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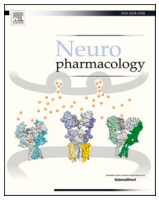

Psychedelic drug abuse potential assessment research for new drug applications and Controlled Substances Act scheduling

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ABSTRACT

New medicines containing classic hallucinogenic and entactogenic psychedelic substance are under development for various psychiatric and neurological disorders. Many of these, including psilocybin, lysergic acid diethylamide (LSD), and 3,4-methylenedioxymethamphetamine (MDMA) are Schedule I controlled substances of the United States Controlled Substances Act (US CSA), and similarly controlled globally. The implications of the CSA for research and medicines development, the path to approval of medicines, and their subsequent removal from Schedule I in the US are discussed. This entire process occurs within the framework of the CSA in the US and its counterparts internationally in accordance with international drug control treaties. Abuse potential related research in the US informs the eight factors of the CSA which provide the basis for rescheduling actions that must occur upon approval of a drug that contains a Schedule I substance. Abuse-related research also informs drug product labeling and the risk evaluation and mitigation strategies (REMS) will likely be required for approved medicines. Human abuse potential studies typically employed in CNS drug development may be problematic for substances with strong hallucinogenic effects such as psilocybin, and alternative strategies are discussed. Implications for research, medicinal development, and controlled substance scheduling are presented in the context of the US CSA and FDA requirements with implications for global regulation. We also discuss how abuse-related research can contribute to understanding mechanisms of action and therapeutic effects as well as the totality of the effects of the drugs on the brain, behavior, mood, and the constructs of spirituality and consciousness.

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1. Introduction

Concerns about the abuse potential of psychedelic substances[1] emerged in the 1960's as the use of lysergic acid diethylamide (LSD), psilocybin, and other hallucinogenic substances surged in the United States (US) with global consequences for access, research, and medicinal development (Hofmann, 1992; Carhart-Harris and Goodwin, 2017; Belouin and Henningfield, 2018). The United States (US) Drug Abuse Control Amendment (DACA) which amended the US Federal Food, Drug, and Cosmetic Act (FDCA) addressed societal concerns about these substances by enabling the Secretary of Health to essentially ban their sale and interstate commerce, likely contributing to reduced interest in pharmaceutical development (U.S. Congress, 1965; Belouin and Henningfield, 2018). In describing the history, issues, and challenges to psychedelic medicines development, the main focus of this article is on the US, however, international implications are mentioned in discussion of international regulatory approaches (Spillane and McAllister, 2003; Calderon et al., 2015).

Many types of substances can have hallucinogenic effects at high dosages, and both "hallucinogen" and "psychedelic" are used as umbrella labels for diverse substances. The focus of this article is on what are often referred to as classic indoleamine hallucinogenic psychedelics (e.g., LSD and psilocybin), and to a lesser extent, phenethylamines (e.g., mescaline and 3,4-methylenedioxymethamphetamine (MDMA)) which likely have higher abuse potential (Bauer et al., 2013; Fantegrossi et al., 2004; Halberstadt and Nichols, 2020; Nichols, 2004; Sakloth et al., 2019).

Many of the most prominent users and promotors of psychedelic substances have espoused social and political views contrary to those of political leaders in the US, which increased efforts to restrict access to these substances as part of the 1960's and 70's "War on Drugs." These efforts culminated in controlling psychedelic substances of abuse, and because they did not have accepted medical use they were placed in the highly restricted Schedule I of the 1970 US Controlled Substances Act (CSA) (Belouin and Henningfield, 2018; Bonson, 2018). The CSA criminalized the handling, possession, and distribution of hallucinogens except for highly constrained US Drug Enforcement Administration (DEA) registered research. In turn, US efforts contributed to generally similar global regulation by their inclusion in the United Nations (UN) Convention on Psychotropic Substances of 1971 (Spillane and McAllister, 2003; United Nations Office on Drugs and Crime, 2013; Bonson, 2018; Lampe, 2021; US Drug Enforcement Administration, 2022c; US Drug Enforcement Administration, 2022a). Schedule I control effectively and drastically reduced uncontrolled access to psychedelic substances by researchers and clinicians (Nutt et al., 2013; Belouin and Henningfield, 2018), however, US survey global monitoring showed that psychedelics and many other Schedule I substances, including cannabinoids, continued to be readily available and used for recreational and other purposes (Aikins, 2015; International Narcotics Control Board, 2021a; International Narcotics Control Board, 2021b; Substance Abuse and Mental Health Services Administration, 2021; Johnston et al., 2022).

In the mid-1980s, animal behavioral pharmacology research to address abuse potential began to increase around the same time that MDMA was added to Schedule I in 1985. Abuse potential research included animal intravenous drug self-administration (Beardsley et al., 1986; Yanagita, 1986; Lamb and Griffiths, 1987; Fantegrossi et al., 2002), and drug discrimination studies (Glennon et al., 1983). This research and its escalation into the early 2000s has been reviewed by Fantegrossi et al. (2008). Later research applied emerging techniques for studying the neural mechanisms of action to better characterize the neuropsychopharmacology and potential medicinal applications of psychedelic substances (Strassman, 1996; Nichols, 2004). Based on the unique pharmacology of MDMA, Nichols (1986) proposed that it represented a new and different therapeutic class of drug apart from classic hallucinogens and amphetamines called entactogens (see also Müller et al., 2020); Nichols (2022). By the time the 2018 special issues of Neuropharmacology (Heal et al., 2018b) and Psychopharmacology (Curran et al., 2018) were published, there were significant new original research and reviews addressing the mechanisms of action and the development of psychedelic based therapeutic medicines, as well as more detailed knowledge about the abuse potential of these drugs.

Psychedelic substances with abuse potential and no accepted therapeutic use are currently in Schedule I of the CSA. Developing therapeutic medicines for approval by the Food and Drug Administration (FDA), and rescheduling by the DEA prior to marketing, requires a broad range of research and evidence supporting efficacy and safety in the form of New Drug Applications (NDAs) consistent with the Federal FDCA, which provides the framework for NDA development and submissions (U.S. Food and Drug Administration, 2022a). NDA submissions require abuse potential assessments with CSA scheduling recommendations as required by the CSA (U.S. Drug Enforcement Administration, 2022a) and following FDA's 2017 Guidance, Assessment of the Abuse Potential of Drugs (U.S. Food and Drug Administration, 2017), hereafter referred to as "abuse potential guidance." By "abuse-related," this article follows the approach of FDA's 2017 abuse potential guidance when referring to all lines of scientific evidence, including chemistry, nonclinical in vitro and animal studies, physiological dependence and withdrawal, clinical trial adverse event reports, historical patterns of use, and surveys of current use patterns in the population. It is also important to keep in mind that abuse potential is "conducted as a component of its [the drugs overall] safety evaluation" by FDA (U.S. Food and Drug Administration, 2017), with other components like toxicity also playing a significant role. Although not specifically codified in the CSA, these lines of evidence mirror the requirements for the scientific and medical evaluation or "8 Factor Analysis" (8FA) required to be conducted by the US Department of Health and Human Services (DHHS) and DEA under the CSA prior to scheduling and rescheduling a drug or other substance (see the 8 factors in Table 1 and summary of the process in the Scheduling Process section).

An ongoing point of discussion with FDA and among pharmaceutical developers is how many and what kinds of abuse-related studies will need to be conducted to support the approval of psychedelic medicines. Abuse potential research on psychedelic substances was conducted in the 1960s and 70s, however, methodological limitations noted in Bonson's overview of LSD regulation are important to keep in mind and bear careful consideration by today's researchers, because many of these studies are at best considered pilot or exploratory and not adequate to guide regulatory decision making (Belouin and Henningfield, 2018; Bonson, 2018; Calderon et al., 2018). At that time, all hallucinogens with abuse potential were placed in Schedule I since they were determined to have no accepted medical use in the US, whereas opioids, stimulants, sedatives, and other substances with abuse potential but which were recognized to have medical use were placed in Schedules II, III, IV, or V commensurate with their recognized level of abuse potential.[2]

This article addresses the CSA framework for how abuse potential is assessed and how abuse-related research informs drug scheduling,

[1] This review uses the term psychedelic as a broad umbrella for the category of substances that includes the classic hallucinogenic type 5HT2A receptor modulating substances such as psilocybin, LSD, and DMT, as well as entactogenic psychedelic-like substances such as MDMA. Note that the CSA and 1965 DACA terms included hallucinogen and hallucinogenic, not psychedelic.

[2] Another term for "schedule" is "class". The labeling and packaging requirements for controlled substances requires all packaging to include the schedule by the symbol C–I, C-II, C-III, C-IV or C–V (the hyphens are optional) (US Code of Federal Regulations, 21 CFR 1302.03), hence the common reference to a controlled substance by its "C" code.

Table 1
The 8FA and types of studies and data used to guide CSA scheduling.

