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Invited review

Human abuse liability evaluation of CNS stimulant drugs

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ABSTRACT

Psychoactive drugs that increase alertness, attention and concentration and energy, while also elevating mood, heart rate and blood pressure are referred to as stimulants. Despite some overlapping similarities, stimulants cannot be easily categorized by their chemical structure, mechanism of action, receptor binding profile, effects on monoamine uptake, behavioral pharmacology (e.g., effects on locomotion, temperature, and blood pressure), therapeutic indication or efficacy. Because of their abuse liability, a pre-market assessment of abuse potential is required for drugs that show stimulant properties; this review article focuses on the clinical aspects of this evaluation. This includes clinical trial adverse events, evidence of diversion or tampering, overdoses and the results of a human abuse potential study. While there are different types of human experimental studies that can be employed to evaluate stimulant abuse potential (e.g., drug discrimination, self-administration), only the human abuse potential study and clinical trial adverse event data are required for drug approval. The principal advances that have improved human abuse potential studies include using study enrichment strategies (pharmacologic qualification), larger sample sizes, better selection of endpoints and measurement strategies and more carefully considered interpretation of data. Because of the methodological advances, comparisons of newer studies with historical data is problematic and may contribute to a biased regulatory framework for the evaluation of newer stimulant-like drugs, such as A_2 antagonists.

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

1. Introduction

Psychoactive drugs that increase alertness, attention and concentration and energy while also elevating mood, heart rate and blood pressure are referred to as stimulants. This class of drugs traditionally includes amphetamines, methylphenidate and cocaine. Recently, many compounds have been developed that are either structurally similar to and/or have pharmacologic effects and mechanisms of action which resemble those of the classical stimulants (e.g., modafinil, atomoxetine, tesofensine, triple uptake inhibitors). The newest class, as yet not approved, include adenosine receptor 2 (A_2) antagonists such as preladenant. Closely related to stimulants are "designer" drugs manufactured illicitly (e.g., MDMA). These compounds typically use an existing stimulant or precursor as a starting point, and have aspects of the classical pharmacology of stimulants but have substituents that result in hallucinogenic/psychotomimetic effects. For example, mescaline is a ring substituted phenylethylamine ring structure (3, 4, 5-trimethoxyphenethylamine) – a substructure that has spawned thousands of variants of stimulants and perception-altering drugs. This chapter does not consider these highly abusable drugs, even though they are a more serious public health concern than stimulants, because they combine stimulant effects with distortions of perception and judgment that may lead to accidents and harm to self or others. This high risk is recognized in the national and international Controls placed on these drugs, none of which are approved for marketing.

The majority of classical stimulant drugs act by causing the release and/or inhibiting the reuptake of monoamines, primarily norepinephrine (NE) and dopamine (DA), but some have also been shown to also block sodium channel activity (Brauer et al., 1996; Kegeles et al., 1999; Leviel, 2001; Rothman et al., 2001; Silvia et al., 1997). The increased levels of dopamine in the nucleus accumbens in particular are believed to be responsible for the feelings of "euphoria" associated with these drugs.

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Despite some overlapping similarities, stimulants cannot be easily categorized by their chemical structure, mechanism of action, receptor binding profile, effects on monoamine uptake, behavioral pharmacology (e.g., effects on locomotion, temperature, and blood pressure), therapeutic indication or efficacy. This is true also with respect to properties relevant to abuse potential. Thus "stimulants" comprise a large and heterogeneous group of drugs that include "pure" stimulants to compounds with mixed effects (Table 1 lists stimulants regulated by the World Health Organization [WHO] and the United States [US] Controlled Substances Act [CSA]).

1.1. Public health concern with abuse and dependence on stimulants

The large increase in prescriptions for stimulants in the last 20 years has raised public health concerns about their diversion and misuse (NIDA, 2011). From 1991 through to 2012, prescriptions for CNS stimulants in the US increased approximately nine-fold (Horton et al., 2013; NIDA, 2011).

In the past, prescription stimulants were used clinically to treat conditions such as obesity, but now are used primarily for treating neurological (e.g., narcolepsy) and psychiatric disorders (e.g., Attention Deficit Hyperactivity Disorder [ADHD], depression). Contemporary stimulants, such as methylphenidate and modafinil, are perceived as being relatively safe, hence are widely available. These drugs demonstrate effects on improving alertness, energy and sense of well-being, and are widely used non-medically to enhance "cognition" and alertness in high school and college students and performance in athletes and other professionals (Novak et al., 2007).

Thus, the increasing medical use of stimulants, and corresponding rise in abuse and misuse, have led to public health concerns, since acute and chronic misuse of stimulants can lead to irregularities in heart rate, cardiac failure, pulmonary hypertension, hyperthermia, seizures, stroke, hepatotoxicity, and psychiatric symptoms (Carvalho et al., 2012). When these drugs are used by alternative routes, such as intranasal or intravenous, additional health concerns can arise, such as multi-organ talcosis and granulomas. In addition to prescription stimulants, the abuse of "designer" stimulants has also contributed to the public health problems associated with these drugs.

2. International control of stimulants

Stimulants under international and US control are listed in Table 1. In part, the CSA (1971) is the regulatory framework that the US has adopted to comply with its obligations as a signatory to the

Table 1
Stimulants scheduled internationally and in the United States.

