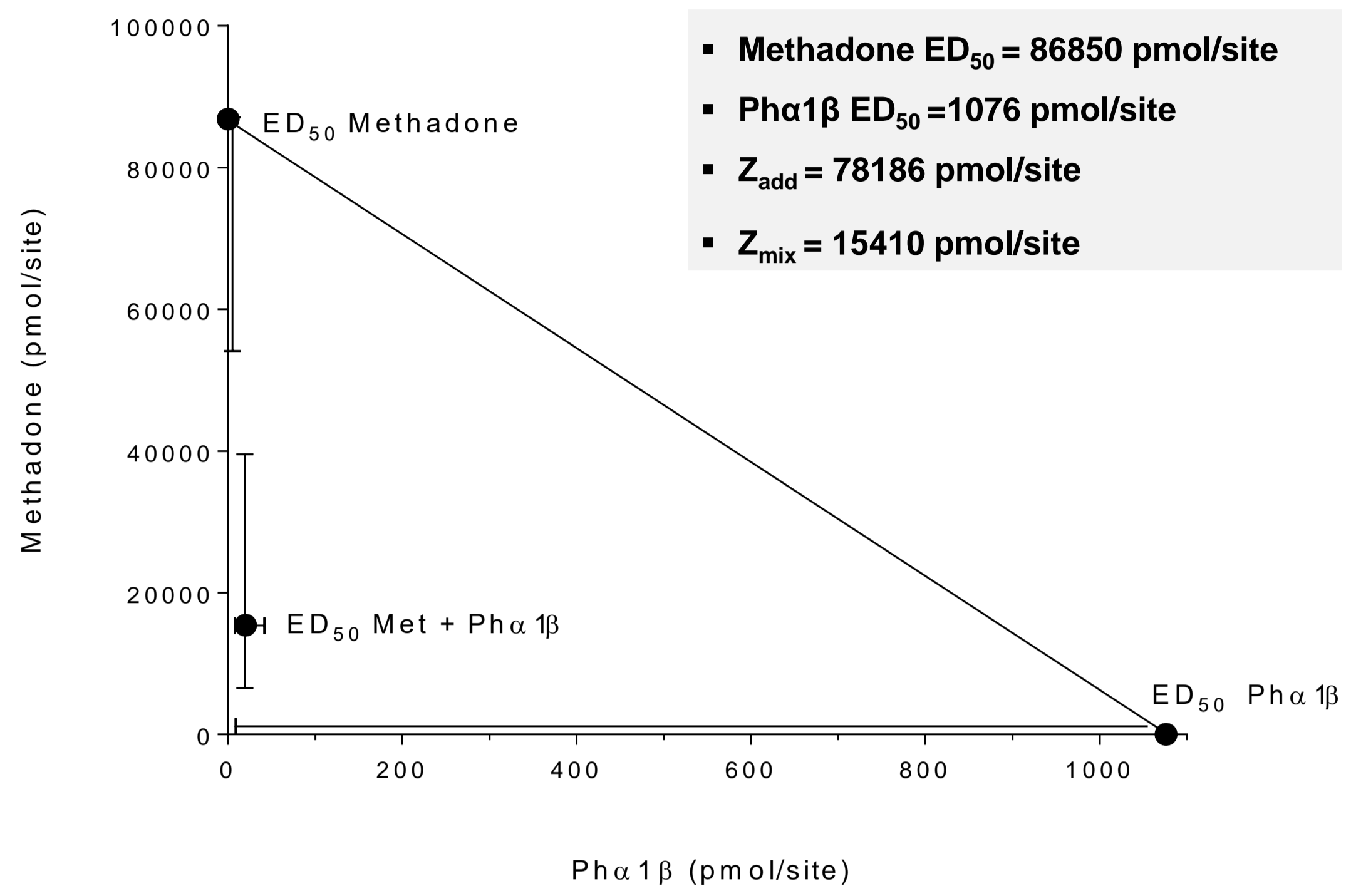
Acute treatment with methadone, $\text{Ph}\alpha 1\beta$, and their combination were able to reverse mechanical hyperalgesia induced by B16-F10

Graphs (A-C) shows a linear regression with all doses plotted in log for each type of treatment described on the x-axis. The maximum possible effect is described on the y-axis. Effects of Methadone and $\text{Ph}\alpha 1\beta$ alone or in combination, following 30 minutes subcutaneous or intrathecal administration in the mechanical nociceptive test using Von Frey filaments. (D) Only the intermediate doses of each treatment.

Conclusions

Our data show that a synergism occurred when s.c. methadone was administered simultaneously with i.t. $\text{Ph}\alpha 1\beta$ suggesting potency on the analgesic effect of these drugs when both are added together even in lower doses.