In practice, there is variation in the types of evidence and studies considered in each factor. For example, functional behavioural observation studies in animals are often among the earliest studies conducted and may be discussed in factor 1 or 20 (U.S. Food and Drug Administration, 2017; Gauvin and Zimmermann, 2019. Thus, the examples provided in this table are intended to provide reasonable representations of current practice (see Calderon et al., 2018, 2022; U.S. Food and Drug Administration, 2017; and Johnson et al., 2018), for examples of potential research that may be included in each factor. Note that no single factor (except Factor 8 in practice) is determinative of the outcome and both FDA and DEA must develop 8FAs. In practice, for novel substances, FDA develops its 8FA with input from the National Institute on Drug Abuse (NIDA), and if that leads to a recommendation for CSA control, then DEA develops its 8FA. For drugs that contain Schedule I substances and are approved for therapeutic use by FDA, rescheduling and descheduling require 8FAs from both agencies.
1. Its actual or relative potential for abuse.
Evidence: Surveys of naturalistic and recreational use, diversion from legitimate channels to illicit markets for distribution for recreational and other nonmedical use from surveys; animal and human abuse potential studies.
2. Scientific evidence of its pharmacological effect, if known.
Evidence: Neuropharmacology and abuse-related effects including binding to receptors thought to mediate abuse conferring effects; functional observational batteries; animal and human pharmacology including studies relevant to mechanism of action and therapeutic effects.
3. The state of current scientific knowledge regarding the drug or other substances.
Evidence: Nonclinical research including animal research, as well as clinical pharmacokinetics, mode of use, and formulation factors that may contribute to abuse.
4. Its history and current pattern of abuse.
Evidence: Trends in use over time as characterized by annual surveys including the Monitoring the Future Study and National Survey on Drug Use and Health, as well as drug detection reporting trends from the National Forensic Laboratory Information System. While not typical for 8FAs for most substances, in the case of psychedelics, anthropological data (e.g., use by indigenous peoples in diverse settings and circumstances including ritualized settings) may provide insights concerning use patterns, as well as elements addressed in factors 5 and 6.
5. The scope, duration, and significance of abuse.
Evidence: FDA Adverse Event Reporting System (FAERS), clinical case reports, and adverse events in clinical trials.
6. What, if any, risk there is to the public health.
Evidence: Risk of overdose and other serious health effects; Poison Control Center data. Risk to others including violence and auto accidents. Potential patient, medical, and public health benefits including implications for scheduling that promotes benefits with appropriate approaches to minimize risks.
7. Its psychic or physiological dependence liability.
Evidence: Clinical evidence of potential to lead to a substance use disorder (SUD) as well as physiological dependence and withdrawal, primarily from evaluation of abuse and withdrawal-related adverse events in clinical studies. May also include dedicated Human Abuse Potential (HAP) and withdrawal studies and reference to relevant data such as animal drug self-administration studies.
8. Whether the substance is an immediate precursor of a substance already controlled.
Evidence: This is a factual or administrative determination based on prior scheduling actions and chemical structures and synthesis of the substances.

labeling, and risk management approaches. It also discusses how such research may contribute to a fuller understanding of the neuropsychopharmacology of psychedelic substances, their effects on the brain, behavior, and constructs of spirituality and consciousness that may contribute to their therapeutic effects in medical use, and other effects that contribute to their voluntary use in the absence of disease. We begin with a brief overview of the CSA itself which is a key consideration with all research on psychedelic drugs and has legally binding implications for how FDA approved products may be regulated, restricted, and labeled.

2. The US Controlled Substances Act in the context of psychedelic medicines development

The CSA is a US statutory framework with legally binding implications for the who, how, what, and where with regard to limitations on psychedelic drug research and development (U.S. Food and Drug Administration, 2017; Lampe, 2021; U.S. Drug Enforcement Administration, 2022c). This includes implications for the kinds of evidence from nonclinical and clinical studies, as well as population surveillance, that are needed to evaluate abuse potential and guide rescheduling of any FDA-approved drug products that contain substances currently in Schedule I. The focus of this section is on the US CSA, however, the aforementioned international treaties, and the 1971 Convention on Psychotropic Drugs in particular, have generally similar implications globally (see also Calderon et al. (2015)). Abuse potential related research is done in the context of and often influenced by both national and international drug control regulations.

The CSA was developed by the Nixon administration and passed into law in 1970 to replace earlier legislation including the DACA, and its development contributed to the development of the 1971 international UN Convention on Psychotropic Substances (Belouin and Henningfield, 2018). It was intended to provide a framework for regulating abusable but therapeutically approved drugs with restrictions that were commensurate with their relative risks of abuse and harm, as well as controlling other abusable substances that were not approved for therapeutic use.

The CSA provides specific mechanisms and criteria for adding or removing substances and transferring substances between schedules ("rescheduling"). While the key element considered in any control determination is the abuse potential of a substance, the CSA does not actually provide a specific definition of abuse potential. The legislative history of the CSA (Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91–1444, 91st Cong., Sess. 1 [1970], reprinted in 1970 U.S.C.C.A.N. 4566, 4603), describes the potential for abuse of a substance by the following criteria for determining if a substance should be controlled, and, if it is already controlled, for determining if it should remain controlled.

a) Individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community;
b) There is significant diversion of the drug or substance from legitimate drug channels;
c) Individuals are taking the substance on their own initiative; or
d) 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.

FDA also uses this general context when discussing abuse potential in its guidance document (U.S. Food and Drug Administration, 2017; Calderon et al., 2018, 2022). The 4th prong of this definition is most often used for new drugs since they have no history of abuse or diversion. As discussed in the Scheduling Process section below, the 8FA contributes to the assessment of new drugs based extensively on their pharmacological equivalence and effects compared previously controlled drugs (e.g., Factors 1, 2, 3, and 7), and potential public health effects to the extent that comparisons can be drawn from experience with related or similarly acting substances (Factors, 4, 5, and 6). The need for this predictability has given rise to the development of many of the types of studies used in today's abuse liability assessments.

Drug scheduling in the US is also influenced by and contributes to international drug control efforts due to US obligations to international drug control treaties, including the 1961 Single Convention on Narcotic Drugs and 1971 Convention on Psychotropic Substances. International control did allow flexibility for parties to the treaties to meet their international obligations while still addressing their own national interests. For example, approved drugs do not have to have equivalent numerical schedules, but they do have to have controls in the US equivalent to or greater than those imposed by the treaties. Thus, any member party can schedule a substance more restrictively domestically

than occurs internationally. When it was signed into law in 1970, the CSA included lists of drugs in various schedules (Schedule I – Schedule V) based in part on the earlier international 1961 UN Single Convention on Narcotic Drugs, which included opium, coca, and derivatives such as morphine, heroin, and cocaine, as well as cannabis and similar substances determined to be particularly liable to abuse by the World Health Organization (WHO). In addition to these substances, many newly identified and abused substances were added to both the 1970 CSA and the 1971 UN Psychotropic Convention. These substances were added to the CSA based on whether they had an accepted therapeutic use (e.g., FDA approved) and on the nature and level of their abuse and dependence-related properties in the US on the advice by scientists and clinicians along with Department of Justice and law enforcement officials during development of the CSA (Bonson, 2018). Table 2 provides an overview of a few features of the CSA relevant to psychedelic medicines research and development.

Another implication of the international control treaties obligations is that Schedule I drug products that are approved by a member state may be removed from Schedule I and rescheduled in that member state, as long as the controls of the new schedule for the product satisfy the party's obligations under international treaties. Since controls under international treaties are generally less restrictive generally for products or preparations than for bulk substances, the drug substance typically remains in Schedule I both internationally (United Nations Office on Drugs and Crime, 2013; U.S. Drug Enforcement Administration, 2016; Lampe, 2021) and domestically, while the newly marketed product is controlled in a less restrictive schedule domestically. This was the situation in 1986 when DEA transferred the *trans*-delta-9-tetrahydrocannabinol-containing drug product Marinol from Schedule I to Schedule II after Marinol's NDA approval by FDA in 1985. The transfer of Marinol from Schedule I to Schedule II of the CSA by the DEA in 1986, however, left control of tetrahydrocannabinol in Schedule I of the CSA. Marinol was rescheduled to Schedule III in 1996 (U.S. Drug Enforcement Administration, 1999).

It is also possible for a party to petition the WHO to review the substance in light of new medical and scientific evidence for possible rescheduling under international treaties. In practice, how each nation schedules approved drug product and substances that are not approved drug products is complex (Calderon et al., 2015). A recent example of the complexities of harmonizing national drug regulation approaches with international treaties is provided by the approach to the FDA-approved drug product Epidiolex®, which was considered a cannabis extract and subject to the controls of the 1961 Convention even though the substance, cannabidiol (CBD), has no clinically meaningful abuse potential. (U.S. Drug Enforcement Administration, 2018; U.S. Drug Enforcement Administration, 2020; United Nations Office on Drugs and Crime, 2020).

As described in Table 2, the CSA includes five schedules for various drugs and substances considered to be of sufficient abuse potential to merit CSA placement. Schedules I and II are for substances with a high abuse potential while Schedules III – V have progressively lower levels of abuse potential. As noted above, Schedule I is also reserved for those substances with no currently accepted medical use in treatment in the US and for which there is no established safety for use under medical supervision. Schedule II is for substances with a high degree of physical and/or psychological dependence liability while Schedules III – V have progressively lower levels of dependence liability. Regulatory restrictions on FDA-approved CSA-controlled drugs are greatest for Schedule II drugs, but generally similar for schedules III – V. DHHS is the scientific and medical authority for scheduling actions and its recommendations are binding on DEA regarding scientific and medical matters. DEA is the ultimate authority for making the final determination and defending any legal or other actions, including international issues. Both DEA and DHHS must consider 8 factors determinative of control under the CSA, ranging from predictive nonclinical data to actual abuse, dependence, and public health data (See 21 USC811© in the CSA (U.S. Drug Enforcement Administration, 2022a)). Fig. 1 illustrates the process according to the CSA for scheduling drugs that are approved by the FDA for therapeutic use.

Scheduling usually occurs by substance (molecule or chemical entity) and not by product, but it is possible to differentially schedule substances and products as noted with tetrahydrocannabinol (THC) and Marinol. Scheduling encompasses the salts and optical isomers (enantiomers) of substances and includes geometric and positional isomers of Schedule I hallucinogens, which adds to the confusion over research with some of these molecules. Related to development of new chemical entities, whereas derivatives of opium and thebaine are Schedule II opioids until they are approved and rescheduled, the CSA did not take this regulatory approach with hallucinogens, thus, novel analogs of LSD that are under development as potential medicines are not scheduled during development as new drug products. If the product is approved for therapeutic use FDA will make a recommendation for whether or not it should be scheduled and if so, which schedule is recommended (See Fig. 1). Developers of novel psychedelics should consult with DEA and FDA to ensure compliance with appropriate laws and recommendations. Although FDA approval is not codified in the CSA as a requirement for determining that a drug or substance has a currently therapeutic or medical use, it has become the de facto standard for this determination.