WHO psychotropic convention	Controlled substance Act (USA)
Schedule I	
Numerous phenethylamine substituted psychedelics including DOB, DMA, DOET, MDOH, MDMA, mescaline, MMDA, 4-MTA, PMA, MDA, STP, TMA	Numerous phenethylamine substituted psychedelics including DOB, DMA, DOET, MDOH, MDMA, Mescaline, MMDA, 4-MTA, PMA, MDA, STP, TMA plus other uniquely scheduled in the United States
Various structural analogs and precursors	Various structural analogs and precursors
• Cathinone	Pseudoephedrine as precursor
• Methcathinone	
• 4-Methylaminorex	
Schedule II	
• Amphetamine	• Cocaine (used as a topical anesthetic): treatment of cancer
• Amineptine	• Methylphenidate (Ritalin), Methylphenidate HCL (Concerta), and Dexmethylphenidate (Focalin): treatment of ADHD
• Dextroamphetamine	• Amphetamines (originally placed on Schedule III, but moved to Schedule II in 1971) and Dextroamphetamine (Dexedrine): treatment of ADHD, narcolepsy
• Methamphetamine (dextro)	• Methamphetamine and Dextromethamphetamine (Desoxyn): treatment of ADHD, obesity
• Fenethylline	• Mixed amphetamine enantiomers/mixed salts (Adderall) and Lisdexamfetamine (Vyvanse): treatment of ADHD, narcolepsy
• Levoamphetamine (scheduled despite being inactive isomer)	
• Levomethamphetamine (scheduled despite being inactive isomer)	
• Methamphetamine (racemic)	
• Methylphenidate	
• Phenmetrazine	
Phenethylamine psychedelics:	
• 2C–B	
Schedule III	
• Cathine	• Phendimetrazine Tartrate, a stimulant synthesized for use as an anorexiant;
	• Benzphetamine HCl (Didrex), a stimulant designed for use as an anorexiant;
Schedule IV	
• Amfepramone	• Cathine
• Aminorex	• Diethylpropion
• Benzphetamine	• Fencamfamin
• Etilamfetamine	• Fenproporex
• Fencamfamine	• Mazindol
• Fenproporex	• Mefenorex
• Mazindol	• Modafinil and stereoisomer armodafinil
• Mefenorex	• Pemoline
• Mesocarb	• Phentermine
• Pemoline	• Pipradrol
• Phendimetrazine	• Sibutramine
• Phentermine	• (−)-1-dimethylamino- 1,2-diphenylethane
• Pipradrol	
• Pyrovalerone	
Drugs with both stimulant and opioid effects:	
• Lefetamine (SPA)	

WHO Single Convention (1961) and WHO Psychotropic Convention (1971). The principle underlying these regulatory controls is that Schedule I (C-I) drugs have no approved medical use and have high abuse liability. Schedule II (C-II) drugs have approved medical indications but also have high abuse risk. Successively lower schedules reflect a lesser degree of abuse risk. However, for all practical purposes only C-II drugs are subject to onerous restrictions (e.g., quotas on manufacture, special storage requirements and record keeping, written prescription). From a clinician's perspective, all lower scheduled stimulant drugs appear as prescription drugs even though there are some restrictions applied to pharmacies, manufacturers and to import and export procedures.

3. Terminology

In this chapter, **abuse potential** will refer to the intrinsic pharmacologic effects of a drug that are reported as "liked" by consumers or positive subjective effects thought to be related to behavioral reinforcement. These effects are believed to lead to abuse or "addiction". We stress that **abuse potential** is a net or balanced assessment, where positive effects can be tempered or offset by unpleasant or punishing effects of a drug. The term **abuse liability** will be used to mean abuse potential in the broader community (post-market) setting, which considers not only the intrinsic positive and reinforcing effects of the drug, but also factors which influence the risk of actual misuse, abuse or diversion of the drug. These include factors such as therapeutic indications, market size, fads, market competitors, ease of tampering for injecting or snorting, context of use, opportunities for diversion, and medical consequences of overdose and toxicity, among others.

The reader should note that over time and across organizations terminology for these same concepts varies. e.g., The College on problems of Drug Dependence (CPDD) and Health Canada tend to use the terminology we employ (College on Problems of Drug Dependence, 2003), the US FDA tends to use the term "abuse potential" in its formal guidance documents in New Drug Application Guidelines (Calderon and Klein, this special issue; CDER/FDA, 2010) (CDER/FDA, 2013); and the World Health Organization Expert Committee on Drug Dependence has historically used the term "dependence potential" or "dependence liability" largely eschewing the term "abuse liability" although this may be changing (WHO, 2012).

4. Scope of this chapter

Fig. 1 provides an overview of the data required by the FDA for an abuse liability evaluation of a drug prior to marketing approval. This chapter focuses on the clinical aspects of the evaluation. These include clinical trial adverse events (AEs), evidence of diversion or tampering, overdoses and the results of a human abuse potential study. This data collection should begin early in development so that the information gathered can be used early and sequentially to direct the course of clinical testing.

We have decided to not consider the rather substantially different approach taken by the European Medicines Agency (and other jurisdictions) since most new drug approval applications are done at least in both the USA and the EU. Since the US requirements are more complex and stringent any sponsor de facto will have the appropriate data for an EMA filing. Difference in Europe include, trials in drug-experienced subjects are not required for European CNS drug registrations and are not mentioned in the EMA (2005) guidelines. All abuse/dependence evaluations are based on the preclinical package of work described by EMA (2005) and a review of the adverse events in the Phase 1–3 clinical trials database. Similarly, there is no equivalent of the US 8-Factor Analysis. All descriptions of preclinical and clinical abuse/dependence findings are contained within the Market Authorisation Application (MAA) dossier. In practice the section in the dossier relating to this issue is much shorter than for a New Drug Application in the US.

We have also not included any detailed discussion about the world's most commonly used stimulant namely, caffeine and related substances. Our reasons for this are that the literature is vast and extends far beyond what is possible to manage in a single chapter and because caffeine is not a controlled substance internationally.