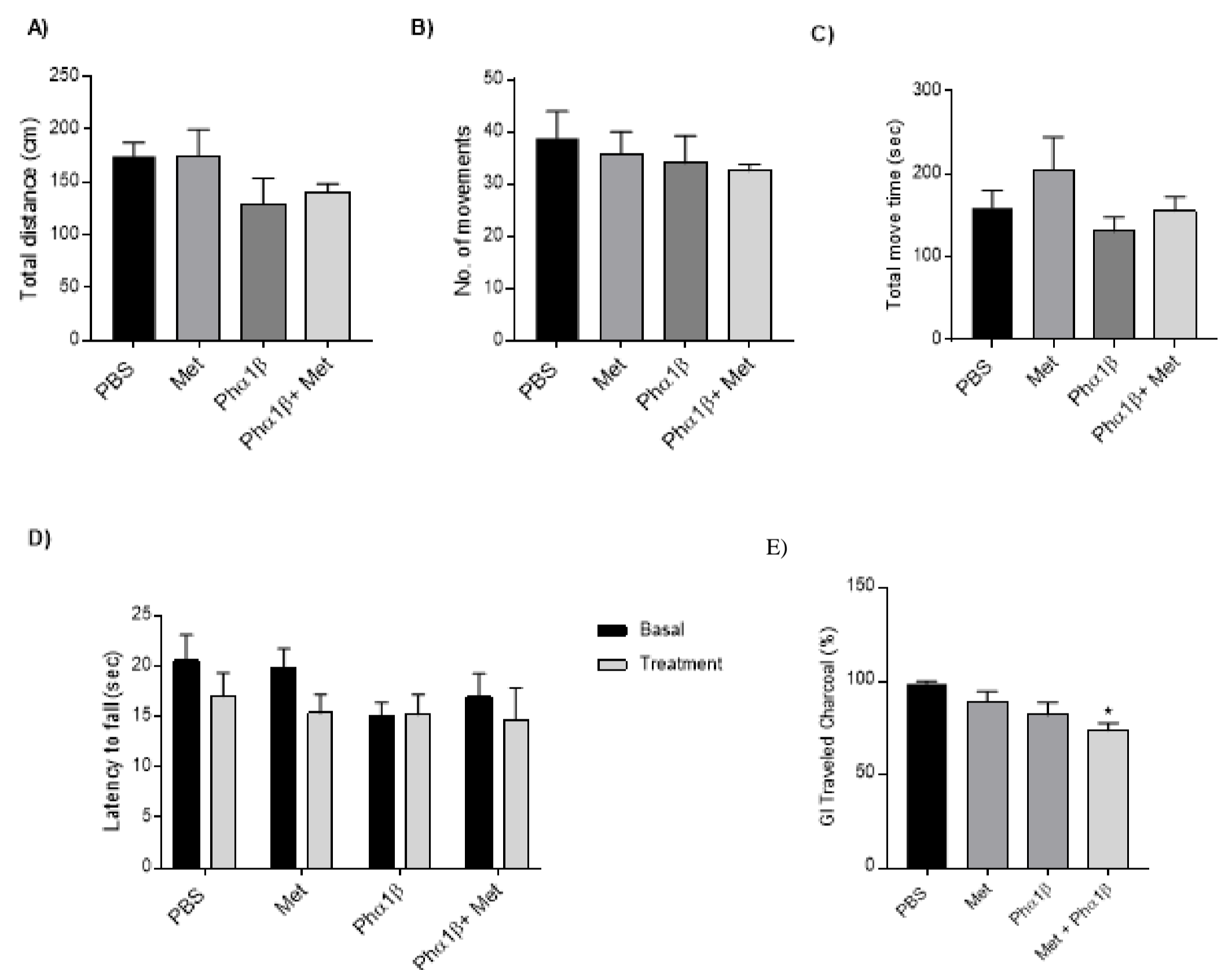
Isobologram indicating synergism



Isobologram of the antinociceptive effect of Methadone (s.c) combined with $\text{Ph}\alpha 1\beta$ (i.t.) in the Von Frey test.

The point on the graph denotes the experimentally obtained ED₅₀ (with 95% confidence intervals) of combined $\text{Ph}\alpha 1\beta$ and Methadone. The line connecting the ED₅₀ values is the theoretical additive line. Points over the axis denote the ED₅₀ of $\text{Ph}\alpha 1\beta$ (x-axis) and Methadone (y-axis) administered alone.