Table 2
Summary of the controlled substances Act*.

The CSA includes 5 schedules for drugs with abuse potential, that is, considered "meaningful" or sufficiently high enough to warrant control, and which are determined to be potentially dangerous to users and the public health.
Schedules II – V are for drugs with an accepted therapeutic use in 1970 by FDA and those approved for therapeutic use by FDA since 1970. Abuse- and dependence-related labelling and the level of restrictiveness and control depend on the relative abuse potential of substances from the least restrictive Schedule V for the lowest abuse potential drugs (e.g., low-dose codeine combination products, pregabalin, and lacosamide) to the most restrictive Schedule II for the highest abuse potential drugs (e.g., morphine, amphetamine, and cocaine). Benzodiazepines are placed in Schedule IV, and phencyclidine (PCP) and ketamine are in Schedule III.
Schedule I is for "high" abuse potential substances that are without accepted safe therapeutic use – *regardless of their relative level of abuse potential and how they might have been scheduled if they were FDA-approved drugs.* Drugs listed in Schedule I in 1970 included heroin, LSD, psilocybin, mescaline, N,N-dimethyltryptamine (DMT), and marijuana and most of its constituents including tetrahydrocannabinol (THC). In 1985, MDMA was added to Schedule I.
Since 1971, administrative drug scheduling actions have been guided by evaluation of abuse potential according to the CSA's 8FA (Table 1 and Fig. 1). Substances can be and have been scheduled without regard to the findings and criteria established by the administrative process 1) by Congress, 2) because of international treaty obligations,3) by definition, or 4) on a temporary or emergency basis. The vast majority of new drugs have been placed under the CSA using the administrative process involving the 8FA.
Removal of a substance or product from Schedule I requires that FDA approve a drug product containing the Schedule I substance. Following FDA approval, the CSA requires the product and/or substance to be rescheduled into one of the four schedules for drugs with accepted therapeutic use based on assessment of its abuse potential by an 8FA (described in Table 1) and following the process summarized in Fig. 1. In some cases, approval can result in removal from control (e.g., dextrorphan and samidorphan; see these and other examples in the DEA listing (Dworkin et al., 2022)). Usually, however, all forms of a drug substance except the approved drug(s) remain in Schedule I when the approved product containing that substance is rescheduled, e.g., all forms of THC are in Schedule I except approved drug products which are either in Schedule II (nabilone (Cesamet®)) or III (dronabinol (Marinol®)) (McCormick et al., 2009; Sacco, 2020; U.S. Drug Enforcement Administration, 2021)[a]

*(See U.S. Drug Enforcement Administration (2022a) for actual wording of the law and its amendments since 1970. See additional information in Belouin and Henningfield (2018); U.S. Food and Drug Administration (2017); Lampe (2021); Spillane and McAllister (2003). See the DEA's listing of drug scheduling actions (sometimes referred to as the "DEA Orange Book") that have occurred since 1971 (U.S. Drug Enforcement Administration, 2021)).

[a] An unusual example that is consistent with this was actually accomplished by an act of congress and not via DEA. That was the placement of all forms of gamma hydroxybutyric acid (GHB) in Schedule I except the approved GHB-containing drug products which are in Schedule III.

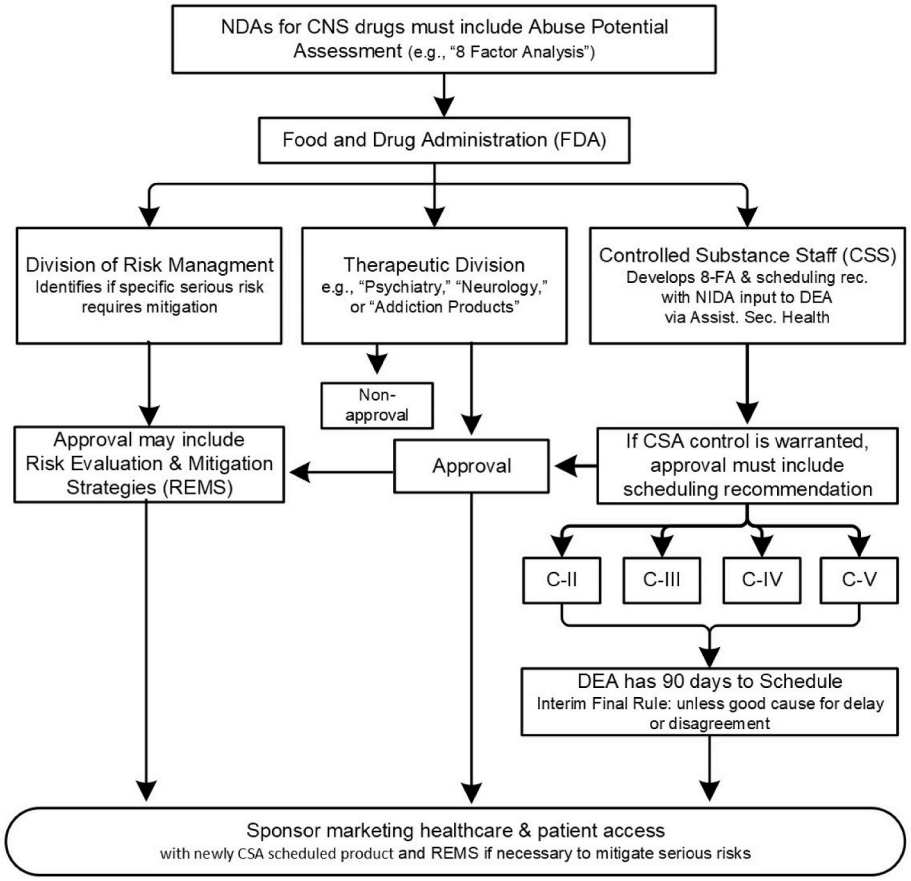

Fig. 1. FDA drug approval and the FDA and DEA scheduling process.

(See discussion in the Forward of U.S. Drug Enforcement Administration (2022c)). Similarly, the 1961 and 1971 International drug control conventions do not define accepted therapeutic or medical use as approved by drug regulatory authorities but in practice that appears to be the de facto standard (see also Calderon et al. (2015)).

All drugs deemed to merit CSA control but not approved for therapeutic use by the FDA are placed in Schedule I, regardless of their relative level of abuse potential. Thus, heroin and THC are both in Schedule I despite the evidence demonstrating substantial differences in their abuse potential, overall public health impact, and overdose risks. Because none of the classic psychedelic drugs under development today were previously accepted for therapeutic use, they were placed in Schedule I, likely contributing to the impression that they were of similar abuse potential as heroin (see additional discussion by Nutt et al. (2013)).[3] The history of LSD regulation by Bonson (2018) provides an insightful summary of the process and studies that are relevant to psychedelic drugs in general. The degree to which such historical studies may be helpful in guiding FDA evaluations of NDAs for safety and effectiveness, as well as evaluations of abuse potential, will likely differ on a drug-by-drug and NDA-by-NDA basis by FDA, NIDA, and DEA (Fig. 1 illustrates the process), however, it is important to keep in mind the international treaty situation for each substance.

When a drug product containing a Schedule I hallucinogen is approved for marketing by FDA, it must be removed from Schedule I before it can be marketed. Either the "substance" can be rescheduled to a lower schedule, or some subset of the substance (specific product or formulation) can be rescheduled. In the case of Marinol, only a specific formulation was rescheduled while for some other substances, such as levo-α-acetylmethadol (LAAM), the substance itself was transferred from Schedule I to Schedule II. If attempting to reschedule the substance itself, FDA will require that all types of formulations and routes of administration be addressed. If attempting to reschedule a product whose active ingredient is in Schedule I to a schedule that is less restrictive than Schedule II, there must be evidence that the abuse potential is lower than that of Schedule II drugs. For Schedule I drugs with long histories of research and real-world use in the community, this might be more strongly supported with existing evidence than novel chemical entities, regardless of whether the novel entities are derived from or are structurally similar to substances with such histories.

3. Impediments to research imposed by schedule I

The CSA was not intended to prohibit research with Schedule I drugs or prevent researchers from having access to Schedule I drugs. However, it was intended to ensure that researchers, their research proposals, the physical sites of the research, and the physical and administrative systems to assure security of the drugs required by DEA would need to be reviewed, approved, registered, and monitored by DEA (U.S. Drug Enforcement Administration, 2022b). Many researchers and their institutions report that the approach to registration, reviews, and inspections is costly with respect to time and resources, and approval by institutional review boards (IRBs, i.e., ethics review committees in Europe and other regions) and discourages researchers and institutions

[3] The reasoning was that substances that had not gone through a government approval process could not be determined to be effective, of known and consistent composition, and safe for labeled use as determined by experts, and therefore there was no reason for anyone to consume these substances. To set up an additional set of schedules for substances with lower abuse potentials as was done for approved drugs was considered cumbersome and unnecessary (personal communication to F. Sapienza by drafters of the CSA).

from pursuing efforts to study Schedule I substances. Many of these same researchers conduct Schedule II research, which is also highly regulated by DEA and FDA, but is considered by the researchers to be more manageable and acceptable. Many researchers support efforts to regulate Schedule I research by similar standards as discussed below to those imposed for Schedule II research.

The foregoing issues are widely recognized and have been discussed as they pertain to research with cannabinoids, psychedelics, and novel illicit opioids placed in Schedule I (Nutt et al., 2013; National Academies of Sciences Engineering and Medicine, 2017; Belouin and Henningfield, 2018; Cooper et al., 2021; National Institute on Drug Abuse, 2021). The impact of Schedule I placement was substantially increased in 2018 by enactment of an emergency ban on fentanyl-related substances or compounds (FRS) by placement in Schedule I based simply on chemical structure and not due to the pharmacology or any documented public health risk, thus impeding critical medications development research (Comer et al, 2021). Although the emergency order is specific to FRS, its impact on medication development with broader barriers is a concern discussed by Comer et al. (2021).