5. Pre-market assessment of abuse potential

Pre-approval review of abuse potential is required for prescription stimulants and drugs with potential stimulant properties. The Food Drug and Cosmetics Act (FDCA) and regulations governing New Drug Applications stipulate that if a drug has stimulant properties, "all data" must be submitted to permit an assessment of the drug's abuse liability. With such concerns in mind, the Food and Drug Administration (FDA) (CDER/FDA, 2010), Health Canada

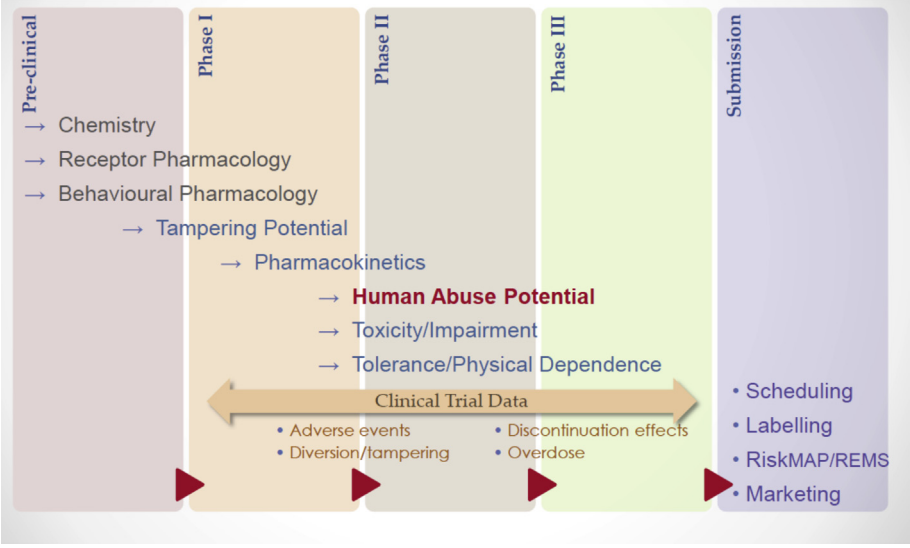

Fig. 1. Typical data requirements for a new drug submission assessing abuse liability.

(Health Canada, 2007) and the European Medicines Agency (EMA) (European Medicines Agency, 2005) have published Guidance documents outlining the recommended pre-approval abuse potential testing requirements for new and reformulated psychotropic drugs, including stimulants. The Canadian and FDA document address both non-clinical and clinical testing, while the EMA document outlines non-clinical testing requirements. The FDA guidance emphasizes the importance of methodologies to evaluate abuse potential utilizing data from a number of sources, both preclinical and clinical. These, as applied to stimulants, are discussed below. A recent review outlines the requirements for such studies in greater detail (Schoedel and Sellers, 2008).

6. Clinical methodology to assess stimulant abuse potential

6.1. Strategies

Two categories of clinical data are normally considered for the pre-market assessment of abuse potential in humans:

1. Human Experimental Studies
   a. Drug discrimination
   b. Self-administration
   c. Behavioral Economic
   d. Human Abuse Potential
2. Assessment of Clinical Trial Data
   a. Treatment Emergent Adverse Events (TEAEs)
   b. Drug Discontinuation-Emergent Adverse Events
   c. Assessment of "diversion" and other reports of abuse/misuse in clinical trials

Only the human abuse potential study and clinical trial data studies are required for drug approval and will be discussed in this chapter; other types of studies, including survey studies (stimulant abusers, Internet surveys) and post-market epidemiologic studies are discussed elsewhere in this volume. An older but still pertinent and excellent review considers other study options in detail (Foltin and Fischman, 1991).

6.2. Human abuse potential studies

Over the years, the methodology for these studies has evolved but the goal of abuse potential assessment has not changed, namely to determine if the drug produces subjective and/or behavioral effects that may be associated with an increased likelihood of repeated consumption or administration of the drug (i.e., reinforcing effects).

6.2.1. Study designs

The procedures used to evaluate abuse potential include measuring

1. Ability to discriminate effects of one drug from another (drug discrimination);
2. Drug self-administration self-administration involves a cost/benefit analysis by the consumer of those subjective effects that are usually rated as positive e.g., euphoria, against those experienced as negative e.g., anxiety, dysphoria (Foltin and Fischman, 1991);
3. Behavioral economic and choice procedures (monetary or other); and
4. Subjective effects and "liking" of drug, as well as other subjective effects, such as drug class identification (human abuse potential study) (Foltin and Fischman, 1991).

Some studies may combine features of more than one category, such as self-administration and reported subjective effects.

6.2.1.1. Human abuse potential studies. The human abuse potential study is the most critical data set of the pre-market regulatory dossier. This methodology has been in use for over 50 years, but has evolved. Subjects in earlier studies were described and selected as primarily "addicts", "post-addicts", or "incarcerated subjects" whereas since the 1990s, studies have selected and described volunteers as "recreational drug users" (Jasinski and Henningfield, 1989; Martin et al., 1971). Other changes have included the prequalification of subjects to test their ability to discriminate between placebo and drug effects, a choice of the measures used and choice of endpoints based on the improved measurement properties of modified scales, larger sample size and more comprehensive interpretation of the results (Schoedel and Sellers, 2008). Since many of the older "historical" studies used different subject populations without pre-qualification, smaller sample sizes and different endpoints, direct comparison of these older studies to more recent ones is almost impossible.

The most effective study design to assess abuse potential is considered to be one in which the dose and time profiles of pharmacologic and subjective effects of the drug of interest are compared against placebo and a comparator that is a known drug of abuse (Schoedel and Sellers, 2008). The studies are repeated single dose, randomized, double blind crossover studies in "recreational" drug users, i.e., subjects who are not dependent on known substances of abuse but are "familiar" with their pharmacologic effects. The time between dosing is determined by the half-life of the longest half-life drug included in the study. Detailed design and analysis considerations for such studies can be found in published reviews (Balster and Bigelow, 2003; Griffiths et al., 2003; Schoedel and Sellers, 2008) the essential components of the currently generally accepted study design are listed in Table 2.

For drugs with stimulant-like properties, prototypical comparator drugs include amphetamine, cocaine, and methylphenidate. Cocaine is typically not used because of its potential toxicity, limited availability (as it is no longer in use as a prescription drug) and poor oral bioavailability. Methylphenidate has also been used for some studies. Finally, phentermine has been included as a comparator in some studies, where the stimulant effects of the investigational product are thought to be relatively weak (Schoedel et al., 2012b).

