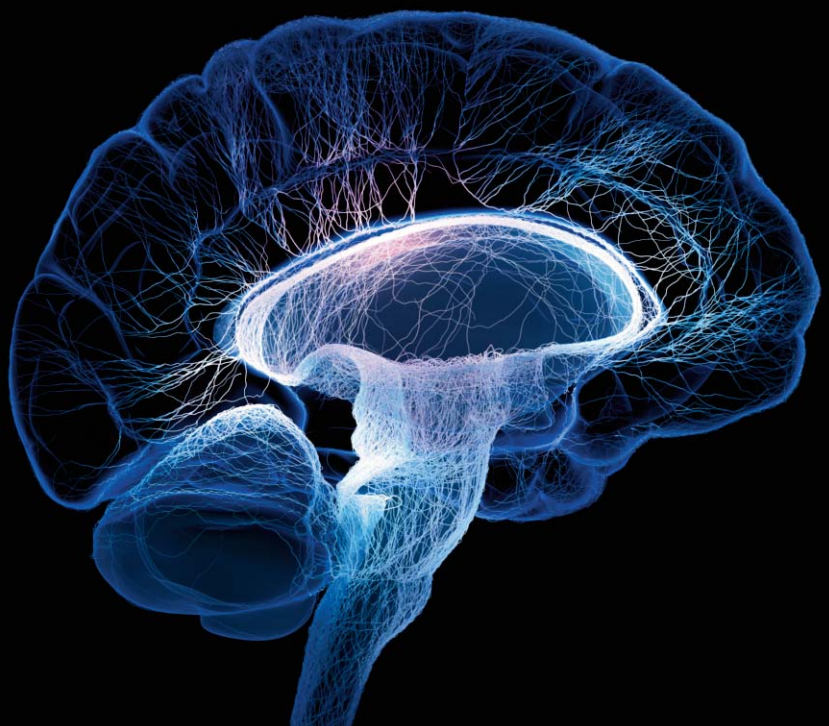
Scientist-to-Scientist

DRUG ABUSE & DEPENDENCE

Porsolt

THE IDENTIFICATION OF ABUSE AND DEPENDENCE LIABILITY IS AN IMPORTANT ISSUE FOR CNS SAFETY PHARMACOLOGY AND REGULATORY BODIES IN BOTH THE U.S. AND EUROPE ARE WORKING TO PRODUCE STANDARD GUIDELINES. IN BOTH CASES THE APPROACH IS BASED ON LOOKING FOR SIMILARITIES WITH KNOWN DRUGS OF ABUSE.

THIS LEAFLET DESCRIBES THE STRATEGY AND THE PROCEDURES AVAILABLE AT PORSOLT FOR ASSESSING ABUSE AND DEPENDENCE LIABILITY.



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Early indicators of abuse liability

Evaluating the potential of a novel test substance to possess properties indicative of abuse liability can start at an early stage in a project's development.

Interactions with certain receptors or evidence for certain behavioral signs common to many abused would suggest that the class of substance under study might have the potential to be abused.

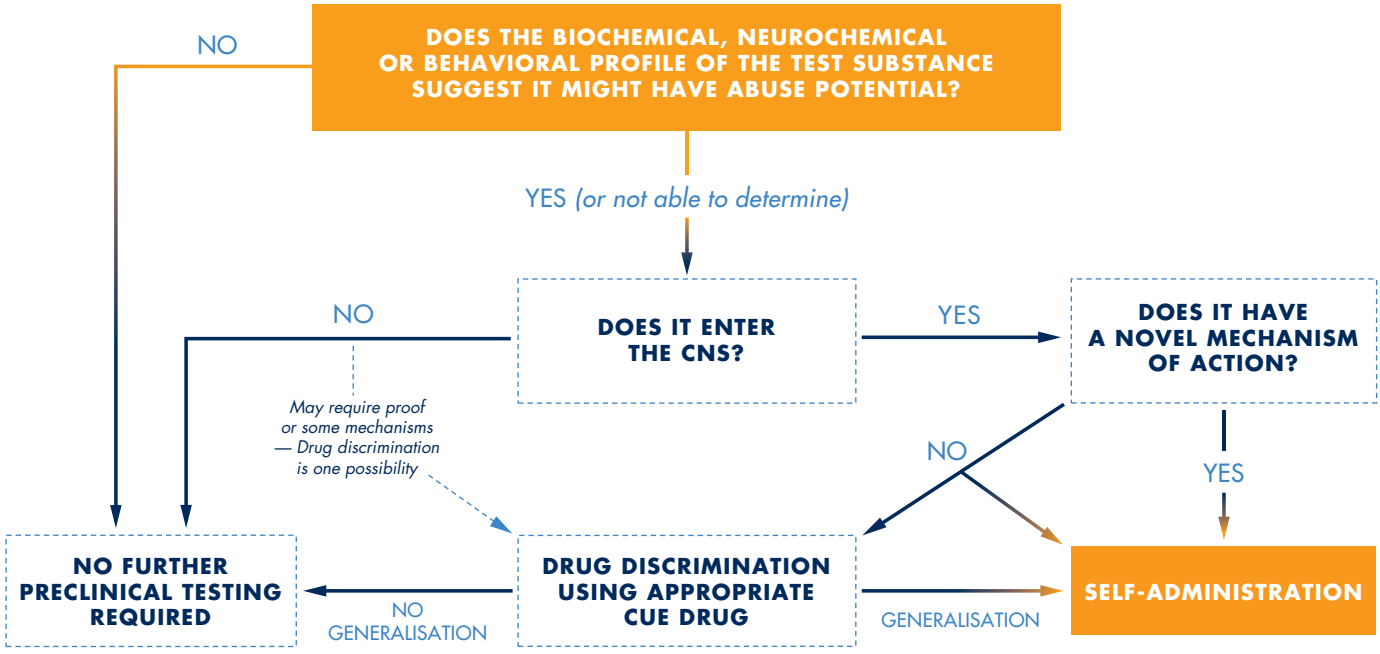
Under these conditions, a more formal demonstration of this potential will usually be required by regulatory bodies.