The National Institutes of Health (NIH) and NIDA summarized some of the impediments to Schedule I research in a report to the US House of Representatives Appropriations Committee (Jaeger, 2021b; National Institute on Drug Abuse, 2021). As stated in its report: "These challenges can impede critical research on Schedule I substances and deter and prevent scientists from pursuing such work …. an overarching concern expressed by researchers is the lack of transparency regarding registration requirements for Schedule I and Schedule II-V substances, and differing interpretations of those requirements by DEA field agents and research institutions." (National Institute on Drug Abuse, 2021). Table 3 summarizes issues and impediments raised to the NIH, NIDA 2021 report to Congress.

Table 3
Categories and examples of Schedule I Research Barriers and other costly requirements*.

- Process barriers for obtaining Schedule I research registration
  Time consuming and administratively complex process that includes review by DEA as well as other agencies, with DEA also conducting background checks on the researcher, and site visits to determine if storage safeguards meet DEA's criteria.
  Every drug studied by a researcher requires a substance-specific application, thus requiring applications for each substance if multiple substances are under study.
  DEA may require new drug storage systems or enhancement beyond the sites' existing storage, which can lead to additional time and expense for procurement, installation, and possibly a DEA inspection to confirm that it is adequate.
  Minor changes in protocols require amended protocols that can take many months to be reviewed and authorized by DEA and FDA.
  Modifications can trigger additional DEA inspections, further slowing approval and delaying research.
- Challenges to obtaining and modifying a Schedule I research registration
  Initial registration can take more than a year and minor modifications can take many months.
  In some cases, each investigator in a research team may be required to apply for and have approved their own registration, though this is not required by law.
  Individual researchers may be required to hold separate registrations for each site (e.g., adjacent buildings) on the same campus.

*(summarized from NIH, NIDA (2021), p.3).

The general goals and requirements for Schedule I research are described in the CSA, however, the DEA has the authority to determine the specific procedures and many details as to how these goals will be achieved. Description of some of the registration and oversight protocols are available at the DEA research registration website (U.S. Drug Enforcement Administration, 2022a), and DEA staff slide presentation (Miller, 2019), each of which provide links to more documents and protocols describing the process.

There is increasing pressure from researchers and from NIH (National Institute on Drug Abuse, 2021) to find ways to streamline the process and increase the diversity of researchers and institutions to participate.[4] NIDA Director Nora Volkow also testified to Congress on the impediments to Schedule I research and advocated for modification of registration procedures to support broader participation of researchers and more timely progress (Volkow, 2020). In October 2021, the Office on National Drug Control Policy (ONDCP) Acting Director, Regina LaBelle, included the following recommendation in a letter to congressional leaders that was primarily focused on FRS but had clear implications for other areas of Schedule I research. She wrote, "Establish a simplified process that would align research registration for all Schedule I substances, including FRS, more closely with the research registration process for Schedule II substances." (Jaeger, 2021a, 2021b, The White House, 2021). Such recommendations have been informed by researchers who routinely conduct Schedule II research, We do not expect rapid or radical change in Schedule I research requirements. We encourage researchers interested in conducting Schedule I research to contact NIDA, FDA, and DEA for advice as to what they might do to minimize delays and unnecessary costs and burdens, and to be clear on what could be done to make such research less burdensome and more efficient. In this area of research and regulation, it is apparent that NIH, FDA, and DEA are all making efforts to facilitate research and development as illustrated by the NIH-led lecture series that is the basis for this special issue and introductory commentaries and editorials to the special issue by various DHHS staff.[5]

4. The scheduling process: abuse potential assessment and the 8-factor analysis

The CSA included a framework to guide the potential scheduling of new drugs approved by the FDA, as well as rescheduling from one schedule to another, and for removal from the Act. As required by the CSA, these actions are determined by an analysis of the eight factors, often referred to as the 8FA, which are shown in Table 1, and follow the

[4] The devastating contributions of many Fentanyl-Related Substances (FRS) to overdose death rates and rapid proliferation of new FRS led to congressional action to pass the Temporary Reauthorization and Study of the Emergency Scheduling of Fentanyl Analogs Act, and proposals from the White House to, extend the duration of "temporary scheduling" and place many FSR in Schedule I permanently, without the need for assessment of factors, 4, 5, and 6, largely on the basis of their chemical structures. At the time of this writing, various potential laws were under consideration in effort to protect public health without restricting the research that is vital to better understand their mechanism of action and if some FRS might actually be considered candidates for new medicines (White House, 2021; Jaeger, 2021a; 2021b; U.S. Congress, 2020).

[5] There have also been congressional inquiries to encourage FDA and NIH to document their efforts to support this area of research, as illustrated by a letter from Senator Schatz to FDA and NIH in 2019 (accessed June 28, 2022 at https://maps.org/wp-content/uploads/2019/06/FinallettertoNIHFDArepsychedelicdrugresearch04.04.19.pdf) and reply (accessed June 28, 2022 at https://maps.org/wp-content/uploads/2019/06/ResponsefromFDAandNIHre.psychedelicresearch06.17.2019.pdf) and from Senators Schatz and Booker to FDA and NIH in 2022 (accessed June 28, 2022 at https://www.schatz.senate.gov/download/nih-and-fda-psychedelic-research-letter) and reply (weblink FORTHCOMING FROM SENATOR SCHATZ OFFICE).

process illustrated in Fig. 1.

The CSA does not specifically list the types of studies and/or the evidence required for evaluation in the analysis of each factor, however, Table 1 also provides examples of commonly used types of studies and evidence considered in each of the factors. The evolution of 8FAs over time and variation in how they are performed, including what kinds of studies are included in each factor, can be surveyed by examination of many of the 8FAs performed by FDA and DEA to support DEA's proposed and final scheduling actions ("Rules"), many of which are published in the DEA Orange Book (U.S. Drug Enforcement Administration, 2021) and Federal Register. FDA's 2017 abuse potential assessment guidance summarizes the approaches to abuse potential assessment and can be consulted along with other evaluations (Jasinski et al., 1984, Expert Panel, 2003; Rocha, 2013; Calderon et al., 2018). Also see additional discussion and peer-reviewed published examples of abuse potential assessments (Belouin and Henningfield, 2018; Johnson et al., 2018; Henningfield et al., 2022).

In addition to the 8FA guided process for scheduling, rescheduling, and in some cases descheduling FDA-approved drugs, the CSA provides an abbreviated process for relatively rapid "temporary" or "emergency" scheduling of substances of concern which places the substance in Schedule I. Temporary scheduling only requires consideration of Factors 4, 5, and 6 to determine if the substance is known or predicted to have sufficiently high abuse potential and safety concerns to pose an "imminent threat" to public health (U.S. Drug Enforcement Administration, 2022a). Such scheduling results in Schedule I placement for two years during which the DEA typically develops an 8FA to ensure permanent placement (Lampe, 2021).[6] This CSA tool has been used in recent years to list synthetic psychedelic substances with LSD-like chemical structures and/or mechanisms of action that have appeared on the "designer drug market" (U.S. Drug Enforcement Administration, 2020) and other novel tryptamine-type psychedelics in Schedule I (U.S. Drug Enforcement Administration, 2022d).

5. The role of FDA, NIDA, and DEA in drug scheduling: FDA is the focal point during drug development

Although DEA issues and defends the final Schedule for a newly approved drug, during drug development, FDA should be the main source of guidance for the sponsor regarding study needs and study design, because FDA will take the lead on the abuse potential assessment and 8FA that will ultimately be considered by DEA. In situations where the product under development contains a substance controlled under one of the international drug control treaties, it is advisable for the sponsor to also meet with appropriate DEA staff early in the process to better understand the potential options for rescheduling upon approval.

The co-involvement of FDA and the DEA in drug scheduling emerged from the 1968-70 development of the CSA for which there was collaboration and also disagreement between the Department of Justice (DOJ) and the Department of Health, Education, and Welfare (HEW), and within the US Congress as to which department would lead the scheduling process, and whether drug scheduling should primarily be a legal matter or a health matter. This was reflected in the potential name of the act in which the Senate proposal, favoring the DOJ, suggested naming it the "Controlled Dangerous Substances Act; " whereas the House of Representatives proposal, favoring HEW, suggested naming it the "Comprehensive Drug Abuse Prevention and Control Act" (Congressional Quarterly, 1970). The compromise was the Controlled Substances Act in which the DOJ's Attorney General was empowered to schedule, reschedule, and deschedule substances but was "bound by the Secretary of HEW regarding scientific and medical matters before placing a substance under control or removing it from control."

The process of developing the CSA also made evident the need for consolidation of efforts within DOJ and HEW to facilitate CSA scheduling and provide additional means to comprehensively address substance abuse. At HEW, FDA was given the lead on CSA matters with recommendations communicated by the Assistant Secretary of Health (ASH) to DOJ. DEA was established within DOJ in 1973 and it became DOJ's focal point for CSA actions (U.S. Drug Enforcement Administration, 2022c). The National Institute on Drug Abuse (NIDA) was created to take the lead on drug abuse science, becoming operational in 1974. However, NIDA's input on FDA drug scheduling actions was not made a formal requirement until 1985 (U.S. Food and Drug Administration, 1985). While there has been some evolution in the scheduling process over the years, the current process is illustrated in Fig. 1.

As shown in Fig. 1, and consistent with FDA's 2017 abuse potential guidance, NDA submissions for drugs with central nervous system (CNS) activity must include an abuse potential assessment (though this does not need to be in the form of an 8FA). The FDA therapeutic division which has overseen the product development will review the NDA for approvability. If approval with a recommendation for CSA control appears likely, then recommendations for scheduling and rescheduling of new drugs, including potential removal from control (descheduling) is led by FDA's Controlled Substances Staff (CSS). CSS will perform its abuse potential assessment and 8FA, with NIDA input, so that the DEA can be advised simultaneously that the drug product will be approved and provided with FDA's scheduling recommendation. As stated in the FDA's 2017 guidance (p. 11), since the 2015 Improving Transparency in Medical Therapies Act went into force in 2016, "FDA approval of a new drug may not take effect until DEA issuance of an interim final rule" establishing its CSA schedule.

