

OPIATE WITHDRAWAL

Key-words: Pharmacodependence, Drug abuse, Opiates, Withdrawal, Morphine

Rationale

The abrupt cessation of chronic opiate use results in a well characterized withdrawal syndrome with symptoms that include pain sensitivity, dysphoria, irritability, restlessness, insomnia, diarrhea and hyperventilation. In the present model, rats are chronically treated with a drug (e.g. morphine). Opiate withdrawal syndrome is elicited by an acute injection of the opiate antagonist naloxone.

Method – Male Sprague-Dawley rats are treated intraperitoneally with either vehicle or morphine twice daily (at 9h and at 17h) for seven consecutive days. Initially, on day 1, morphine-treated subjects receive a dose of 5 mg/kg/injection and the dose of morphine is progressively increased to 10 mg/kg/injection on day 2, 20 mg/kg/injection on day 3 and 30 mg/kg/ injection from day 4 to day 7. On day 8, 16-20 hours after the last injection, precipitated withdrawal is induced by administration of naloxone (1 mg/kg; IP) and the rats are observed for the next 60 min. Withdrawal symptoms are recorded and a global withdrawal score is calculated for each individual animal according to the Gellert-Holtzman method ^(1,2), as indicated in Table 1.

Table 1 – Withdrawal scores

Signs	Weighting factor
<i>Graded signs</i>	
Weight loss	1/%
Escape attempts	1-3
Abdominal constrictions	2
Wet dog shakes	2-4
<i>Checked signs</i>	
Diarrhea	2
Facial fasciculations or teeth chattering	2
Swallowing movements	2
Profuse salivation	7
Chromodacryorrhea	5
Ptosis	2
Abnormal posture	3
Erection or ejaculation	3
Irritability	3

Results – Naloxone-precipitated morphine withdrawal induces numerous signs (Fig. 1) and dramatically enhances the global withdrawal score (Fig. 2).

Figure 1 – Scores for several withdrawal signs

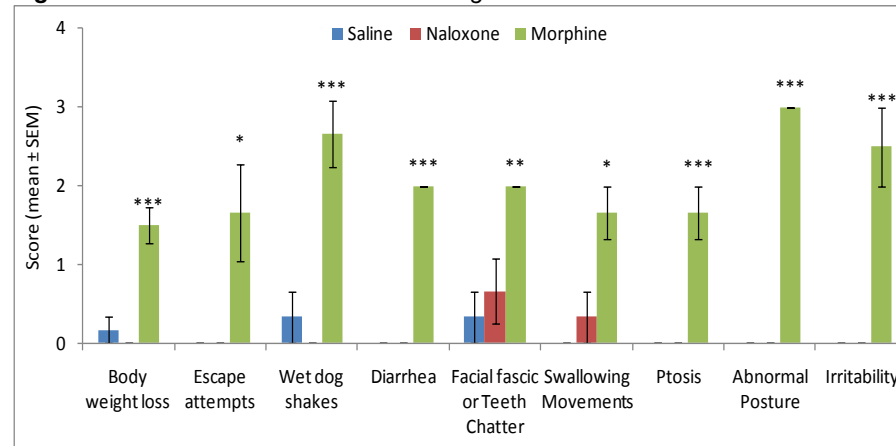
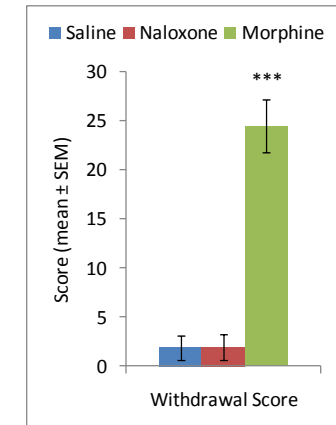


Figure 2 – Global withdrawal score



Difference vs. Naloxone group
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

References:

1. Gellert VF and Holtzmann SG. *J Pharmacol Exp Ther* 205:536-546, 1978

2. Fdez Espejo E et al., *Psychopharmacology* 122:122-130, 1995