Assessment of abuse liability

Models available for evaluating drug abuse liability *(reinforcing properties)* include the following:

- Place preference
- Drug discrimination
- Self-administration

↓ The following diagram, adapted from the EMA guidelines, suggests a possible context for using these tests to establish the abuse liability of a novel test substance.



Place preference

- Beyond drug discrimination and self-administration, which are likely to become regulatory requirements, other tests have a specific utility at earlier stages in drug development.
- If the binding and behavioral profile suggests a clear and major risk, substances may be first evaluated in the place preference test to determine if marked abuse potential is of a similar level to that of opiates and stimulants.

Drug discrimination

• In drug discrimination, study animals learn to distinguish between two internal states: usually those induced by a drug and its vehicle. Drug discrimination is pharmacologically highly specific and the choice of drug for training should be related to the biochemical target of the test substance.

→ The 2-lever operant conditioning procedure is the most popular.

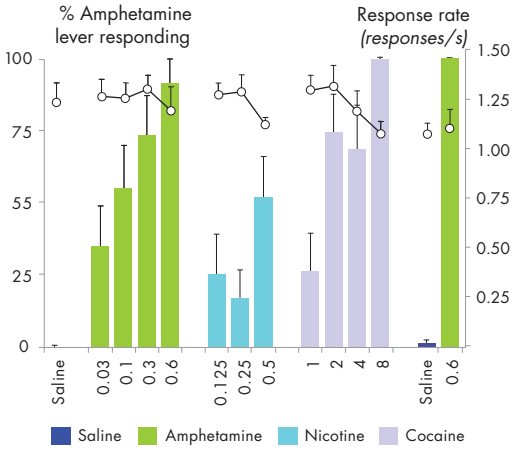
→ Substitution studies can be carried out, during which training drug-appropriate response would suggest that the test drug shares properties with the training drug.

→ The graph shown here illustrates that rats trained on amphetamine identify cocaine as being identical whereas nicotine is identified has having only limited similarity with the training drug.

→ The table indicates the broad range of training substances or reference drugs of abuse from different target classes which can be used to prosecute the effects of novel test substances in rats.

TRAINING SUBSTANCES:
Amphetamine, Cocaine, DOM, Morphine, Fentanyl, Pentazocine, Alcohol, Nicotine, PCP, Ketamine, Chlordiazepoxide, Diazepam, THC, Tianeptine, DOI

Evaluation of cocaine and nicotine in rats trained to discriminate amphetamine *(0.6 mg/kg i.p.)* from saline



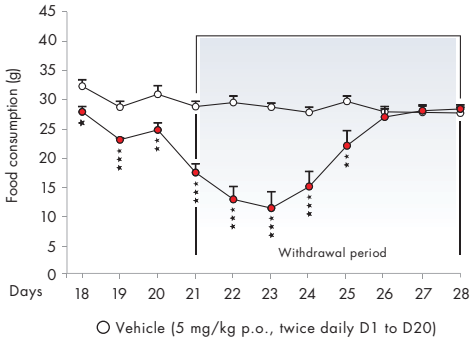
Non-precipitated withdrawal

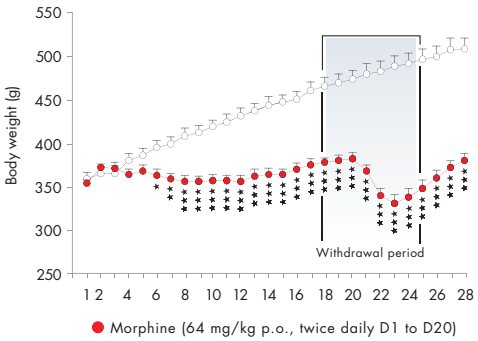
• In addition to assessing abuse liability, regulatory agencies have indicated how the problem of withdrawal symptoms should be addressed. Besides the historically well-known drugs such as opiates inducing withdrawal phenomena more recent examples such as benzodiazepines and SSRIs have been shown to be associated with withdrawal in some patients that may make it difficult to discontinue treatment.