A number of scales and questionnaires have been developed and used to assess the subjective effects of psychoactive drugs. These include Visual Analogue Scales (VAS) and other measures (Likert scales such as the Single Dose Questionnaire or Drug Evaluation Questionnaire) evaluating "drug liking", willingness to "take the drug again" positive and negative drug effects, class specific pharmacologic effects (e.g., anxiety, agitation or feeling energized for stimulant like drugs), and measures of drug class identification or similarity. For stimulant-like drugs, other measures of interest include scores on the short form 49-item ARCI (Haertzen, 1966; Haertzen et al., 1963; Martin et al., 1971), specifically the MBG scale (Morphine Benzedrine Group) to evaluate euphoria and consisting of items related to pleasant feelings, absence of worry, social popularity and effectiveness. The ARCI Amphetamine (A) scale measures the typical subjective effects of amphetamine: alertness, increased energy etc. The ARCI Benzedrine Group scale (BG) is another stimulant-sensitive scale that evaluates intellectual efficiency and mental energy. Essentially, these scales serve to demonstrate both "liking" and other positive effects that are viewed as correlated to repeated drug-taking behavior. In addition, some of these measures may be included primarily because the US CSA and scheduling framework is based on similarity in

Table 2
Best practices for human abuse potential studies.

Parameter Description/considerations
• Subjects recreational drug use experience with class of interest
• No history of dependence or substance abuse treatment
• Pharmacologically qualified (distinguish test drug vs. placebo):
• Face validity
• Objective confirmation of history
• Avoid false negatives (non-drug users)
• Increased sensitivity/reduced noise to decrease risk of study failure
• Sample size typically 20–40: need sufficient power for all contrasts
Selection of comparators typically based on
• Highest appropriate schedule: for unscheduled status compare to IV or V
• Pharmacologic class/mechanism, if from an abused class
• Pharmacologic/side effects profile (for novel classes)
Other considerations:
• Market competitor
• Pharmacokinetic similarity/biotransformation pattern
• Formulation
Doses
• Three dose level (under some special circumstances 2 doses may be sufficient)
• Dose response information and slope (dose-escalation pattern)
• Relevant to drug abusers
• Typical range of therapeutic → maximally tolerated
Measures
• Visual analog scales: drug liking (overall, "at this moment"), take drug again,
• Positive effects (good effects, high, etc.),
• Negative effects (bad effects, feeling sick, etc.), class-specific effects,
• Drug similarity
• Drug vs. money or other choice procedures
• Addiction Research Center Inventory (ARCI)
• Pharmacokinetics: assess exposure
• Objective: neurocognitive, pupillometry, vitals, observerrated scales
Challenges
• Novel drugs: more difficult to select appropriate population/comparator(s)
• Long half-life: incomplete washout, long study duration or nested parallel designs
• Outliers or "atypical" responses: difficult to interpret
• Methods improvement: many current scales are redundant and could be improved

pharmacologic effects to existing drugs of abuse (e.g., hallucinogenic, stimulant or depressant effects as outlined in the CSA) rather than a direct relationship to abuse potential.

As illustrated by the Case Studies below, the selection of appropriate endpoints is critical to making appropriate and predictive conclusions regarding the abuse potential of stimulant-like drugs. In particular, bipolar scales, such as the bipolar Drug Liking VAS (where 0 = Strong disliking and 100 = Strong liking), appear to have superior measurement properties, with lower variability and placebo response, but similar sensitivity to unipolar measures (Schoedel et al., 2012a; Shram et al., 2012). Since it can be difficult to make conclusions when both positive and negative effects are observed, as is the case with many stimulant drugs, the bipolar scales have the advantage that they require the subjects themselves to make conclusions about the overall effects of the drugs (i.e., the "forced choice" nature of the scale). This can greatly alleviate the risk of mis- or over-interpretation from the developer.

Measures of abuse potential are typically administered repeatedly at various time intervals across an 8- to 48-h study session (depending on the properties of the drug), in order to capture the onset, peak and offset of activity. The number of time points can make data interpretation seem complex or difficult, hence data are summarized using derived endpoints such as peak effect (Emax), time to peak effect (TEmax) and measures of overall effect, such as area under the effect curve (AUE). Most guidance documents refer to Emax as being the most appropriate endpoint, because it is easily identified and assumed to be sensitive and appropriate. However, Emax does not take into account the specific pharmacology of the test drug, when effect occurred and how long it lasted, which may be very important in the determination of abuse potential. In addition, Emax may be more susceptible to "expectancy", because a subject need only have a single, sporadic, or even accidently high response at one time point to produce a high Emax value. On the other hand, the AUE endpoint can sometimes suffer from low sensitivity, depending on the time interval selected. End-of-session and/or next-day measures such as "overall drug liking" and "willingness to take the drug again" can provide a more reliable assessment of overall drug effect, according to the subjects' own assessment.

Overall, the abuse potential study design is viewed as scientifically robust and highly sensitive in detecting important differences between drug effects. It is important to emphasize that the human abuse potential study needs to be interpreted in the context of a multidimensional assessment of the pharmacologic and behavioral effects of the drug being investigated, both preclinical and clinically.

7. Selected case studies

The purpose of this section is to highlight some of the methodologic and interpretation issues that affect the pre-market assessment of new stimulants. To summarize, the methodology that has been used for assessing the abuse potential of stimulants arose over 40 years ago from the study of potent and widely abused illicit stimulants (e.g., cocaine, amphetamines). These drugs act as both indirect releasers and re-uptake inhibitors of DA and show steep dose response curves for effects such as "liking" and "use again". Newer drugs may have different mechanisms of action, for example, typically have not been releasers of DA, have less prominent actions in the nucleus accumbens, have different selectivity and specificity for monoamine re-uptake transporters, and/or have considerable off target pharmacology.

