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Appraisal of state-of-the-art

# Current approaches and issues in non-clinical evaluation of abuse and dependence

Paul Moser *, Toni Wolinsky, Vincent Castagné, Mark Duxon

*Porsolt & Partners Pharmacology, 9bis rue Henri Martin, 92100 Boulogne-Billancourt, France*

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ABSTRACT

Preclinical assessment of drug abuse and dependence has been the subject of several recent regulatory guidelines. Both the European and US authorities recommend a tiered approach and are generally aligned on the methods which should be used. The first tier simply compares the pharmacology of the novel substance to known drugs of abuse. The second tier aims to identify abuse and dependence liability more directly. The most direct approach to assessing reinforcing properties is the i.v. self-administration procedure. Unfortunately there is no standardized procedure for evaluating substances with differing potencies, reinforcement properties or pharmacokinetics (PK). Indeed, the choice of training substance, species and procedural parameters can radically affect the outcome. Apart from the lower cost of the rat, the primate presents several advantages for self-administration studies (potentially greater similarity to humans in behavioral effects, active doses and PK). Although it does not measure abuse liability directly, drug discrimination is a powerful method for assessing the similarity of a test substance to a known drug of abuse. In this procedure an animal uses the interoceptive effects of the substance as the discriminative stimulus to determine which of two responses to make. For certain classes of substance, such as hallucinogens acting via the 5-$HT_{2A}$ receptor, discrimination is the only procedure currently able to identify them. Drug dependence is assessed by the occurrence of withdrawal effects on drug discontinuation. Although conceptually simple, many factors (duration and frequency of drug treatment, dose/exposure levels, duration of observation after discontinuation) can complicate interpretation. Telemetry may represent a novel approach which allows continuous observation of somatic and behavioral parameters during drug withdrawal thereby increasing sensitivity. Presently available tools can identify essentially all substances known to cause abuse or dependence with little risk of false positives. It remains unclear how effective these models will be with entirely novel substances. Nonetheless, drug abuse/dependence is an area of safety pharmacology where the predictive value of animal models remains very high.



## 1. Introduction

Drug abuse can be defined as taking a drug for non-medical purposes and is often driven by the ability of the substance to produce positive subjective effects. Dependence, on the other hand, is the need to continue to take a drug and is not necessarily related to positive effects of a drug. Dependence is defined and studied by evaluation of withdrawal effects. The evaluation of abuse and dependence liability has recently been the subject of several documents produced by regulatory authorities, including the Food and Drug Administration (FDA) in the USA, the European Medicines Authority (EMA) and the International Committee on Harmonisation (ICH). The most pertinent of those documents are listed in Table 1. The trigger for this recent activity has been the recognition that many commonly prescribed agents can result in withdrawal signs that represent not only a problem in their own right but may also contribute to dependence. At the same time there are increasing concerns about prescription drug abuse. Thus the EMA and the FDA have given some guidance as to how they would like to see these questions addressed in non-clinical and clinical studies. The ICH document puts similar ideas into the context of clinical drug development. The methods to be used and their timing in the drug development process suggested by the different authorities are broadly similar, both for evaluation of abuse liability and for assessment of withdrawal. However, the EMA documents are more concerned with dependence as clearly indicated by their titles (Guideline on the non-clinical investigation of the dependence potential of medicinal products and Background to the CDMP position paper on Selective Serotonin Uptake Inhibitors (SSRIs) and dependency/withdrawal reactions) and its presentation of the issues in the introductory text. In contrast, the FDA places more emphasis on abuse

*Abbreviations:* CB, cannabinoid; CNS, Central Nervous System; CPP, conditioned place preference; DOI, 2,5-dimethoxy-4-iodoamphetamine; EMA, European Medicines Agency; FI, Fixed Interval; FR, Fixed Ratio; FDA, Food and Drug Administration; GABA, gamma-aminobutyric acid; GLP, Good Laboratory Practice; 5-HT, 5-Hydroxytryptamine; ICH, International Committee on Harmonisation; i.v., intravenous; LSD, lysergic acid diethylamide; NMDA, N-methyl-D-aspartate; PhRMA, Pharmaceutical Research and Manufacturers of America; PK, pharmacokinetics; PTT, 2-beta-propanoyl-3-beta-(4-toluyl)-tropane; SSRI, selective serotonin reuptake inhibitor; THC, delta-9-tetrahydrocannabinol.

* Corresponding author. Tel.: +33 146109990; fax: +33 146109999.
*E-mail address:* pmoser@porsolt.com (P. Moser).