FDA's 2017 abuse potential guidance provides a starting point for study planning. The process of drug development leading to submission of an NDA, including the abuse potential assessment, should have input from FDA at every step (U.S. Food and Drug Administration, 2017; Calderon et al., 2018; U.S. Food and Drug Administration, 2022a, Calderon et al., 2018). For CNS active drugs, that will require an abuse potential assessment, for which sponsors should seek early input from FDA's CSS, and at times input from NIDA, to ensure that NIDA thinking on the state of the art of the science is taken into consideration early in the process. FDA's 2017 abuse potential guidance provides a starting point for study planning as well as early interactions with CSS on abuse potential concerns, study needs, and study designs during drug development, This includes recommendations for the kinds of studies and information that should be provided in the NDA to guide their assessment (U.S. Food and Drug Administration, 2017).

For drug product development involving Schedule I drugs, DEA will be involved from the start of the process due to the required DEA registrations for research, drug procurement, and oversight processes. The registration process may provide opportunities to get input from DEA that might be helpful during the eventual review and scheduling process.

Until 2016, the timeline for DEA's final scheduling actions varied widely, however, since 2016 with implementation of the 2015 Improving Regulatory Transparency for New Medical Therapies Act, following the FDA announcement that a drug product will be approved along with a recommendation for CSA scheduling, the DEA has 90 days to issue an interim final rule for scheduling based on FDA's recommendation, unless there is a compelling basis for delay or difference. The

[6] The devastating contributions of many Fentanyl-Related Substances (FRS) to overdose death rates and rapid proliferation of new FRS led to congressional action to pass the Temporary Reauthorization and Study of the Emergency Scheduling of Fentanyl Analogs Act, and proposals from the White House to, extend the duration of "temporary scheduling" and place many FSR in Schedule I permanently, without the need for assessment of factors, 4, 5, and 6, largely on the basis of their chemical structures. At the time of this writing, various potential laws were under consideration in effort to protect public health without restricting the research that is vital to better understand their mechanism of action and if some FRS might actually be considered candidates for new medicines (White House, 2021; Jaeger, 2021a; 2021b; U.S. Congress, 2020).

product is then officially approved, scheduled, and can be marketed. Since 2016, most DEA interim final scheduling actions have followed this process and allowed for marketing within 90 days of FDA's approvability announcement (U.S. Congress, 2015; U.S. Food and Drug Administration, 2017).

In practice, with a few exceptions including codeine and THC drug products, all FDA-approved drugs containing the same scheduled substance are listed in the same schedule as shown in the DEA Orange Book (U.S. Drug Enforcement Administration, 2021).[7] Thus, if MDMA, psilocybin, and other NDAs for drug products containing Schedule I substances are approved for therapeutic use, the approved products are required by the CSA to be removed from Schedule I and the substance and/or product be rescheduled based on an 8FA. After the first products containing MDMA, psilocybin, and other Schedule I drugs are approved, all subsequent products containing the same active psychedelic substance as the first product would likely be placed in the same schedule as the first approved product.

6. Abuse potential studies required to support NDAs involving schedule I substances

The number and types of abuse-related studies recommended by FDA to support NDA submissions vary widely across medicines in development, with new chemical entities (NCEs) likely requiring the most extensive study. Table 1, which shows the eight factors of the CSA includes examples of the types of studies and data that FDA recommends the sponsor provide in the abuse potential section of an NDA for CNS active drugs in general to inform development of CSA scheduling recommendations (U.S. Food and Drug Administration, 2017). For drugs that have been studied extensively, and for which there are extensive surveillance data documenting patterns of use in naturalistic settings in the community or general population (e.g., Monitoring the Future Study and the National Survey on Drug Use and Health) and other types of real-world evidence (e.g., FDA, (2022b)), there may be little need for new dedicated abuse potential studies. For LSD, psilocybin, and MDMA and other classic psychedelics that have been evaluated for decades in laboratory studies, and for which there are decades of federal surveillance study data, there would similarly seem to be little need for new dedicated animal and human abuse potential studies. However, FDA will undoubtedly recommend that clinical studies carefully collect and analyze adverse events that are potentially suggestive of abuse potential, and report behaviors and signs of potential dependence, abuse, and diversion as recommended in its abuse potential guidance (U.S. Food and Drug Administration, 2017).

As stated by FDA's CSS staff who wrote the article titled *A regulatory perspective on the evaluation of hallucinogen drugs for human use* for the 2018 special issue of *Neuropharmacology* on psychedelics, "From the regulatory perspective, the same regulatory framework that applies to the development of any drug applies to the development of hallucinogens." (Calderon et al., 2018, p. 7). This implies recommendations for studies to determine if the product could be approved for therapeutic use, inform abuse potential assessments, and guide labeling, will be on a drug-by-drug basis taking existing knowledge relevant to safety and efficacy into consideration as recommendations are developed for studies that the sponsors will need to conduct.

7. Studies that may be needed to guide FDA's assessment of psychedelic substances that have been studied and are already controlled in schedule I

Ongoing development of MDMA for post-traumatic stress disorder (PTSD) provides a recent example of how study recommendations are developed on a drug-by-drug basis. MDMA was synthesized in 1912 by the German pharmaceutical company Merck and patented in 1914 for potential medical use. It was used by psychiatrists in the 1970s (though it was not an FDA-approved drug) and became more popular as a "club" drug and social/sexual enhancing drug in the 1980s, leading to its placement in Schedule I in 1985 (Grinspoon and Bakalar, 1986; Bernschneider-Reif et al., 2006; Freudenmann et al., 2006; National Institute on Drug Abuse, 2020). MDMA has been evaluated in many animal and human studies over several decades, and there have been several decades of real-world surveillance of patterns of use in major federal surveys (Parrott et al., 2000; Parrott, 2005; Jerome et al., 2013; Passie, 2018; Sessa et al., 2019; National Institute on Drug Abuse, 2020; Coker et al., 2021) Thus, it was not surprising that the sponsor developing an NDA for an MDMA product for the treatment of PTSD was informed that new dedicated animal and human abuse potential studies would not need to be conducted to guide FDA's eventual rescheduling if the MDMA product is approved for therapeutic use. Given the even longer history of research and surveillance of LSD and psilocybin as compared to MDMA, it would seem that a similar approach by FDA is warranted, while recognizing the many limitations of earlier research discussed by Bonson (2018) and Johnson et al. (2018) in their assessment of the abuse potential of psilocybin, and the fact that decades of epidemiological data provide a substantial basis for characterization of its real-world risks of abuse and other harms in the community.

The foregoing applies to oral formulations and drug products upon which most of the safety and abuse potential related experience are based upon. However, if the formulation or route of administration is novel—for instance, if intranasal or intravenous routes of administration are considered—then FDA may require studies to determine "if the physicochemical properties of the drug product" or route of administration influences the overall abuse potential (U.S. Food and Drug Administration, 2017, p. 12) as was done for products involving intranasal forms of esketamine (Janssen Research and Development, 2019) and alprazolam (Reissig et al., 2015).

To date, most of psychedelic related pharmaceutical development with the indoleamine and phenethylamines that we are aware of involves formulations intended for oral administration and these do not involve extended-release type of formulations though that is an area of discussion among pharmaceutical developers and might be an emerging area of development. The present focus on oral formulations is consistent with decades of surveillance suggesting that the oral route of administration is preferred by the vast majority of users and appears effective in providing desired effects. Non oral routes of delivery and formulations that substantially alter the pharmacokinetics, and/or which may produce effects that might lead to product tampering, would likely require additional safety and abuse related studies as FDA discusses in its 2015 guidance, Abuse-Deterrent Opioids — Evaluation and Labeling (U.S. Food and Drug Administration, 2022b; see also Grudzinskas et al., 2006).

Psychedelic NCEs including analogs of LSD and psilocybin. As mentioned earlier, for CNS-acting NCEs in general, many studies are typically conducted as described in FDA's 2017 abuse potential guidance and in reviews that have addressed potential study needs for psychedelic substances (Bonson, 2018; Calderon et al., 2018; Heal et al., 2018a; Sellers and Leiderman, 2018; Sellers et al., 2018; Henningfield et al., 2022).

These typically begin with in-vitro laboratory studies to determine binding affinities for diverse potential abuse-related targets and animal studies of general behavioral effects employing functional observational batteries (U.S. Food and Drug Administration, 2017; Gauvin and Zimmermann, 2019). If the drug candidate has strong affinity for a known abuse-related target (e.g., 5HT, or morphine opioid receptor) and appropriate functional activity (e.g., as partial or full agonists), then the drug candidate will likely be recommended for evaluation in a variety of animal and human tests (U.S. Food and Drug Administration, 2017;

[7] Various forms of THC and its synthetic form, dronabinol, are listed in either Schedule II or III, with all other forms of THC remaining in Schedule I (see CSA listing and discussion in DEA (Orange Book), 2021; Sacco, 2020; Lampe, 2021).

Calderon et al., 2018; Heal et al., 2018a).

As discussed in FDA's 2017 Guidance intravenous drug self-administration, studies are generally the most predictive among animal studies as to whether the drug will produce rewarding effects in humans; conditioned place preference studies are also accepted with FDA's caveat that it "is not considered to be as sensitive or reliable as self-administration" (U.S. Food and Drug Administration, 2017, p. 19). Drug discrimination studies are also recommended to determine if the interoceptive cues of the test drug are similar to those of known drugs of abuse (see also Fantegrossi et al., 2008). Not discussed in the 2017 Guidance are intracranial self-stimulation tests that are useful in assessing brain rewarding effects and have already been helpful along with self-administrating studies in differentiating the rewarding potential of indoleamines, such as LSD and psilocybin from MDMA and MDMA from D-amphetamine (Bauer et al., 2013; Sakloth et al., 2019; Negus and Miller, 2014).