We illustrate some of these issues in the following discussion of specific drugs, with the goal of encouraging the development of new, additional or more precise measures beyond the classical methodology. In our comments we suggest a critical appraisal of data from atypical stimulants before scheduling decisions are made. We suspect an over-reliance on older measures and older drugs may have resulted in some stimulant-like drugs being scheduled unnecessarily, since many such drugs have not been proven to result in any abuse or post-marketing public health problems (e.g., sibutramine, modafinil). In this context, we think new atypical stimulants such as A_2 receptor antagonists and triple uptake inhibitors are at risk to be evaluated in a simplified and historically-biased framework.

7.1. Phentermine

On some measures – especially in animal studies, phentermine has shown behavioral and reinforcing effects similar to cocaine. However, phentermine is a C-IV drug and does not show any substantial abuse in the community, with Drug Abuse Warning Network [DAWN] emergency department [ED] visits ranging from <30 to 848 per year from 2004 to 2009. Although this may be partly related to availability factors, such as relatively low and short-term medical use relative to other drugs used for ADHD, there may also be intrinsic differences in abuse potential between phentermine and amphetamines (C-II). Fig. 2 shows effect size data for subjective measures from 3 studies performed at a single investigational site (Parasrampuria et al., 2007a; Schoedel et al., 2012b, 2010). Although comparisons across studies may be problematic, versus a within-study comparison, the methodology was very similar for the 3 studies. While the overall effect size of phentermine for "at this moment" measures of liking and good effects are actually

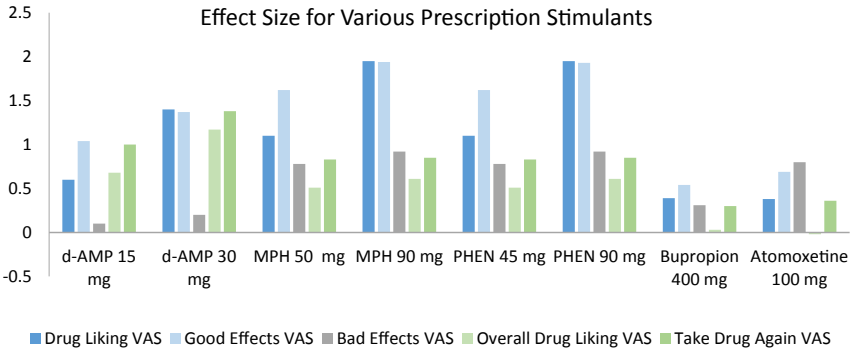

Fig. 2. Effect sizes in human abuse potential studies for different endpoints and stimulants.

larger than for D-amphetamine, the pattern of effects is different. Specifically, the "bad effects" were greater with phentermine compared to D-amphetamine, while the effect sizes for "overall" drug liking/willingness to take the drug again were lower. In contrast, the unscheduled "stimulant" drugs, bupropion and atomoxetine were associated with relatively low effect size across measures, although atomoxetine was associated with some fairly prominent negative effects. The finding of relatively low "overall" liking and willingness to take the drug again has been replicated in at least one additional study performed at the same site (Schoedel unpublished data 2014). Fig. 2 also indicates that the size of the effects with doubling the amphetamine dose are larger than seen with doubling the doses of either methylphenidate or phentermine. From a behavioral economics perspective this suggests that it is more effective and efficient for abusers to use amphetamine than the other two drugs. These differences may account for why phentermine and methylphenidate do not have the same abuse liability as amphetamine.

In addition to the effect size, Fig. 3 below shows that variability (percent (%) coefficient of variation [CV]) patterns may be different between phentermine and amphetamine. These results suggest that the potential negative effects of phentermine may influence an abuser's willingness to use the drug repeatedly. In this case, the percent CV for bad effects was greater for amphetamine and lower for phentermine, while percent CV for end of day/next-day measures of overall liking and take drug again was slightly lower, although the differences were less pronounced with the bipolar scale (overall liking). Put another way, this suggests the possibility that abusers may feel negative effects less consistently with amphetamine and somewhat more consistently with phentermine, with the reverse being true of the end-of-day/next-day measures. With the exception of the bipolar scales, the unscheduled drugs tended to show slightly higher percent CV across measures.

7.2. Methylphenidate

Methylphenidate is interesting for two reasons: first, because while it is a C-II drug (CSA), as shown by surveillance systems such as DAWN ED visits (2011) (4918 ED visits), it has not been abused as frequently as illicit stimulants such as cocaine (505,224 ED visits) or amphetamines/methamphetamines (159,840 ED visits) or even another prescription ADHD drug, mixed amphetamine-d-amphetamine. The latter has shown a marked increase in use in recent years (2303 in 2004–17,272 in 2011), which may be related to an increase in legitimate medical use and/or trends in social media rather than intrinsic abuse potential. Second, it is the only marketed stimulant for which it has been possible to reduce abuse potential by decreasing the rate of rise of plasma concentration after oral administration through reformulation.

7.2.1. Methylphenidate: pharmacokinetic factors

The rate of onset of drug effect is important to the abuse potential of drugs, including methylphenidate. Drugs with a rapid onset of action (e.g., rapid absorption into the brain) are more likely to be abused (Busto and Sellers, 1986), most likely due to greater subjective effects (e.g., liking, euphoria) and greater reinforcement value as a result of a closer temporal pairing of the drug taking behavior with the reward (Abreu et al., 2001; Kollins et al., 1998). In addition, a form of neurobiological adaptation, called behavioural sensitization, is known to be affected by rate of drug onset (Samaha et al., 2004; Samaha and Robinson, 2005; Samaha et al., 2005). Stimulant drugs that act on DAT have been particularly well studied

