How Good Are Current Approaches to Nonclinical Evaluation of Abuse and Dependence?


Abstract

Nonclinical assessment of drug abuse and dependence is the subject of several recent regulatory guidelines, which are generally aligned on the methods to be employed. The most direct approach to assessing reinforcing properties of a drug is the self-administration procedure whereby animals can initiate intravenous injections of the test substance, something they readily do with prototypic drugs of abuse. Complications arise because there is no standardized procedure for evaluating substances with differing potencies, reinforcement properties, or pharmacokinetics. Moreover, the choice of training substance, species, and procedural parameters can radically affect the outcome. Apart from the lower cost of rats, primates present several advantages for self-administration studies with similarity to human pharmacokinetics in particular. The most powerful method for assessing similarities between a test substance and a prototypic drug of abuse is the drug discrimination procedure. In contrast to self-administration, drug discrimination is pharmacologically very specific, often reflecting functional activity at receptor level. Dependence is assessed by the occurrence of withdrawal effects on drug discontinuation. Although conceptually simple, interpretation can be complicated by factors such as duration and frequency of administration and observations as well as the choice of end points. Telemetry allows continuous observation of multiple parameters during withdrawal, thereby increasing sensitivity. Presently available tools identify all substances known to cause abuse or dependence, with little risk of false-positives. It remains unclear, however, how predictive these models are with entirely novel substances. Nonetheless, drug abuse/dependence is an area of safety pharmacology where the predictive value of animal models is remarkably high.