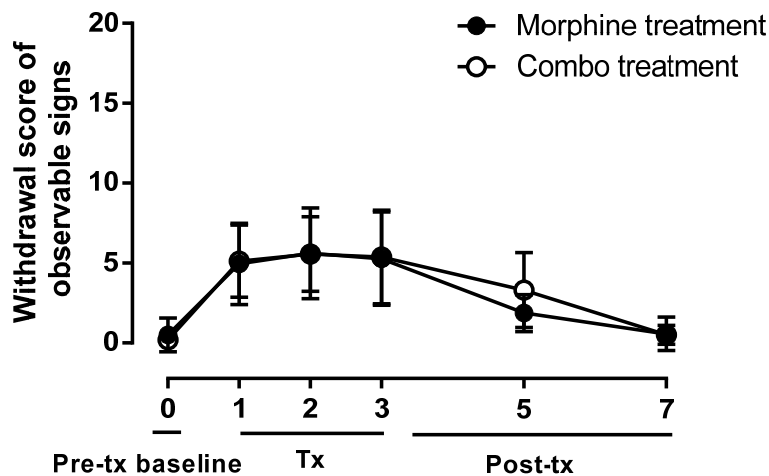


## Supporting Information

### *Measurement of observable withdrawal signs*

To measure the observable withdrawal signs on the naltrexone treatment sessions, immediately after the operant test sessions, rats were individually placed into different standard acrylic home cages with corn cob beddings and the presence or absence of the 17 different behavioral signs were recorded by two observers after a 5 min habituation period. The observation was performed once every 2 min for a period of 10 min. Therefore, a maximum score of 5 could be recorded for each sign, which led to a maximum observation score of 85 for all signs. Observational withdrawal signs included writhing, wet dog shakes, piloerection, jumping, teeth chattering, ptosis, freezing, leaning, salivation, muscle twitches, convulsions, vocalization, retching, vomiting, laying on side, excessive grooming, and yawning (Becker et al., 2010). The withdrawal scores from both observers were averaged for each rat and were used as the score for the specific signs.



**Figure 1.** Average scores of withdrawal signs in rats treated with morphine alone or the combination of morphine and 2-BFI. Withdrawal scores present data collected during the test sessions wherein 17 different observable signs were observed by two trained observers who were unknown of the treatments. In both groups, the observable signs were rarely seen and there were no differences between the two groups. Tx, treatment.

### Reference

Becker GL, Gerak LR, Li JX, Koek W, France CP (2010) Precipitated and conditioned withdrawal in morphine-treated rats. *Psychopharmacology* 209(1): 85-94.