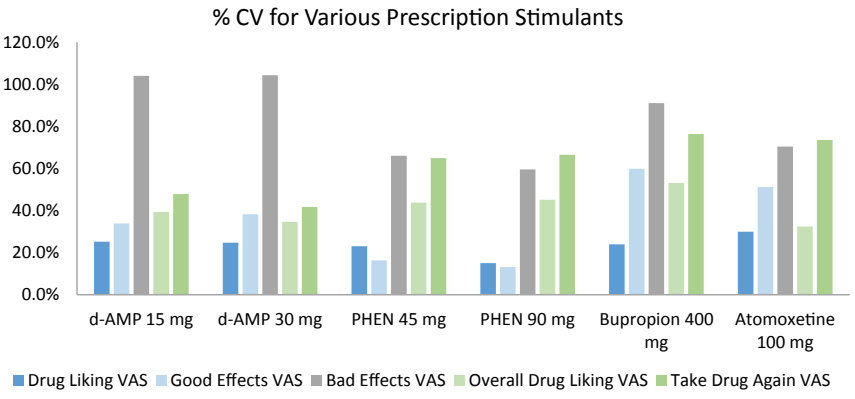

Fig. 3. Coefficients of variation (%) for different endpoints and stimulants.

in this regard. While steady state and stable stimulant-induced DA increases are associated with therapeutic effects, reinforcing and subjective abuse-related effects such as 'liking' are thought to occur when methylphenidate and other dopaminergic drugs cause rapid DAT blockade (Volkow, 2006; Volkow and Swanson, 2003; Volkow et al., 1998a,b). This is demonstrated by the lower subjective effects and drug liking associated with oral methylphenidate, which is more slowly absorbed, despite DAT blockade levels equivalent to those observed with intravenous or intranasal cocaine (e.g., 70–75 percent). This has also been observed with other dopaminergic drugs. For example, several novel triple re-uptake inhibitors, compounds which have high affinity for the DA transporter, as well as norepinephrine and serotonin reuptake sites, have shown limited abuse potential in humans, despite their potent inhibition of DAT. This is most likely due to their slow rate of onset and long elimination half-lives (Learned et al., 2012; Schoedel et al., 2010).

For many years, Ritalin® (IR product), was the only brand-name product available. However, subsequently other IR, extended release (ER), and long acting (LA) methylphenidate products were marketed. Different formulations of methylphenidate differ in their pharmacokinetic properties resulting in different rates of onset, offset and DA transporter (DAT) occupancy. When ingested intact, IR formulations release methylphenidate rapidly with time to peak plasma concentration (Tmax) occurring within 1–2 h after dosing, followed by a steady decline in plasma concentrations (Parasrampuria et al., 2007a,b; Spencer et al., 2006) In contrast, modified release formulations, such as osmotic-controlled extended-release (OROS) methylphenidate tablets (Concerta®) release only a small fraction of the total dose (22%) at a rate similar to that of the IR formulation, followed by slow, sustained release over a period of 6–10 h. This results in a limited initial rise followed by a slower rise in plasma concentrations (and by corollary, brain concentrations) over an extended period (Tmax of 6–10 h) (Parasrampuria et al., 2007a,b). Several clinical studies have shown less abuse potential of modified-release formulations versus IR methylphenidate when administered orally intact (Kollins et al., 1998; Parasrampuria et al., 2007a,b).

The rate of offset is also important to the abuse liability of methylphenidate (Fig. 4). For example, even though methylphenidate and cocaine have nearly identical sites and mechanisms of action, intravenous or intranasal methylphenidate abuse is less than that of cocaine. This is likely due to the longer half-life of methylphenidate (i.e., 3–5 h in plasma, 90 min in the brain) compared to cocaine (i.e., 50 min in plasma, 20 min in the brain)(Volkow and Swanson, 2003). When more than 50% of DAT are blocked, sustained elevations in drug concentrations lead to the saturation of transporters, thereby reducing the drug's reinforcement value upon repeat administration (Swanson and Volkow, 2003; Volkow et al., 2002). For example, plasma levels associated with Concerta are sustained at DAT saturating up until 17–18 h post-dose (Parasrampuria et al., 2007a,b).

Given an identical active ingredient, the differences in subjective effects and drug liking can be explained by pharmacokinetics, and this highlights the important relationship between intrinsic pharmacokinetic factors (such as half-life, as well as drug formulation) and abuse liability. This may also explain some of the differences in actual abuse rates between C-II prescription stimulants and illicit stimulants such as cocaine (primarily intranasal or smoked) and methamphetamine (primarily smoked).

Overall, in addition to pharmacokinetic, formulation and other factors such as availability and trends, differences in abuse of methylphenidate could be related partly to the fact that the subjective effects patterns of methylphenidate do not appear to be identical those of amphetamine, and instead show effects more similar to weaker stimulants, such as phentermine, with greater negative effects and less overall liking and willingness to take the drug again (although as stated above, comparisons across studies may be problematic) (Fig. 1 above).

