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Invited review

Predicting abuse potential of stimulants and other dopaminergic drugs: Overview and recommendations

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ABSTRACT

Examination of a drug's abuse potential at multiple levels of analysis (molecular/cellular action, whole-organism behavior, epidemiological data) is an essential component to regulating controlled substances under the Controlled Substances Act (CSA). We reviewed studies that examined several central nervous system (CNS) stimulants, focusing on those with primarily dopaminergic actions, in drug self-administration, drug discrimination, and physical dependence. For drug self-administration and drug discrimination, we distinguished between experiments conducted with rats and nonhuman primates (NHP) to highlight the common and unique attributes of each model in the assessment of abuse potential. Our review of drug self-administration studies suggests that this procedure is important in predicting abuse potential of dopaminergic compounds, but there were many false positives. We recommended that tests to determine how reinforcing a drug is relative to a known drug of abuse may be more predictive of abuse potential than tests that yield a binary, yes-or-no classification. Several false positives also occurred with drug discrimination. With this procedure, we recommended that future research follow a standard decision-tree approach that may require examining the drug being tested for abuse potential as the training stimulus. This approach would also allow several known drugs of abuse to be tested for substitution, and this may reduce false positives. Finally, we reviewed evidence of physical dependence with stimulants and discussed the feasibility of modeling these phenomena in nonhuman animals in a rational and practical fashion.

This article is part of the Special Issue entitled 'CNS Stimulants'.

1. Introduction

The Controlled Substances Act (CSA) was passed in the United States in 1970 and established five schedules of controlled substances (Title 21USC801; Title 21USC812). The scheduling of a controlled substance is based on its potential for abuse where schedule I indicates no currently accepted medical use and high abuse potential (Title 21USC812). Schedule II through V drugs include those with currently accepted medical use and are categorized within this range (i.e., II–V) based on their abuse potential (Title 21USC812). The Food and Drug Administration (FDA) defines a drug as having abuse potential if it "… is used in nonmedical situations, repeatedly or even sporadically, for the positive psychoactive effects it produces" (FDA/Center for Drug Evaluation and Research; CDER, 2010, p. 4) or by O'Connor et al. (2011) as "…the potential for repeated taking of a drug for its reinforcing or subjective-effects, or the avoidance of associated negative effects" (p. 913).

Abuse-potential assessment predates the CSA and is an essential component to regulation of controlled substances (Balster and Bigelow, 2003). A complete assessment of abuse potential includes data collected at several levels, from cellular action to whole-organism behavior to collection of epidemiological data (Balster and Bigelow, 2003; FDA/CDER, 2010; Horton et al., 2013). The compounds being assessed may be putative therapeutics or emerging "street" drugs that are anecdotally abused but too new to have been characterized empirically. Readers are encouraged to refer to Calderon and Klein (Neuropharmacology, this issue), for a review of US regulatory procedures for evaluating abuse potential of central nervous system (CNS) stimulants. In this review, we focused on behavioral research with nonhuman animals in the characterization of abuse potential of CNS stimulants. The term "CNS stimulant" has been broadly defined as a centrally acting drug with actions on monoamine neurotransmitter systems that increases alertness, attention, energy, blood pressure, and heart and

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respiration rate (National Institute on Drug Abuse; NIDA, 2001). We focused on therapeutics including stimulant medications (i.e., those for attention-deficit/hyperactivity disorder (ADHD) and other dopamine uptake inhibitors) and illicit compounds such as methamphetamine, cocaine, and synthetic cathinones often referred to as "bath salts". While dopamine agonists like those developed as potential therapies for stimulant abuse and Parkinson's disease often lack some of the physiological characteristics associated with CNS stimulants, we reviewed these drugs because they are typically compared to illicit stimulants in assessment of their abuse potential.

1.1. Types of procedures reviewed

The FDA/CDER (2010) describes five types of procedures typically used in assessment of abuse potential in nonhuman subjects: drug self-administration, conditioned place preference, drug discrimination, psychomotor tests, and dependence potential. We reviewed drug self-administration and drug discrimination experiments because they are regarded as "gold-standard" procedures in abuse-potential testing, perhaps because they are good predictors of CSA scheduling status and abuse-potential measures obtained with humans (e.g., Horton et al., 2013; Kamien et al., 1993; Rush et al., 2001). With drug self-administration, we reviewed species differences and the importance of reinforcing effectiveness relative to known and well-characterized drugs of abuse. With drug discrimination, we reviewed the role of training stimulus in obtaining false positives. Finally, we discussed the nature of physical dependence with this drug class and whether it should be included in assessments of abuse potential of CNS stimulants.

