Preclinical assessment of abuse liability of drugs

J. L. Katz and S. R. Goldberg

Preclinical Pharmacology Branch, NIDA Addiction Research Center, Baltimore, Maryland, USA

Abstract
Studies that are used in preclinical assessment of the liability of a drug to become an abuse problem are reviewed. These studies examine the capacity of a drug to produce physiological dependence or to function as a reinforcer. Studies that examine physiological dependence by assessing whether a drug reverses signs of withdrawal from a standard drug are rapid, reliable and inexpensive methods for determining if a drug produces dependence of a type similar to the standard. However, these techniques will not determine if the drug produces a unique type of dependence. Studies that examine whether a drug functions as a reinforcer have been predictive of whether a drug will be abused in human populations. Attempts to rank order drugs with respect to their efficacy as reinforcers, however, are not predictive of measures of extent of abuse in human populations. Since abuse of drugs in human populations is a function of societal variables in addition to pharmacological factors, it is unlikely that preclinical assessments will ever yield more than qualitative information on abuse liability of drugs.

The scientific study of drug dependence has emphasized both pharmacological and behavioral processes. Initial studies of drug dependence emphasized physiological dependence by assessing the withdrawal syndrome that unfolds after repeated administration of drugs, particularly opioids. These studies have concentrated on withdrawal syndromes, and which drugs, at what doses, and for what durations of treatment produce these syndromes. In the development of useful analgesic compounds, it is important to be able to rapidly and reliably assess whether drugs produce physiological dependence. Drug dependence also has behavioral components. Obviously physiological dependence will not be a problem unless there is continued self-administration of the drug. Therefore, in preclinical assessments of abuse liability in laboratory animals, studies also assess whether responses that produce injections are maintained at a frequency greater than when those responses produce vehicle injections, i.e., whether the drug functions as a reinforcer.

Assessment of physiological dependence
Physiological dependence is a state of the organism that develops through drug administration such that, when drug administration is discontinued, a characteristic, time-limited constellation of reactions is observed. Following the suggestion of Himmelsbach [1], investigators have assumed that any drug that can completely reverse the signs of morphine withdrawal, will itself produce a comparable type of dependence. This assumption has been substantiated for opioid
drugs by Deneau [2] and Yanagita [3] who compared the efficacy of a variety of opioids in suppressing morphine withdrawal signs and in producing their own dependence. Thus, the suppression test has been adapted for use as a standard screen of potential analgesic agents for their capacity to produce opioid dependence. The use of rhesus monkeys has been a standard in the preclinical assessment of opioid dependence since the work of Tatum et al. [4] that suggested that the withdrawal reactions of that species closely resembled those of man, and the large subsequent body of work by Seevers and his colleagues. Other species used have included dogs, rats and mice. The constellations of signs obtained in each of these species have been well characterized. Mice and rats have distinct advantages as they are relatively easy to house and inexpensive. While the mouse has been used primarily for studies of antagonist-precipitated withdrawal, weight loss in the rat is a useful sign of withdrawal that develops when opioid treatment stops [5].

Studies of opioid withdrawal in the dog were instrumental in the identification of kappa agonists. While these compounds did not suppress signs of morphine withdrawal [6], they do produce a type of dependence that is distinct from that produced by morphine [7]. Results of studies on suppression of morphine withdrawal from the University of Michigan and from Martin’s laboratories at the Addiction Research Center were instrumental in suggesting that different types of opioid receptors exist, that agonists at each have analgesic actions, and that the types of physiological dependence produced by each are different. These results motivated biochemical studies of binding that have eventually led to present day identifications of highly selective agonists that show little cross-reactivity in displacement studies.

Techniques used in the identification of opioids that produce morphine-like dependence have also been adapted to the study of barbiturates [8] and other sedative/hypnotic agents, including benzodiazepines [9]. These studies have generally rendered subjects dependent on barbital and assessed the efficacy of various drugs in suppressing barbital withdrawal (for a review see) [10]. In summary, studies of suppression of morphine withdrawal signs are a rapid, effective and relatively inexpensive method for assessing whether a drug produces dependence of the type produced by morphine. Studies by Deneau [2] and Yanagita [3] have indicated that these studies yield results similar to those obtained by studying dependence to the test drugs themselves. Sedatives and hypnotics have been studied less frequently, however, suppression of withdrawal of these agents may also be a useful method of assessing whether drugs produce dependence of this type [9].

Assessment of drug-seeking behavior
Repeated administration of many drugs can produce withdrawal reactions when treatment stops. With some drugs, these effects are more often characterized as rebound phenomena. For example, drugs used in treatment of hypertension can produce rebound hypertension. Most rebound phenomena are readily managed, and not all drugs that produce rebound effects are considered as having dependence liability. A rebound effect is typically considered drug dependence when it is accompanied by drug-seeking behavior; this behavioral component makes drug dependence difficult to medically manage. Studies of dependence that have concentrated on this behavioral component of dependence have assessed whether drugs serve as reinforcers.

There are many different laboratory methods for preclinical assessment of whether drugs produce reinforcing effects in laboratory animals. In most procedures, subjects, usually rhesus monkeys, are surgically prepared with indwelling venous catheters and trained to self-administer drugs delivered intravenously. The subject is studied within an experimental chamber which contains various stimulus lights and a response key. Operation of the key by the subject is counted as a response and may produce an injection.

Substitution procedures
In substitution procedures, injections of some standard drug are typically arranged to occur following each fixed number of responses (fixed-ratio schedule). Once responding is reliably maintained by the standard drug, and responding decreases to relatively low rates when vehicle is substituted for the standard drug, tests of other drugs