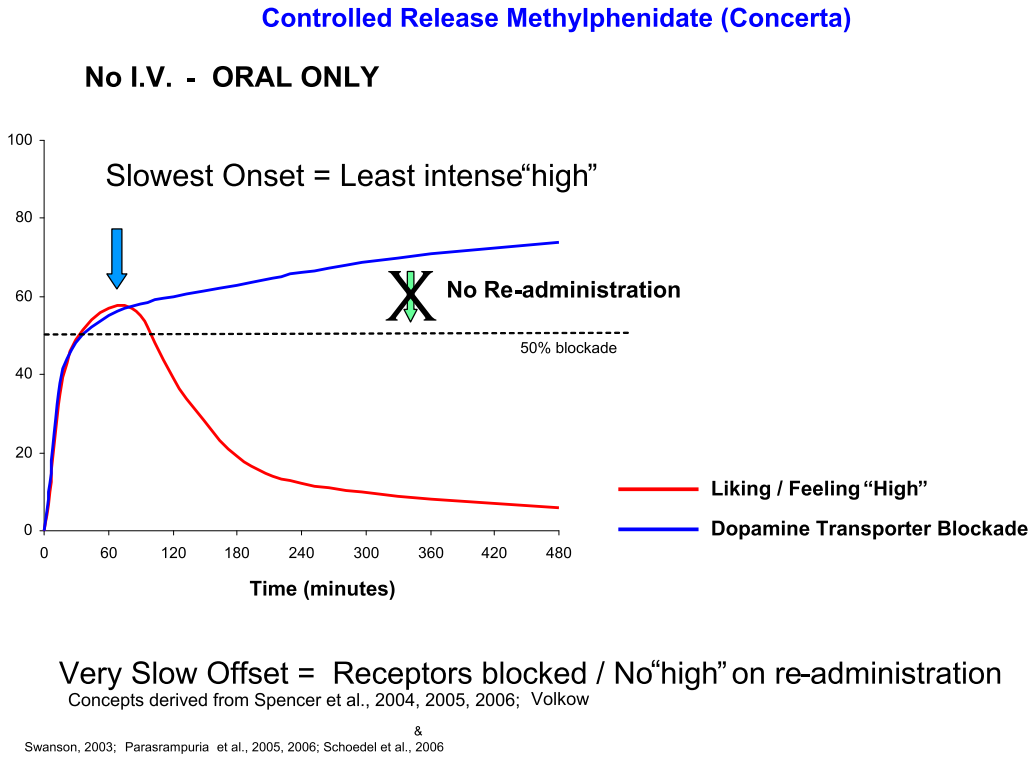

Fig. 4. Relationship between rates of absorption and onset and abuse potential for methylphenidate.

7.3. Tesofensine and GSK372475

A variety of (triple) reuptake inhibitors of NE, DA and 5-HT have been investigated for the treatment of obesity, depression and ADHD (Learned et al., 2012; Schoedel et al., 2010). These drugs are not uniquely triple uptake inhibitors since most stimulants have action at these uptake processes. Two abuse potential studies have been reported for this class of compounds – one with tesofensine (Schoedel et al., 2010) and the other with GSK372475 (Learned et al., 2010). Both these compounds have very long elimination half-lives (e.g., 200 h), a delayed onset of peak plasma concentration (and assumed brain concentration), and have receptor kinetics characterized by a slow offset from the receptor. The results observed with these compounds typify many of the methodology and interpretation issues seen with atypical stimulants. Because of the long half-lives of the drugs (and metabolites), both of these studies used an incomplete block design, where the comparators and placebo were given in the first periods in a fully randomized crossover, and the study drugs (tesofensine or GSK372475) were given in the last two periods in a randomized crossover with a second placebo. Subjective and objective measures were assessed for 48 h after each drug administration. The study results showed that the effects of D-amphetamine were significantly greater than those of placebo on all primary and secondary subjective measures. The effects of tesofensine and GSK372475 were not significantly different from those of placebo and were lower than those of D-amphetamine 30 mg on all primary and most secondary measures. The effects of tesofensine were either lower than or not different from those of bupropion or atomoxetine; a similar result was seen with GSK372475 compared to pseudoephedrine.

These results further support the findings with methylphenidate, in that pharmacokinetic factors play a critical role in the abuse potential of stimulant drugs, particularly those that act on dopaminergic systems. One interesting finding in the tesofensine study was that despite the lack of significant "at this moment" drug liking, subjects reported significantly greater next day overall willingness to "take drug again" compared to placebo. This suggests that there may be drugs where people may want to take them again for reasons other than the acute effects, e.g., alertness, more energy, etc.

7.4. A2 antagonists – new atypical stimulants

A variety of A_2 receptor antagonists have been studied preclinically (Bennett et al., 2013; Chen et al., 2013; Hodgson et al., 2010, 2009; Pinna, 2009; Zhukov et al., 2011) and have been tested clinically for various disorders, such as the treatment of disorders of dopaminergic neurotransmission, including Parkinson's disease (PD) (Cunha and Agostinho, 2010; Factor et al., 2013; Hauser, 2011; Hickey and Stacy, 2012). Radioligand binding assays showed that A_2 antagonists have high specificity (affinity) and selectivity affinity for the human adenosine A_{2a} receptor subtype (referred to as A_{2a} or if specifically human, as hA_{2a}). In contrast, caffeine, while an A_2 antagonist is non-selective with activity at A_1 and A_{2B} receptors with much lower specificity (K_i = 23,400–44,900) (Muller and Ferre, 2007). The mechanism of action of these drugs is an indirect one, with secondary effects related to release of dopamine. This is in clear distinction to drugs like D-amphetamine and cocaine which act directly on DA uptake or are direct releasers and have important actions in the nucleus accumbens.

Pre-clinical data with A_2 antagonists show an increase in locomotor activity, presenting a profile that is similar to weak stimulants such as caffeine in reversing A_2 agonist induced APEC (2-[(2-aminoethylamino)carbonylethyl-phenyl-ethylamino]-5′-ethyl-carboxamidoadenosine)-type locomotion. In a PET study examining orbitofrontal activation, subjective effects and cardiovascular responses to tozadenant 100 mg in cocaine dependent subjects were described (Lane et al., 2012; Moeller et al., 2012). Mild stimulant effects were reported along with modest activation of some prefrontal cortical regions. However the increased brain activation occurred in a relatively localized brain region, which overlapped with regions known to have reduced D_2 receptors in cocaine dependent individuals.

Because of their mechanism of action and behavior pharmacology A_2 antagonists will require assessment of their abuse liability as atypical stimulants. Inevitably, comparisons will be drawn with caffeine, an ingredient of many beverages, which is uncontrolled and very widely used.

The clinical abuse potential of one A_2 antagonist has been studied, but not in comparison to caffeine. A study of preladenant was a randomized, double-blind, balanced, placebo- and active-comparator controlled 6-way crossover trial in healthy recreational stimulant users that compared single oral doses of preladenant (10, 30, 100 mg) to phentermine (45, 90 mg) and placebo. In this study, preladenant showed significant effects on some but not all abuse potential endpoints compared to placebo, with mild stimulant-like effects that were significantly lower than 90 mg of phentermine and similar to 45 mg of phentermine. In addition, the dose relationship was relatively flat for preladenant compared to phentermine on most endpoints. Although direct comparisons cannot be made, as caffeine wasn't included in the study, one could speculate that the effects of preladenant may be similar to a relatively high dose of caffeine (e.g., 200–800 mg) (unpublished data – manuscript submitted).