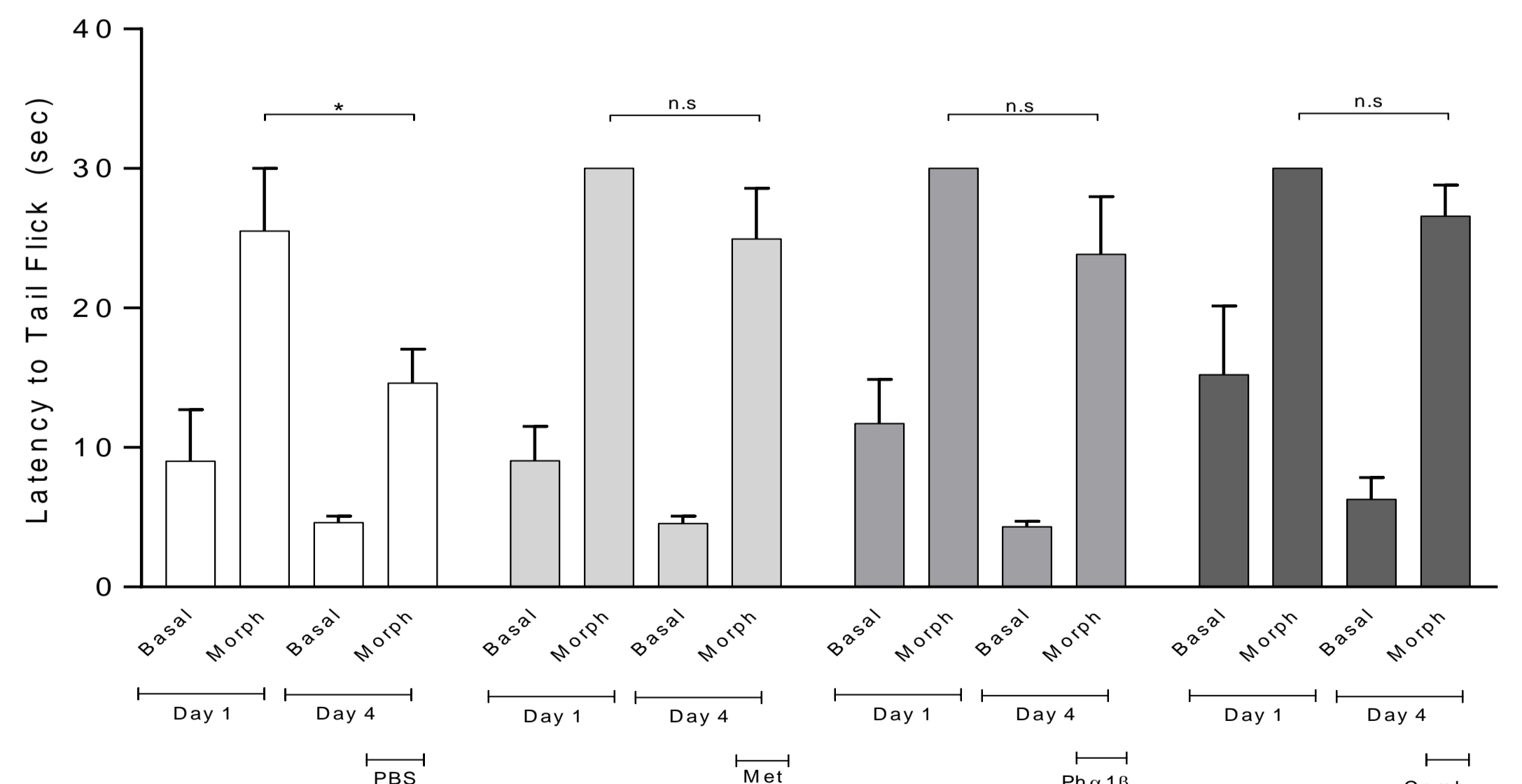
Adverse effects analysis



Antinociceptive doses of $\text{Ph}\alpha 1\beta$ and Methadone (alone or in combination) cause no alterations on motor performance but reduces intestinal transit

(A) Total traveled distance. (B) Total number of movements (including flinch, tail-flick, grooming, jumping). (C) Total duration of the movements. (D) Rotarod test expressed as the latency to first fall that was performed before (black bars) and 25 min after (gray bars) the treatment. (E) The treatments occurred 30 minutes before charcoal administration (via gavage, oral). Evaluation of the traveled distance by charcoal was performed 40 min after its administration

Morphine tolerance



Drugs in a morphine tolerance condition.

$\text{Ph}\alpha 1\beta$, Methadone or $\text{Ph}\alpha 1\beta$ + Methadone at doses necessary to cause 50% of M.P.E. in the mechanical hypersensitivity assays were capable to restore the morphine antinociceptive effect in the tail-flick test. Data are expressed as mean \pm SEM ($n = 6$ animals per group). * $p < 0.05$ was considered statistically significant compared to morphine challenging dose at day 1 (One-way ANOVA, with Bonferroni post-test).

Support