Although assessments can be performed exclusively in the drug candidate, a more in-depth analysis would incorporate the inclusion of reference comparator drugs from various drug schedules, because abuse potential assessment is a comparative process that includes determination of the functional pharmacological equivalence of the candidate drug to known drugs of abuse. Such studies may also include progressive ratio and other techniques (Heal et al., 2018a). Although many countries do not require human drug abuse potential studies (e.g., Australia, Japan, UK, and the European Union), the US FDA and DEA often encourage and highly prioritize human abuse potential study findings.

As described in Table 4, HAP studies allow for the evaluation of a drug's abuse potential and typically assess subjective responses that are predictive of recreational use (Jasinski et al., 1984; de Wit and Griffiths, 1991; Vocci, 1991; Schoedel and Sellers, 2008; Carter and Griffiths, 2009; U.S. Food and Drug Administration, 2017). HAP data are among the most important single lines of pharmacological evidence relied upon by FDA for its scheduling recommendations. In general, for CNS-active NCEs, if animal studies suggest rewarding effects, then FDA may recommend the conduct of one or more HAP studies.

Classic psychedelics such as LSD and psilocybin, as well as NCE analogs based on these substances, raise greater concerns for researchers because doses within the range of those being studied for therapeutic use might produce disturbing visuoperceptual effects and anxiety for some people (Johnson et al., 2008; COMPASS Pathways, 2021), and supratherapeutic doses may pose increased risks of such adverse effects.

Whereas until the early 2000s one HAP study was generally sufficient to support NDAs, in recent years it has become more common for sponsors to conduct more than one HAP study to enable evaluation of a broader range of doses and multiple comparator drugs than can generally be accomplished in a single HAP study (U.S. Food and Drug Administration, 2020a). Table 4 shows the main elements of a typical HAP study as employed to assess most categories of CNS active drugs and as recommended in FDA's 2017 abuse potential guidance.

Early HAP study development and findings suggest both the promise and peril of such models in psychedelic drug product development. Early HAP studies provided the foundation for the designs summarized in Table 4 and have been summarized by Jasinski et al. (1984) and Jasinski and Henningfield (1989). They were developed at the predecessor to NIDA's Intramural Research Program, the Addiction Research Center, based in Lexington, Kentucky. These studies included human evaluation of LSD, psilocybin, and psilocin (Gorodetzky, 1970; Isbell, 1959a, 1959b; Isbell et al., 1959, 1967; Wolbach et al., 1962a, 1962b; Haertzen and Hill, 1963; Hill et al., 1963; Rosenberg et al., 1963a, 1963b, 1964; Gorodetzky and Isbell, 1964; Haertzen, 1964, 1965, 1966a, 1966b; Isbell and Gorodetzky, 1966; Isbell and Jasinski, 1969).

The results of these studies contributed to the development of the Addiction Research Center Inventory (ARCI) and its LSD scale which is often referred to as the "dysphoria" scale because differentiating effects of LSD and other psychedelics included their frequent dysphoric effects, which were thought to limit abuse-related risks (Jasinski et al., 1984; Haertzen and Hickey, 1987; Jasinski and Henningfield, 1989). The Director of the Addiction Research Center, William Martin, made the following observation in a 1973 review article: "The abuse of LSD-like hallucinogens came as somewhat of a surprise to many of the early experimenters [i.e., researchers] with these drugs" (Martin et al., 1973, p. 149). He observed that LSD could produce pleasure in some volunteers but that it was far less robust than prototypic drugs of abuse, including opioids, stimulants, and sedatives, and was frequently accompanied by dysphoric effects (see discussion in Johnson et al., 2018).

Consistent with the findings of the early Addiction Research Center HAP studies, a 1980s overview of animal and human abuse potential studies also suggested lower overall abuse potential of psychedelic drugs since they were generally relatively weak reinforcers in animal drug self-administration studies and produced relatively low abuse-related ratings in the early HAP studies (Griffiths et al., 1980). The authors wrote, "It should be recognized that the finding that animals will not consistently self-administer some hallucinogenic drugs is compatible with the fact that in the 'natural' environment people use hallucinogenic drugs at an extremely low rate and most people spontaneously discontinue use of some hallucinogens such as LSD. It seems plausible that the reinforcing effects of MDA and phencyclidine in animals may be unrelated to the fact that these drugs produce hallucinogenic effects." (Baumann et al., 2017, 2018; Griffiths et al., 1980, p. 15; see also Heal et al., 2018a).

The early findings also suggest that insofar as achieving a powerful acute euphoria does not appear to be the most prominent reason for use of psychedelics, it is not clear that measures and approaches of 21st century drug liking-focused HAP models adequately characterize the experiential effects that contribute to use in the real-world. For instance, following the acute effects of psychedelics, a persisting elevated mood termed "afterglow" may persist for days or weeks (Majic et al., 2015). This suggests that models characterizing experiential effects need to extend beyond the period of acute drug action and account for longer-term persisting outcomes as might be incorporated into modified

Table 4
General characteristics of clinical laboratory HAP studies.

Conducted in healthy volunteers who recreationally use drugs in the same class as the experimental drug. To be assured that they can tolerate the drug and respond with robust liking scores to drugs in this class, they are pretested with a prototypic drug of well characterized abuse potential. This is important for safety as well as scientific reliability and validity.
HAP studies typically compare ratings of drug liking for at least two doses of the test drug, as compared to placebo and a "positive control drug" (e.g., the prototypic drug with well-characterized abuse potential). A drug that produces increases in ratings of strength of the drug effect but not drug liking (e.g., diphenhydramine) is sometimes used as a "negative control drug."
These studies typically evaluate therapeutic doses as well as at least one dose that is at least 2–3 times higher than the intended highest therapeutic dose, because recreational drug use is often at higher than therapeutic doses, i.e., "supratherapeutic" doses.
Measures of drug liking ratings are assessed to determine time of onset, offset, and peak liking of the "drug-induced state" and are typically the primary outcome measure of interest to support characterization of human euphoriant (i.e., "rewarding") effects that might lead to recreational use. Note that FDA recommends bipolar drug liking scales from 0 to 100 to provide ratings from strong disliking to strong liking (50 is neutral).
Other measures include physiological signs of drug action such as heart rate and pupil diameter. Pharmacokinetic data are often assessed as well.
Other instruments can also be used to help characterize the subjective effects profile. For example, the Profile of Mood States (POMS) and the 49-item version of Addiction Research Center Inventory (ARCI) were common in the 20th century but have been less frequently used since the late 1990s, unless there is interest in more fully characterizing the nature of the cognitive effects profile of the experimental drug.[a]

[a] Some ARCI Morphine Benzedrine Group (MBG) items appear generally similar to some items on the Mysticism, NIH-HEALS, and other measures of consciousness, but further study will be needed to tell if they perform similarly, e.g., "I feel in complete harmony with the world and those about me"; "I feel a very pleasant emptiness"; "I can completely appreciate what others are saying"; and, "I felt so good that I knew other people could tell it."

HAP designs and other clinical studies.

Psychedelic treatments and outcomes are strongly influenced by "set and setting" as has been thoroughly described over their long history (Leary et al., 1963; Hofmann, 1992; Griffiths et al., 2006; Johnson et al., 2008; Gukasyan and Nayak, 2021). Thus, therapeutic use of these substances typically employs doses and parameters of set and setting intended to support positive outcomes to contribute to safety and effectiveness, including study monitors who provide reassurance and efforts to prevent and mitigate serious adverse events. Thus, these settings may underestimate abuse related effects including adverse events that might occur in unsupervised settings and nonmedical use.

Clinical studies involving hallucinogenic drugs that have been increasingly adopted in in the 21st century and are generally consistent with recommendations by Johnson et al. (2008). Such approaches have contributed to the fact that in a clinical setting most adverse effects are readily manageable, serious adverse effects have occurred at low rates overall, and there have been no deaths or documented persistent psychosis in clinical trials of psilocybin and LSD conducted in the US and elsewhere in the 21st century that we are aware of (Carbonaro et al., 2016; COMPASS Pathways, 2021 Griffiths et al., 2016; Mitchell, 2021; Ross et al., 2016; Ross, 2018).

To mitigate the risk of serious adverse events, and increase the likelihood of a positive healing experience, study participants and patients are typically screened for potential contraindications (e.g., cardiovascular illness or a personal or family history of psychosis) and prepared for challenging experiences such as anxiety and panic and how to manage them. Participants often meet with their assigned study monitors prior to testing to develop rapport and trust and then during test sessions, a staff monitor ("guide" or "counselor") is seated next to the participant to provide comfort and assistance as needed (Griffiths et al., 2006; Johnson et al., 2008). Thus, the emerging practices which are thought to contribute to therapeutic experiences, might also reduce the validity of HAP studies which have been designed over decades to minimize the impact of expectation and bias, supporting the rationale for HAP studies being conducted outside the context of a therapeutic study.

As mentioned earlier, conventional HAP studies generally follow FDA's guidance, which recommends the use of at least one dose that is 2–3 times the highest intended therapeutic dose, if that is safe to do ((U. S. Food and Drug Administration, 2017), p. 26–27); note this might not be considered safe for classic hallucinogenic and similarly acting substances. Recreational psychedelic users, however, vary widely in their use and whereas some may take higher than therapeutic doses, others use very low doses ("microdoses") in effort to experience beneficial cognitive and consciousness related effects while minimizing potential hallucinogenic and disturbing experiences (Johnson et al., 2018; Anderson et al., 2019; Rootman et al., 2021). This suggests that evaluation of very low doses may be important in human studies to better characterize nonmedical and abuse-related risks.