1.2. Use of rodents and nonhuman primates (NHP)

The use of nonhuman animals in preclinical assessments of abuse potential offers distinct advantages compared with human participants, and there are ethical and safety reasons for understanding drug effects in nonhuman animals prior to their study in humans. Newly developed compounds can be characterized relatively early in the drug-development process, often as part of the safety/toxicology profile of the compound. A wider range of doses can be examined for a longer period of time. Studies with nonhuman animals can be conducted with greater experimental control than is feasible with humans because the investigator can control many of the environmental conditions such as drug history, enrichment, nutrition, and so on. In some cases with nonhuman primates (NHP), but particularly with rodents, each organism's history is known and can be controlled by the experimenter. With rodents, subjects with similar genetic composition (e.g., inbred strains) or specific genetic modifications (e.g., knockout mice) can be selected and used depending on the experimental question. On the other hand, it is impossible to test drugs on naïve humans, and when conducting inpatient studies with drug abusers, extra-experimental events and genetic differences are extremely difficult, if not impossible, to control.

An important consideration in abuse-potential testing is the choice of animal model. Rodents and NHPs each have advantages and disadvantages (discussed below). In the current review, we distinguished between studies with rodents and NHPs to highlight the common and unique attributes of each model in characterizing abuse potential of CNS stimulants.

2. Drug self-administration

Drug self-administration is a procedure used to determine whether behavior can be maintained by the administration of a drug, a characteristic that defines a drug as a reinforcer. The drug is generally delivered intravenously (though other routes have been used, e.g., oral; Lemaire and Meisch, 1985; Meisch, 2001) contingent on a specific behavior, such as a lever press, or a pattern of lever presses (see Ator and Griffiths, 2003 for a methodological review). For a drug to be considered a reinforcer, it must maintain meaningfully higher levels of responding compared to a vehicle control.

2.1. Schedules of reinforcement in the characterization of drugs as reinforcers

The current approach to drug self-administration in abuse-potential assessment is often to use a simple fixed-ratio (FR) schedule to determine whether a drug functions as a reinforcer. With this schedule, drug delivery occurs after a specified number of lever presses. Particularly with rodents, it is common to use the simplest version of an FR, in which every lever press results in drug delivery (referred to as FR 1 or continuous reinforcement). Other simple schedules (fixed interval, variable interval, and variable ratio) and second-order schedules have been used less often. Under fixed-interval schedules, a specified period of time must pass before a single response results in drug delivery. Under variable-interval schedules, the specified period of time changes from delivery to delivery, yielding an average period of time. Variable-ratio schedules require an average number of responses per drug delivery, and the exact number or responses changes from delivery to delivery. All of these schedules have in common response rate and number of drug deliveries as primary dependent measures.

In the context of drug self-administration, many procedures have been used to determine whether a drug has abuse potential. However, it is common to use a "substitution" procedure, where a known drug reinforcer (or in some cases, the drug being tested for abuse potential) is used during acquisition and until responding is stable. Then, vehicle or different doses of drugs are substituted for the baseline drug for a fixed number of sessions (e.g., Caine and Koob, 1995; Gold and Balster, 1996; Motbey et al., 2013; Self and Stein, 1992) or for at least as many sessions as it took for responding to extinguish when vehicle was made available (e.g., Freeman et al., 2012; Sinnott et al., 1999; Woolverton et al., 1984).

An important characteristic of self-administration of drugs under simple schedules is that the dose–response function is typically biphasic (higher response rates are maintained by smaller doses and lower response rates by larger doses; Pickens and Thompson, 1968; Wilson et al., 1971). Fig. 1 (top panel) shows biphasic functions for three hypothetical drugs (A, B, C) that might be obtained with a substitution procedure. All three drugs would be considered reinforcers because each shows behavior maintained above vehicle levels. Drugs A and B are similar in terms of potency as reinforcers because the ascending and descending portions of the curve occur at similar doses, while drug C would be considered less potent than A and B because the ascending and descending portions of the curve occur at larger doses.

Determining drugs as reinforcers with outcomes like those depicted in the top panel of Fig. 1 yields a binary, yes-or-no classification and does not provide quantitative information about *how* reinforcing a drug is. This is because response rate and number of injections can depend on several properties of the drug in addition to or other than its reinforcing properties (e.g., Balster and Bigelow, 2003; Richardson and Roberts, 1996; Wee et al., 2005). In Fig. 1 (top panel), drugs A and C may have shorter durations of action, resulting in higher response rates and more injections per session while drug B may have a longer duration of action, resulting in lower response rates and fewer injections per session. In this example, we would not conclude that drugs A and C were more