SUGGESTED APPROACH

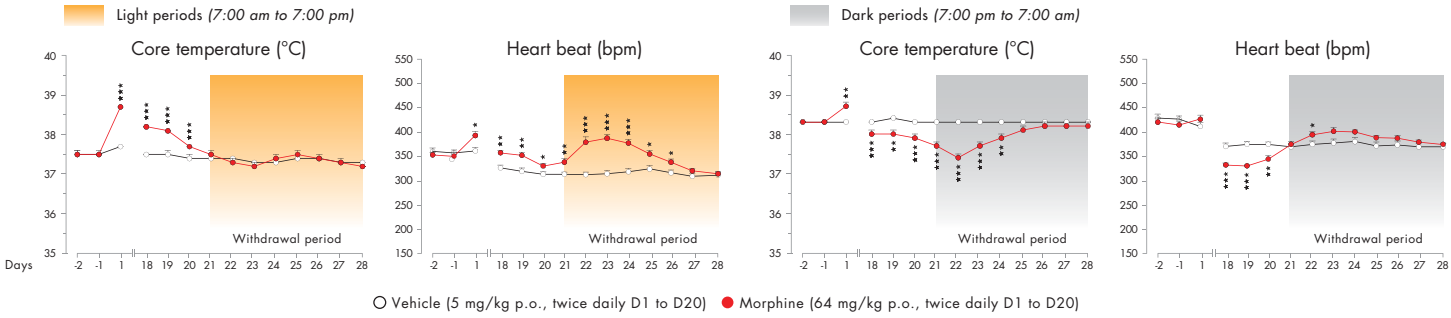
- Twice a day dosing for 20 days + 8 days withdrawal
  - Low dose at upper end of therapeutic range
  - High dose = NOAEL
- Non-specific somatic measures — e.g. food intake, body weight, body temperature

Effects of morphine on food intake and body weight in the non-precipitated withdrawal test in the rat





Effects of morphine on additional non-physical aspects of withdrawal in the rat

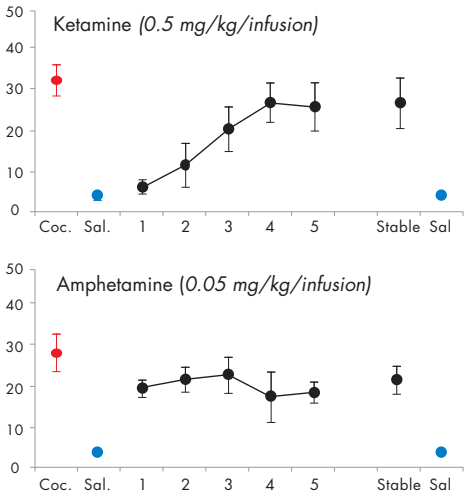


We have been exploring the use of telemetry to examine additional parameters and to allow monitoring over 24 hours, during both treatment and withdrawal phases. This approach gives a more complete picture of the state of the animal during the withdrawal phase.

Self-administration

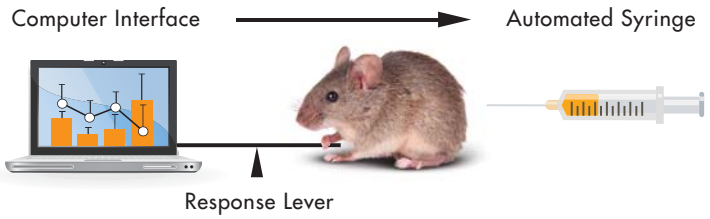
- Self-administration is considered as the 'gold standard' for assessing abuse potential as it gives few false positives and negatives and is considered equally valid in both rats and primates *(i.e. both species have concordance rates close to 100% with human data)*.
- Our rat procedure involves an initial training phase where animals learn to self-administer cocaine by pressing a lever *(FR10 schedule)*. This is followed by a saline extinction phase.
- Then a series of sessions under test substance, cocaine and saline is used to evaluate the ability of the test substance to maintain self-administration at levels greater than saline.

Evaluation of Ketamine and Amphetamine in rats trained to self-administer cocaine *(0.25 mg/kg/infusion i.v.)*



Coc. & Sal.: Mean of infusions over the last 3 sessions for cocaine and saline:
- Mean number of infusions over the last 2 sessions of Ketamine.
- Mean number of infusions over the last 5 sessions of Amphetamine.

TRAINING SUBSTANCES:
Cocaine, Remifentanil, Amphetamine



First day infusion rates, stable infusion rates and sessions to achieve stable infusion rates

Substance	Day1 infusion rate	Stable infusion rates	Sessions to achieve stable rates
Ketamine	5.2 ±1.8	29.8 ± 4.2	5.5 ± 0.8
Amphetamine	21.4 ±1.8	24.0 ± 3.8	5.4 ± 0.5

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