Editorial

Current approaches to the laboratory assessment of abuse potential

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It has been more than 70 years since Spragg showed that a morphine-dependent chimpanzee would actively seek experimenter-delivered injections of morphine rather than food, and approximately 50 years since pioneering work by Weeks and by Thompson and Schuster showed that morphine-dependent rats and monkeys would press a lever to self-administer morphine through indwelling intravenous catheters. These early demonstrations of the reinforcing effects of morphine in morphine-dependent subjects were quickly followed by an outpouring of self-administration studies showing that physical dependence was not a necessary pre-condition for drug reinforcement and also documenting the reinforcing effects of CNS drugs from other pharmacological classes, such as barbiturates, ethanol and monoaminergic stimulants. The importance of this early wave of self-administration research was profound. Evidence of the reinforcing effects of drugs in laboratory animals forced both a dramatic change in the general understanding of drug addiction and a new appreciation of the close relationship between the reinforcing properties of a drug and its abuse potential. In turn, these developments contributed to the creation of regulatory agencies in many countries to control access to drugs with abuse potential. For example, the Controlled Substances Act was enacted in 1980 to regulate all aspects of drug production, use, and distribution in the United States, and commanded the classification of known and novel psychoactive drugs into one of five schedules of controlled substances. Secondarily, these developments also highlighted the need for methodology with which to assess the abuse potential of drugs and, thereby, provide essential evidence to the regulatory agencies charged with controlling their availability. The intent of this Special Issue is to describe the status of such methodology, identifying strengths of current laboratory procedures as well as recent conceptual and experimental advances toward the assessment of a drug's abuse potential.

This Special Issue includes two groups of papers on the laboratory assessment of abuse potential, a set of reviews and overviews, and empirical research reports. The Special Issue opens with a review of the abuse potential of 'designer' stimulants that have proliferated in the underground market, presenting a worldwide challenge to governmental regulation. Watterson and colleagues survey studies of selected 'designer' drugs in laboratory animals and show that, notwithstanding differences in chemical structure, these drugs have neurochemical and abuse-related behavioral effects that are similar to those of conventional monoaminergic stimulants with abuse liability. This clear indication of comparable abuse potential for 'designer' and conventional stimulants is followed by a series of four papers presenting conceptual or methodological developments for assessing abuse potential. They begin with the advocacy by Edwards and Koob of the view that the escalation of drug self-administration is an integral part of the addiction process and, thus, can serve as a strong marker of addiction potential. Their position is based on a theoretical perspective on addiction processes, and commands attention. It is followed by another theory-based argument – a thoughtful exposition by Verendeev and Riley of the complex stimuli that comprise the motivational effects of abused drugs. In particular, the authors argue that aversive, as well as reinforcing, effects of drugs are prime determinants of their abuse potential and need to be considered in that assessment. The third paper, by Collier and Echevarria, is not theoretical but, rather, proposes to extend the range of practical approaches to assessing abuse potential to include the measurement of conditioned place preference in zebrafish. At the very least, this economical approach provides a testament to the universality of conditioning and motivational processes across phyla, and offers the opportunity to employ non-mammalian laboratory subjects that are now widely accepted for many types of biological study. In the final review in this series, Jones and Comer provide a succinct and clear overview of the self-administration procedures used in human preclinical research, emphasizing the value of incorporating them into a multi-faceted approach that also includes subjective, physiological, and cognitive endpoints.

The first part of the Special Issue concludes with a series of three contributions from researchers in the pharmaceutical industry where, as a result of regulatory oversight, abuse potential testing has been a critical feature of CNS drug development. The first paper, by Swedberg, offers a roadmap for testing new CNS drugs for abuse and dependence potential in the preclinical laboratory. Although an apparently step-wise process utilizing a range of procedures, the hazards in abuse potential testing are also clearly enunciated and the strong emphasis is on avoiding costly mistakes late in the development process. However, even for compounds that successfully advance through preclinical testing for abuse potential in laboratory animals and humans, negotiating the shoals of the regulatory process represents a formidable challenge. This is detailed by Rocha in the next paper, which presents an

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overview of the legal and regulatory framework that governs the marketing of drugs with abuse potential. In the final paper in this section, Horton and colleagues take on the difficult challenge of evaluating the utility of preclinical methods for forecasting governmental regulatory decisions regarding abuse potential. To do this, they conducted a statistical analysis of the predictive value for the eventual scheduling status of 100 drugs by the U.S. FDA of a wide range of in vitro and in vivo assays in laboratory animals and human subjects, alone and in combination. Not surprisingly, some procedures appear to be better predictors than others, and the authors discuss the implications for assessing the abuse potential of newly-developed compounds.