8. Assessment of treatment emergent adverse events

At present the recommended monitoring for clinical adverse events which may be related to abuse consists of the evaluation of treatment emergent adverse events in volunteers and patients, which are observed during dosing and after discontinuation of drug. Various lists of predefined 'terms of interest" have been compiled both by industry and the FDA as potential signals of abuse potential. There is much overlap of terms but no final list of consensus has been published. Essentially the numerous terms fall into the categories of mood elevation, CNS depression, stimulation and anxiety, perceptual disturbances and other psychotomimetic effects, cognitive effects and discontinuation/neuroadaptation symptoms Table 3 (Mansbach et al., 2010; Romach, 2011a,b; Romach et al., 2012) For stimulant-like drugs, terms in all of these categories, except for CNS depression, would be relevant. It is highly recommended that case narratives accompany the AEs of interest which are observed and recorded to ensure a detailed description and chronology of events are documented (Mansbach et al., 2010; Schoedel and Sellers, 2008).

With respect to drug diversion or tampering with medication, trial records are examined for documentation of missing or lost medication, compliance, protocol deviations, overdoses, drug seeking and other aberrant behaviors.

More systematic and rigorous approaches to adverse event terminology, recording and assessment of causality using methods applied successfully to vaccines using Adverse Event Ontology would be an important contribution to the field and address some of the criticisms leveled at the current unvalidated approaches (Mansbach et al., 2010) (Brady et al., 2003; Romach et al., 2012; Romach and Sellers, 2014).

9. Assessment of discontinuation treatment emergent adverse events

In the assessment of abuse liability sponsors are required to assess "physical dependence" of a new drug. This old term refers to the appearance of signs and symptoms when a drug is abruptly or

Table 3
Treatment Emergent Adverse Event Terms that may Reflect Abuse Potential in Clinical Trials.

Mood elevation	CNS depression	Stimulation and anxiety	Perceptual disturbances/Psychotomimetic effects		Cognitive effects
Elevated mood	Asthenia	Agitation	Abnormal dreams	Hostility	Memory impairment
Euphoric mood	Fatigue	Anxiety	Acute psychosis	Hallucination	Memory enhancement
Feeling drunk	Lethargy	Energy increased	Aggression	Hypoesthesia/Paraesthesia	Confusion
Feeling abnormal	Sedation	Feeling jittery	Anger	Illusion	Forgetfulness
Inappropriate affect	Sluggishness	Hypervigilance	Communication disorder	Indifference	Alertness
Feeling of relaxation	Somnolence	Nervousness	Confusional state	Muscle rigidity	
	Stupor	Psychomotor hyperactivity	Delirium	Nightmare	
		Restlessness	Delusion	Paranoia	
		Mania	Depersonalisation	Psychotic disorder	
		Hypomania	Derealisation	Sensory disturbance	
			Disorientation	Somatic delusion	
			Dissociation	Somatic hallucination	
			Dissociative disorder	Thinking abnormal	
			Dysarthria	Thought blocking	
			Flashback	Transient psychosis	

slowly discontinued after chronic administration. The focus on this arises from older concepts that physical dependence caused persistent drug taking (i.e., to prevent withdrawal). While this can be a reason drugs are taken (negative reinforcement) the more practical concern may be, is there a safety concern and what to tell physicians about how to discontinue a drug. While physical dependence can be assessed preclinically this is not straight forward with stimulants because they tend to produce an apathetic state in animals. In patients, it is important to systematically structure the discontinuation phase of a drug trial for an NCE to get this information. A validated instrument for assessing symptoms and signs typical for stimulant withdrawal syndrome needs to be incorporated into the trial design and utilized at the time of drug discontinuation at frequent intervals that persist beyond the half-life of the drug. Two scales based on cocaine and amphetamine withdrawal can serve as a guide in developing approaches to detect a discontinuation syndrome after stimulants (Kampman et al., 1998; Srisurapanont et al., 1999).

10. Research needs

Methodology for assessing abuse potential has evolved over many years. When older stimulants were the focus of study, fairly insensitive tools were needed to show the effects. As drugs with much lower abuse potential have been developed there has arisen a need to improve the sensitivity of measures. Particular attention should be given to the role that other study approaches (e.g., drug discrimination, self-administration and behavioral economic studies) could play in providing data useful for review by Regulatory Authorities. This has not happened to date.

In addition, more attention needs to be paid to assessing subtle differences (e.g., slope of dose response curves, concurrent bad effects and lower responses on next-day measures) that are often evident with atypical stimulants. Such compounds may provide signals suggestive of abuse potential when evaluated by traditional "at this moment" scales, but in practice these often do not translate into actual abuse liability. The reason for this are not entirely understood.

The methodologic advances in the area suggest that human abuse potential studies can be considerably simplified. Only a few measures have the robustness required and all other weaker measures are highly correlated with these few key measures (e.g., bipolar VAS "liking at the moment", negative effects and end-of-day/next-day measures).

11. Conclusions

The principal advances that have improved the assessment of abuse potential include using study enrichment strategies (pharmacologic qualification), larger sample sizes, better selection of endpoints and measurement strategies and more carefully considered interpretation of data. Much of the literature on stimulants is quite old and because it was done with drugs with such prominent and substantial abuse liability has probably brought a bias to how newer agents are viewed. This problem is typified by novel compound such as A_2 antagonists that will be very caffeine like – caffeine being a drug with interesting behavioral pharmacology but not associated with the problems typical of drug abuse and dependence.

Methodical strategies to assess treatment emergent AEs and those during drug cessation should ensure that this aspect of evaluation is robust and systematic. This is needed to ensure scheduling decisions that are data driven.

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