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Method of data interpretation for the determination of abuse liability in rodent self-administration studies under the FDA guidance document

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ABSTRACT

All new molecular entities that enter the CNS and exert an activity in the brain must be assessed for abuse liability prior to a New Drug Application approval by the US Food and Drug Administration. One element of the screening process is the assessment of the reinforcing properties of the drug candidate using the regulatory-preferred species, the rat. We describe one method of data review from the standard rat IV SA study design that can be used to conclude the relative abuse liability of the new drug entity. While we do not claim the process as the only way to review or interpret the data, we believe the steps described highlight a process that the pharmaceutical development team can use as a starting point for a discussion during study protocol development.

1. Introduction

The manufacturer of any new drug that enters the central nervous system (CNS) and exerts an activity in the brain must either screen the compound for the liability of abuse and dependence potential or develop a defense for not conducting such testing based on the known pharmacology and toxicology of the drug as part of the new drug application (NDA) approval process. Three core behavioral assays are recommended to be conducted in the regulatory-preferred species (rat) prior to NDA submissions: self-administration, drug discrimination, and drug dependence/withdrawal assays. Assessing the abuse liability of new CNS-active drugs is essentially a procedure for assessing the pharmacologic equivalence with the standard drugs of abuse (Jasinsky & Henningfield, 1989). The industry "gold standard" for the assessment of the characteristic features of a common drug of abuse, such as hedonic (euphoria/dysphoria), reward (approach, avoidance) or motivating properties (reinforcement, punishment) of that drug candidate is the intravenous self-administration assay in rats.

Federal regulators have developed a strategy of preclinical abuse liability risk assessment analysis that focusses on "real world" patterns and expectations of actual "street" drug use. Many real-world examples of preclinical abuse liability data sets include multiple comparisons between test article and positive comparator data. Drug history can play a significant role in altering or modifying the response to novel drug administrations. Statistical analyses of behavioral data, especially in "learning" or "conditioning" paradigms often violate the assumptions of parametric statistical tests. These studies involve repeated testing of animals that may be 1) contingent upon the demonstration of stable baseline performance criteria, 2) continued "learning" sessions which are interspersed between independent test sessions, such that 3) the tests may not be conducted in the exact same subset of trained animals or 4) rely on small sample populations. All of these standard practices may set the stage for complex interpretations of what Milliken & Johnson (1998) have referred to as "messy data".

This purpose of this review is to consolidate and describe the process of data review, analysis and conclusions derived from the standard rat self-administration study design described within the FDA's (2017) Assessment for Abuse Potential for Drugs: Guidance for Industry. The FDA

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has recommended the training of rats to press a lever for programmed IV drug delivery under a fixed-ratio 10 schedule of lever press responding (10 consecutive responses required to earn a single bolus of drug) of a known drug-of-abuse controlled by the U.S. Drug Enforcement Administration (See Gauvin, Guha, & Baird, 2015; or Gauvin, Dalton, & Baird, 2017 for details). Following demonstration of stable day-to-day voluntary intake of a known positive comparator, (such as cocaine) a series of 3 or 5 day substitution tests are conducted to document the propensity of the animals to initiate and maintain lever press responding that results in repetitive and self-controlled delivery of the test article within and between daily sessions. The determination of a relative abuse liability must be based on data that is scientifically sound, legally defensible and timely, relevant to schedule control reviews conducted by both FDA and DEA as part of the NDA approval and drug labelling regulatory requirements (McClain & Sapienza, 1989). The method of classification by comparing new substances to prototypes is not only important for pharmacological theory and clinical utility; it was also the basis for legal/regulatory actions of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (Title 21, Chapter 13, §811 op cit.; Jasinsky & Henningfield, 1989). The CSA controls drug substances, not upon their chemical structure, but rather upon their degree of pharmacologic equivalence to various prototypic addicting drugs (Martin, 1977). It is important to note that under legal statutes drug control includes the modifier "relative" when describing abuse potential. This means that the abuse potential of a new substance should be compared to that of a substance with a known abuse potential. It is essential, therefore, that abuse liability studies contain a quantitative as well as a qualitative component. For example, in dependence potential studies it is not sufficient just to list or categorize the constellation of behaviors expressed during an observational period following abrupt withdrawal from repeated high dose treatments (qualitative approach). For drug scheduling purposes, it is also imperative to assess the