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**Table 1**
Current regulatory guidelines and discussion documents from regulatory authorities addressing non-clinical abuse and dependence.

| Authority | Document title | Date | URL |
|---|---|---|---|
| ICH | M3 (R2): Non-clinical safety studies for the Conduct Of Human Clinical Trials and Marketing Authorization for Pharmaceuticals | Jul 2008 | http://www.ema.europa.eu/pdfs/human/ich/028695endraft.pdf |
| EMA | Background to the CDMP position paper on Selective Serotonin Uptake Inhibitors (SSRIs) and dependency/withdrawal reactions | Apr 2000 | http://www.ema.europa.eu/pdfs/human/press/pp/277599en.pdf |
| | Background to the CDMP position paper on possible preclinical studies to investigate addiction and dependence/withdrawal related to the use of Selective Serotonin Uptake Inhibitors (SSRIs) | Dec 2000 | http://www.ema.europa.eu/pdfs/human/press/pp/227800en.pdf |
| | Guideline on the non-clinical investigation of the dependence potential of medicinal products | Mar 2006 | http://www.ema.europa.eu/pdfs/human/swp/9422704en.pdf |
| FDA | PhRMA-FDA Dialogue Session Abuse Potential Assessment | Feb 2008 | http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM180770.pdf |
| | Assessment of Abuse Potential of Drugs | Jan 2010 | http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf |

liability, again as indicated by the title (Assessment of Abuse Potential of Drugs) and also by the introduction which places the issue within the context of the Controlled Substances Act as related to abuse and diversion of medical substances. Over the past few years there have been several reviews of non-clinical assessment of abuse liability and dependence, which should be consulted for more information on some of the topics raised later (Ator & Griffiths, 2003).

In addition to these official documents, a dialogue between the FDA and PhRMA (Pharmaceutical Research and Manufacturers of America) has given further indication as to the current thinking of US regulatory bodies as to how to approach this question (Lindgren et al., 2008; Markgraf & Kallman, 2009).

The first guideline documents from the EMA addressed the issue of withdrawal effects related to the use of selective serotonin reuptake inhibitors (SSRIs; see Table 1). This was perhaps the first suggestion from a regulatory authority that withdrawal effects at a substantially milder level than those seen with more traditional withdrawal-inducing drugs such as morphine, nicotine and benzodiazepines were of concern and should be addressed non-clinically. Examination of the clinical literature related to withdrawal effects of SSRIs indicates that those effects include increased headaches, irritability, dizziness, etc. — none of which are easily amenable to study in animals. A possible approach to address this will be suggested later.

The ICH M3 document is mainly concerned with clinical evaluation of abuse liability but also indicates which non-clinical models should be used in parallel.

The most recent FDA discussion document adds little to the EMA and ICH documents but perhaps goes further in suggesting that GLP compliance is desirable. However, the actual wording is hardly different to that of the ICH S7A guidelines.

Both the FDA and EMA describe an evaluation in two parts: firstly an evaluation of the basic pharmacology of a test substance compared to known drugs of abuse followed, if necessary, by a secondary evaluation using specific behavioral techniques. To a large extent the procedures suggested are very similar across different regulatory authorities and so no further distinction between the various bodies will be made.

## 2. First tier evaluation

The essence of the first level of evaluation is to compare all that is known of the novel substance with existing abused substances. This approach is clearly set out in several guidelines but was outlined as long ago as 1970 in the Comprehensive Drug Abuse Prevention and Control Act (US Federal Law, Pub. L. No. 91-513, 84 Stat. 1236), which states that: "*The substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community*". Similar ideas are put forward in the more recent EMA and ICH M3 guidelines, both of which recommend a tiered approach to abuse liability evaluation.

At this stage a critical evaluation of what is already known about the test substance is carried out. Among the questions that should be asked are: Does the test substance enter the CNS? Does it interact with receptors or uptake sites associated with abused drugs? Does it have a therapeutic activity that has been associated with drugs of abuse?

Thus substances with poor CNS penetration are not considered as having any marked potential for abuse liability, although there may be a need to demonstrate that this is the case functionally. For example, one could use drug discrimination in this context to demonstrate that a test substance did not generalise to an abused substance even though it had high affinity for the target receptors. Use of *ex-vivo* binding procedures may also provide some information on this.

The CNS sites associated with the rewarding effects of drugs of abuse have been well characterised (Koob & Volkow, 2010) and thus any drug that interacts with opiate, dopaminergic, cannabinoid, nicotinic, GABAergic, serotonergic 5-$HT_2$, glutamatergic NMDA or sigma receptors or uptake systems for dopamine or serotonin might require further evaluation. Even if the test substance apparently has the opposite *in vitro* pharmacological activity at a given site compared to a drug with abuse potential (e.g. 5-$HT_2$ antagonist activity rather than agonist activity that hallucinogens such as LSD and DOI have) the regulatory authorities may require a more formal demonstration that the test substance does not show any *in vivo* functional activity comparable to the reference abused substance.

Finally, there are several therapeutic areas where current treatments are strongly associated with abuse. Analgesics, anxiolytics and sedatives are the three main categories. Stimulants, such as amphetamine and modafinil, would also fit into these lists, although the actual therapeutic domains (i.e. treatment of attention deficit hyperactivity disorder or narcolepsy) may vary.

Thus a substance that does not enter the CNS in detectable quantities or does not tick any of the other boxes listed previously would probably need little in the way of further evaluation. How much additional work CNS-penetrant substances need depends on numerous factors such as the strength of the 'signal' seen in these early tests, the impact scheduling may have on the therapeutic use of the substance and the risk-aversiveness of the company developing the substance. These elements will be touched on later when the timing of supplemental tests is addressed.

## 3. Second tier evaluation

Once a risk of abuse liability has been suggested indirectly from the first tier evaluation, there are only a limited number of tests that then need to be considered to directly evaluate this risk. Although other tests are briefly mentioned by the regulatory authorities, the tests