While these designs may limit the generalizability of the findings with respect to abuse potential, they may more fully characterize the drug induced experiences that contribute to reports of perceived benefits that may contribute to repeated use and increased prevalence of use in the community. The diverse measures used to characterize subjective experiences may also provide complimentary information to Phase 2 and 3 studies of efficacy and safety which typically rely on specific outcome measures for determining efficacy in treating the disorder or disease.

Should HAP study designs as recommended in FDA's 2017 guidance be used for psychedelic drug products?

HAP studies have long been recognized as having strong predictive value in premarket evaluations of new chemical entities (Jasinski and Henningfield, 1989; Vocci, 1991; Expert Panel, 2003; U.S. Food and Drug Administration, 2017). However, we recommend that FDA not require new HAP studies for evaluation of existing psychedelics that have been well studied such as LSD, psilocybin, and MDMA. These drugs have been extensively studied over more than a half century from basic neuropharmacology to animal and human research, along with epidemiology to understand patterns of use and public health consequence (e.g., see an 8FA evaluation of psilocybin, Johnson et al, 2018). In fact, as discussed above, HAP methodology development in the 1950s and 60s involved LSD, psilocybin, and other psychedelics (also see Johnson et al., 2018), and it is not clear that new HAP studies would be needed to help FDA develop its rescheduling recommendation if drug products containing these substances are approved. As discussed in FDA's 2017 abuse potential guidance, in addition to all other evidence, FDA also relies on data from safety and efficacy clinical trial to inform its scheduling recommendations. Indeed, it has been publicly disclosed that MAPS Public Benefit Corporation, which is developing MDMA for post-traumatic stress disorder, was informed by FDA that a HAP study would not be required,[8] and development of several indications for psilocybin appear to be progressing without FDA requests for HAP studies.

New chemical entities, however, may require HAP studies to help inform scheduling recommendations by FDA, NIDA, and DEA, following the earlier described scheduling process (Fig. 1). As FDA has made clear related to developmental study needs and regulation, "the same regulatory framework that applies to the development of any drug applies to the development of hallucinogens" (Calderon et al., p. 2), and we encourage FDA to make its study recommendations on a drug-by-drug basis as is its practice with new CNS acting drugs. However, as discussed below, there are safety and scientific validity questions that should be addressed before HAP studies are recommended by FDA.

It would seem important to resolve the safety and validity issues with respect to the evaluation of psychedelic substance with HAP studies, because they could be important in the evaluation of novel psychedelic substances as they are for novel substances in other drug classes. It is possible that relatively minor modifications in current designs would result in studies that could be acceptable, safely conducted, and yield valid and predictive outcomes, but these designs need to be evaluated for safety and scientific validity before they are recommended. Developing and validating these models would seem best done through a collaboration involving NIDA, FDA, and leading clinical research organizations (CROs) with experience conducting pivotal studies with diverse substances and including input and oversight from an outside Expert Panel of researchers, clinicians, ethicists, and diverse community representatives to develop a modified psychedelic HAP (mp-HAP) approach.

8. Challenges and opportunities to better understand abuse related effects and other influences on psychedelic substance use: The Griffiths et al. (2006) model

Decades of study with variations on the currently recommended HAP model indicates that these studies can substantially advance the understanding of mechanisms of drug action as well as effects that promote use (Jasinski et al., 1984; Jasinski and Henningfield, 1989; de Wit and Griffiths, 1991; Expert Panel, 2003; Griffiths et al., 2003; Carter and Griffiths, 2009). However, as discussed in this article elements of HAP design recommended in FDA's 2017 Guidance may not be safe and its focus on peak liking may not capture the diverse effects of psychedelics

[8] Public discussion included that by J.E. Henningfield, with permission by MAPS Public Benefit Corporation to discuss this FDA's communication during his presentation at the Development and Regulation of Psychedelics for Therapeutic Use, virtual workshop. Duke-Margolis Center for Health Policy, April 12–13, 2021.Additional note: We believe that, although our position does not represent FDA and may not be identical to their position we are not at odds with their actions or thinking. However, we understand that by August, FDA Controlled Substance Staff (CSS) will be submitting a commentary on their current thinking to this same special issue. .

Table 5
Summary of clinical study by Griffiths et al. (2006).

See the original article for additional important additional design and assessment details including the three-session phase of the study.
Thirty healthy subjects (16 female) without histories of hallucinogen use were randomly assigned to methylphenidate (40mg/70 kg) or psilocybin (30mg/70 kg) orally. The psilocybin dose was selected "as a high safe dose." The methylphenidate dose was selected as a "high, discriminable but safe dose" with similar time course as psilocybin. Subjects met with their same-sex session monitors on four occasions prior to the 8-h sessions "to develop and maintain rapport and trust." During sessions, monitors offered comfort and advice if subjects became anxious or fearful. Sessions were separated by two months.
Ten minutes before dosing and 30, 60, 90, 120, 180, 240, 300, and 360 min after dosing, heart rate and blood pressure were measured, and monitors completed a 20-item questionnaire rating mood and behavior.
Seven hours post drug, subjects completed: the Hallucinogen Rating Scale (99 items), the APZ ("altered states of consciousness") scale (72 items), the Addiction Research Center Inventory (49-item version), the States of Consciousness Questionnaire (100 items), and the Mysticism Scale (32 items).
Seven to 8 weeks after each session, subjects completed the Persisting Effects Questionnaire (89 items), the Mysticism Scale-Lifetime (24 items), the NEO Personality Inventory (NEO PI-R, 241 items), the Positive and Negative Affect Schedule Expanded Form (PANAS-X, 60 item), and Community Observer ratings of behaviour and attitude, which were communicated to study staff by telephone interviews.
Key elements of FDA recommended HAP studies that were not followed by Griffiths et al. (2006): employment of participants with recreational drug use histories, a drug liking assessment scale, and the administration of supratherapeutic doses of the test drug (psilocybin).

that may serve both to limit compulsive use and abuse, but may also contribute to reasons for use beyond getting high and experiencing euphoria.

The clinical study in healthy volunteers by Griffiths et al. (2006), was not designed or described as a HAP study by the authors because it did not employ some of the key elements of HAP studies (Table 5). However, it illustrates the potential of a modified design and a broad range of outcome measures to more extensively capture the totality of effects and potential reasons for use and thereby contribute to a comprehensive abuse potential assessment that relies on many lines of evidence (e.g., the psilocybin 8FA published by Johnson et al. (2018). The study did employ one classic abuse potential instrument that is less commonly used in 21st century HAP studies and not mentioned in FDA's 2017 Guidance, namely, the Addiction Research Center Inventory (ARCI), which assesses diverse subjective changes, some of which overlap with the other scales employed in the study. The ARCI, along with other scales employed by Griffiths et al. captured diverse perceived and desired outcomes such as increased creativity, empathy, spirituality, harmony, appreciation of the universe and other people, and enhancement of consciousness using a variety of measures.

The Griffiths et al. (2006) study was titled "Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance." It involved a comparison of methylphenidate (a Schedule II stimulant prescribed in the treatment of attention-deficit/hyperactivity disorder [ADHD] with robust dose related liking effects) to psilocybin in a controlled laboratory setting with the types of safety elements summarized above (see also Johnson et al., 2008). For predicting and understanding psychedelic drug use, its approach might be more informative than the standard HAP model as recommended by FDA (2017).

A shown in Fig. 2, the Griffiths et al. study documented the expected time course of acute effects of both drugs with onset within 30 min and return to near baseline levels within about 6 h. These included increased heart rate, increased blood pressure, and overall observer ratings. Both drugs produced positive effects indicative of abuse potential on various scales. Though both drugs were tested at doses that are considered "high" but generally tolerable, since only one dose of each drug was given (rather than the comparative doses typical in HAP studies), the difference in magnitude of the effects should be cautiously considered

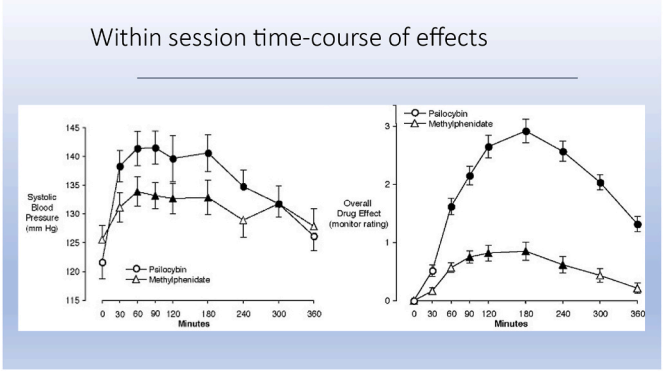

Fig. 2. From Griffiths et al., 2006. Time-course of observer-rated effects since capsule administration (time 0 was the 10 min before administration baseline). Filled symbols indicate significant differences from baseline. Brackets show ±1 standard error.

(see more discussion in Griffiths et al., 2006).

Ratings by the study monitors, community observers, and several self-report scales revealed striking qualitative differences along a variety of dimensions. These included overall stronger and more frequently observed effects of psilocybin on measures related to mystical and spiritual experiences, personal meaningfulness, and harmony, as well as more significant lifetime experience effects, compared to the effects seen with methylphenidate.

More closely related to classic abuse potential measures, both drugs produced increases in ARCI scales suggesting some degree of euphoria, a typical marker of abuse potential (e.g., the A, BG, and/or MBG scales). However, only psilocybin produced strong effects on the LSD scale, suggestive of dysphoria and decreased abuse potential. Together, these effects replicate and extend early human abuse potential findings discussed in Johnson et al. (2018), suggesting that abuse potential is meaningful but overall substantially lower than prototypical amphetamine and opioid-type Schedule II drugs.