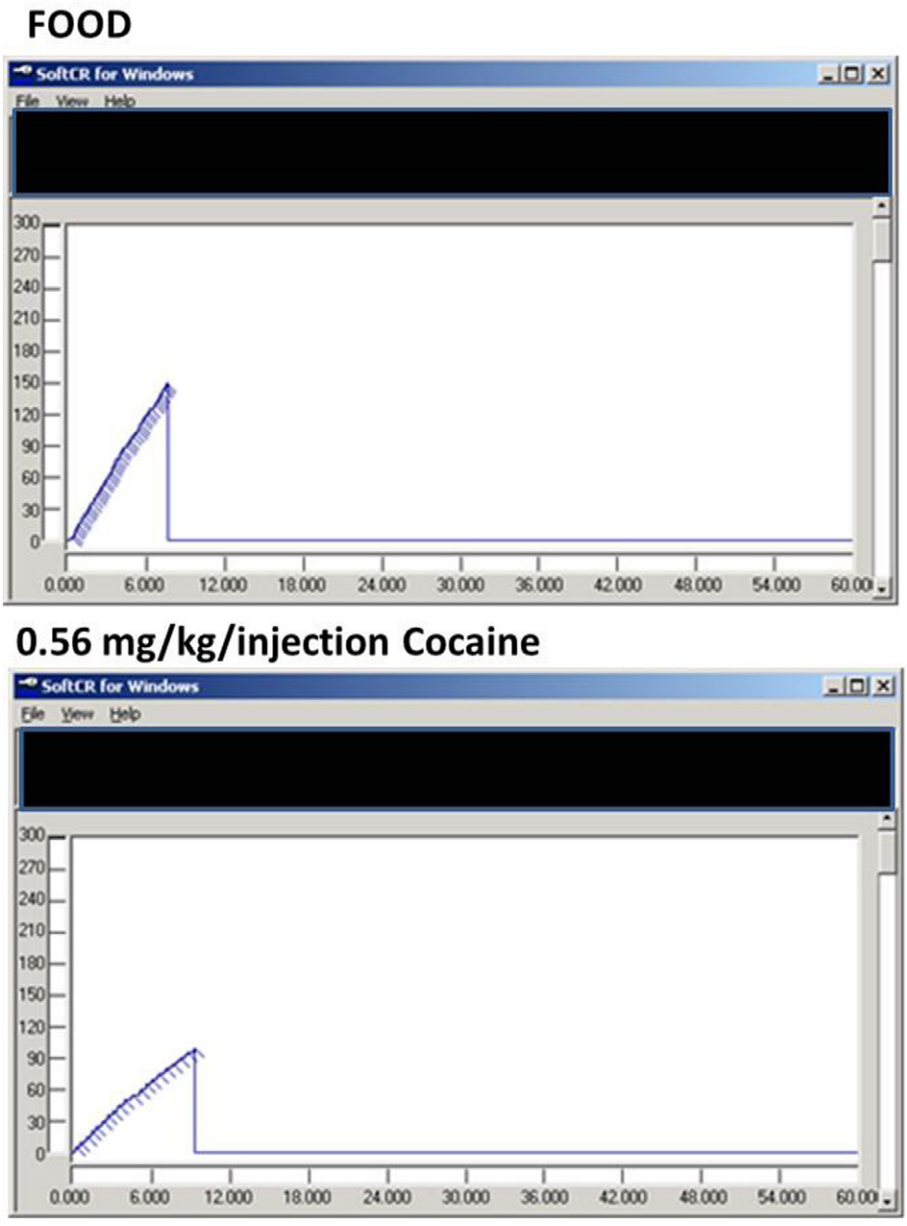

Fig. 1. Cumulative records for a training session using food (top panel) or cocaine (bottom panel) in the same animal under behavioral contingencies in effect at the time of training. Cumulative records from a single one-hour lever press operant task under a fixed ratio 10 schedule of food deliveries during initial training in a self-administration study (top panel). Following stable daily response rates for food deliveries, the animal is switched over to cocaine deliveries under the same FR10 schedule of lever press responding (bottom panel). The cumulative record shows the moment-to-moment changes in response rates (slope of function) and the patterns of delivery (downward tics) of the available reinforcer: food (top panel) or the maintenance dose of cocaine (bottom panel).