The second group of papers in this Special Issue, reporting original research, addresses topics ranging from the straightforward evaluation of the abuse potential of previously unregulated drugs to the exploration of traditional and advanced methods for assessing abuse potential, including the evaluation of the comparative reinforcing strength of abused drugs. Like the earlier reviews section, this series of papers also opens with a study of 'designer drugs'. Using standard locomotor activation and drug discrimination procedures, Gatch and colleagues examine the abuse potential of a range of compounds sold under the deceptive heading of 'bath salts' as legal alternatives to amphetamine or cocaine. Their study provides a fine example of how such designer drugs can be efficiently evaluated for abuse potential and, depending on results, quickly presented for governmental regulation. The next two papers, using established behavioral principles of rate-dependency, offer a novel twist to the reward-related endpoint of intracranial self-stimulation (ICSS). First, Bauer *et al.*, analyze the correlation between the rate-dependent effects on ICSS of d-amphetamine and other monoamine releasing psychomotor stimulants and their effects in other assessments of abuse potential. The authors conclude that the expression of rate-dependent effects may serve as a useful metric of drug reward and, thus, abuse potential. These conclusions are extended by Altarifi *et al.*, in the following paper, which shows that a second class of abused drugs, opioids ranging in agonist efficacy, can also increase ICSS rates in a rate-dependent manner, especially after chronic exposure.

Subsequent papers provide a change of pace, and illustrate various types of research within the general topic of reinforcing strength. First, Salas *et al.*, examine the regulation of Cocaine and amphetamine-related transcript (Cart) gene expression as a biomarker of addiction vulnerability, i.e., differences in the reinforcing strength of a drug in populations that are thought to differ in addiction vulnerability. Using rats differing in a reward-related phenotype, the authors measure Cart expression after treatment with cocaine or morphine, which serves to demonstrate the complexity of the original proposition. Martelle *et al.*, also take up the question of addiction vulnerability, this time in nonhuman primate studies, asking whether a history of methylphenidate exposure during adolescence might change the reinforcing strength of methylphenidate later in life. This Short Report nicely describes that prior methylphenidate exposure has limited, if any, effects: the results have clear relevance to the frequent prescription of anti-ADHD medications to adolescents in modern society.

The next several papers continue to deal with the measurement of reinforcing strength using self-administration methodology. A Short Report by Lile *et al.*, describes the use of progressive ratio procedures to scale the reinforcing strength of cocaine, methamphetamine, and d-amphetamine, monoaminergic stimulants with well-characterized abuse liability. The data indicate that the reinforcing strength of d-amphetamine may be less than that of the other two drugs; however, the authors appropriately note that pharmacological reinforcing strength is only a starting point in the evaluation of relative abuse potential, which, even for strong reinforcers, can be modified by contextual and societal factors. The next paper, by Paronis, reports on the reinforcing effects of oral alcohol, a drug that is typically difficult to establish as a reinforcer in laboratory animals. A series of detailed parametric 'choice' experiments in rats demonstrate that ethanol added to milk easily and clearly shifts behavior to its self-administration under concurrent and otherwise identical schedules of milk delivery. Continuing the theme of the reinforcing effects of alcohol, a paper by Pyszczynski and Shahan, probes the influence of contextual factors in the strength of alcohol-seeking behavior in rats following extinction. Their simple yet elegant approach – removing the availability of food reinforcement in another component of the experimental session – reveals a direct impact on the strength of alcohol-seeking after extinction, illustrating some of the complex behavioral interactions that surely play a role in relapse to drug-seeking behavior. The next paper takes us from alcohol back to opioids, this time in human subjects. In this study, Comer and colleagues evaluate different alternative reinforcers in 'choice' procedures for studying the relative reinforcing strength of abused opioids. Their results indicate that the type of alternative reinforcement – e.g., money or other drugs – can dictate the relative reinforcing strength of abused drugs, even of opioids in opioid-addicted individuals. In addition to its value for expanding our understanding of the reinforcing effects of abused opioids, this paper serves as an important reminder that data on a drug's abuse potential are only as robust as the assays that are designed to study it. The final paper on manipulations that modify the reinforcing effects of abused drugs is a straightforward examination by Wing and Shoaib of a pharmacological principle elaborated in early work on cocaine, that the reinforcing strength of an intravenously administered drug is inversely related to infusion duration. These authors nicely extend this concept to nicotine, which typically serves as a weak reinforcer, and show that its reinforcing effects can

be profoundly reduced by increasing infusion duration – again emphasizing the importance of robust assay conditions in abuse liability assessment.

The final two full-length papers in this Special Issue, from the same group, reexamine the relationship between the discriminative-stimulus and reinforcing effects of a drug in laboratory animals and its subjective effects in humans. Reynolds and colleagues present data on the relationship between the subjective and discriminative-stimulus effects of oral d-amphetamine in human subjects, while Bolin and colleagues tackle the relationship between the subjective effects of d-amphetamine and its reinforcing effects under a progressive-ratio schedule of oral self-administration. In both studies, the results indicate that the several procedures capture distinct and complementary aspects of abuse potential, suggesting that one endpoint cannot easily replace the others.

Overall, the contributions to this Special Issue make it clear that, in the five decades of drug abuse and addiction research since the first demonstrations that drugs can serve as reinforcers, our understanding of the reinforcing properties of drugs and how they are modified by contextual and individual factors has vastly improved. In turn, this improved understanding has been translated into clear methodological advances in assessing the abuse potential of known and newly-developed drugs. However, it also is clear that our understanding of drug abuse and addiction is not yet complete, and our appreciation of its complexity expands regularly through advances in this field of research. Concomitantly, the assessment of abuse potential, though steadily improving through technological and methodological advances, remains imperfect. Overall, this is still very much a work in progress, which undoubtedly will continue to be refined in the coming years.

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