The diverse effects identified by observers, community observers, and the various consciousness scales administered at the end of the sessions and 7–8 weeks later provide insights relevant to abuse potential and other influences on use and patterns of use. For example, the diverse but personally meaningful experiences associated with joy, tearfulness, transcendence, harmony, and peace were tempered by feelings of fear and anxiety, which would seem more likely to discourage chronic daily patterns of psilocybin self-administration that is commonly reported in recreational users of methylphenidate and similarly acting stimulants. In this regard, inclusion of measures like the NIH-HEALS instrument, a 35-item valid and reliable measure of psychosocial spiritual healing with 3 factors: Connection, Reflection/Introspection, and Trust/Acceptance, may be useful additions to HAP studies to better understand the motivations for psychedelic drug use. NIH-HEALS outcomes are associated with healing in patients with posttraumatic stress disorder (PTSD) and may provide useful information in better understanding the effects of psychedelic substances that may contribute not only to their healing effects but also to motivations for use outside of medically-guided treatment (Ameli et al., 2018; Ross et al., 2022). The richness of the outcomes with diverse measures of acute and longer-term effects with a variety of measures of consciousness and spirituality may help better understand potential effects that might contribute to use in some, discourage use in others, and contribute to healing across diverse diseases, as is discussed in the subsection below regarding implications of psycho-socio-spiritual healing assessment. In these respects, findings from such instruments might provide a complimentary approach to traditional measures of drug liking and euphoria for understanding and predicting nonmedical use.

Finally, by the "Griffiths et al., 2006 model", we do not mean that all

elements need to be identical as in Griffiths et al. (2006). Outcome measures might vary so long as they capture aspects of consciousness and subjective states reported to be important reasons for and effects of use, beyond "drug liking" and "euphoria" which have increasingly been the primary focus of HAP studies as recommended by FDA in its 2017 abuse potential guidance (U.S. Food and Drug Administration, 2017). Additionally, in such designs, multiple doses of each drug might be administered, and the intersession intervals might be substantially shorter. Furthermore, bimodal scales of liking/disliking effects that are commonly used in standard HAP studies would seem important to consider, given that a distinguishing characteristic of psychedelics is that they frequently produce both positive and negative effects within a few hours of drug administration. However, elements of set and setting are likely to continue to be employed as elements to assure safe use which includes the use personal subject study monitors. Observations by the study monitors may also provide valuable sources of information that are not captured in standard HAP models.[9]

Two recent studies support the viability of modified HAP study designs in which both limited the doses of the psychedelic to those under exploration for potential therapeutic use, used personal study monitors, and used a variety of instruments to assess various states of consciousness (Carbonaro et al., 2020; Holze et al., 2022). The Carbonaro et al. study compared 10, 20, and 30 mg/70 kg psilocybin to 400 mg/kg dextromethorphan, and placebo, in 20 healthy participants. Holze et al. compared 100 and 200 μg LSD to 15 and 30 mg psilocybin, and placebo, in 28 healthy participants and included a drug liking scale typical of HAP studies along with the States of Consciousness Questionnaire. Both studies found dose-related increases in ratings of positive and negative effects, as well as alterations in various measures of states of consciousness that appear to contribute to nonmedical real-world use in the community. The designs appeared acceptably safe and dysphoric effects were managed.

9. Psycho-socio-spiritual (PSS) healing assessments in clinical trials involving healthy volunteers

Clinical trials intended to assess safety and efficacy, or abuse liability, generally include well accepted instruments for such assessments, e.g., liking scaled in HAP studies as discussed above and standard instruments for assessing depression in studies evaluating major depressive disorder as a potential indication (e.g., Griffiths et al., 2016; Ross et al., 2016). However, both of the foregoing studies also included a variety of instruments to assess spirituality, mystical experience and other effects known to be produced by administration of psilocybin and other similarly acting substances, and these measures appeared to provide a fuller characterization of the effects and potential benefits of the treatments (Griffiths et al., 2016; Ross et al., 2016).

As mentioned earlier, assessment of states of consciousness including spirituality may contribute to the understanding and prediction of the likelihood of use outside of medically supervised therapeutic administration in addition to conventional abuse potential assessment. Such approaches can include assessment approaches employed in the Griffiths et al. (2006) study in healthy volunteers, which was an example of the types of exploratory clinical trials that can contribute to understanding the safety and effects of substances and products in development as potential new therapeutic drugs. Whereas psycho-social-spiritual (PSS) healing and other assessments of consciousness and spirituality might appear unrelated to abuse potential assessment, if we consider that abuse potential assessment has been used to help characterized drug effects that contribute to the use of substances outside of medically supervised contexts (e.g., including "recreational" use), such measures may help to characterize the effects that contribute to the apparently diverse motivations for use. Whether these are appropriately considered "abuse-related" is not clear to these authors. This is not a novel concept and as discussed earlier, the ARCI as well as the POMS were among the widely used measures employed in abuse potential assessment and continue to find value in the assessment of substances with novel mechanisms of action and effects (Jasinski et al., 1984; Jasinski and Henningfield, 1989; Vocci, 1991; Expert Panel, 2003).

Phenomena related to PSS Healing have been reported in analyses of psychosocial adjustment trajectories among breast cancer survivors (Helgeson et al., 2004), among patients diagnosed with head and neck cancer and their spouses (McCabe Ruff and Mackenzie, 2009), and also in the measurement of PTSD among trauma victims (Tedeschi and Calhoun, 1996).

PSS Healing's positive outcome often occurs despite substantial pain and suffering during illness. Kearney (2000) contrasted the "treatment for pain" and "healing of suffering" perspectives in relation to chronic or life-threatening illness. The opioid epidemic in the US provides recent evidence of the intertwining of pain and addiction and the subjective effects of opioids that contribute to both (Volkow and McLellan, 2016; Henningfield et al., 2019). Observations include recognition of pain as an experience that includes emotional components (Institute of Medicine, 2011) and that distraction and changes in mood can have a powerful effect on the perception of pain (Villemure and Bushnell, 2009). The possibility that psychedelic medicines may have a place in the management of chronic pain is discussed elsewhere and increases the importance of better understanding the diverse effects of psychedelics on consciousness that may contribute to nonmedical use for reasons that include greater acceptance of pain and suffering (Bornemann et al., 2021; Zia, 2022).

Another approach to assessing various aspects of consciousness and potential motivations for psychedelic substance user in clinical trials is the NIH HEALS, which is a validated tool made up of multiple factors – connection, introspection and reflection, and trust and acceptance (Ameli et al., 2018). This tool and other such tools may have utility in studies measuring the healing experiences, as well as more comprehensive assessment of the effects of psychedelics that may contribute to their desirability for use as therapeutic medicines, general enhancement of well-being and quality of life, and possibly recreational purposes of psilocybin and other related medications (see further discussion addressing therapeutic assessments in Ross et al. (2022).

10. Application of abuse potential data to drug labeling and REMs

In addition to informing drug scheduling, abuse-related findings inform the drug label and the Risk Evaluation and Mitigation Strategies (REMS), which will likely be required for classic psychedelics and many similarly categorized NCEs. The FDA-approved drug label for most CNS active drugs includes Section 9 – Drug Abuse and Dependency. As summarized by FDA, [it] "Conveys information about a drug's potential for abuse, misuse, addiction, physical dependence, and tolerance to inform prescribing decisions for safe and effective use. This section is generally inapplicable and omitted from the labeling for oncology drug products; however, this section may be important for other drugs used to palliate cancer-related symptoms (e.g., pain) or manage adverse reactions associated with an oncology drug product (e.g., nausea/vomiting)" (Bonson, 2018; Calderon et al., 2018; Lerner and Klein, 2019; U.S. Food and Drug Administration, 2021). Section 9 generally includes information on how to prevent and mitigate withdrawal symptoms in drugs that produce physical dependence and withdrawal.

Risk Evaluation and Mitigation Strategies (REMS). REMS are a legally enforceable, congressionally mandated category of risk management for some drug products. As summarized by FDA, "A Risk Evaluation and

[9] It is noteworthy that the earliest HAP models as developed by Addiction Research Center researchers were typically conducted with nearby observer monitors who completed observer rating scales as described by Jasinski et al. (1984) and Jasinski and Henningfield (1989), and this approach was common through the 1990s.

Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication …. REMS are not designed to mitigate all the adverse events of a medication; these are communicated to health care providers in the medication's prescribing information. Rather, REMS focus on preventing, monitoring and/or managing a specific serious risk by informing, educating and/or reinforcing actions to reduce the frequency and/or severity of the event." See more detailed information in FDA's 2020 REMS guidance (U.S. Food and Drug Administration, 2020b).

Serious risks for medications with abuse potential can include development of substance use disorders, diversion of medications for recreational use, and abuse-related adverse events. For medications with abuse-related risks, an abuse potential assessment contributes to the goals and designs of the REMS with differing approaches across drugs and drug classes related in part to the level and nature of their abuse-related and other safety risks. Thus, the REMS for sodium oxybate, Extended Release and Long Acting ("ER/LA") opioids, Transmucosal Immediate Release Fentanyl (TIRF), and nasal esketamine (which has hallucinogenic potential), differ substantially from one another (e.g., Brooks, 2014; Cepeda et al., 2017; Strunc et al., 2021; Traynor, 2019). For example, as described in the foregoing articles, although there are overlapping goals and elements across these REMS, the sodium oxybate REMS has a strong focus on preventing diversion with a centralized pharmacy and distribution approach, whereas the major focus of the ER/LA REMS is prescriber and provider education to encourage broad but appropriate access. By contrast, the TIRF REMS is more focused on restricting use to the relatively small population indicated for transmucosal fentanyl given the high risk of fentanyl for abuse and overdose. The nasal esketamine REMS addresses patient safety during drug administration due to the risk of sedation and hallucinogenic dissociative effects and includes a restricted distribution program to limit use to certified health care settings.

As discussed by Belouin et al. (2022) in this special issue and Belouin and Henningfield (2018), it is expected that potentially approved psychedelic drug products will require REMS to consider abuse-related risks and that these REMS and their requirements might differ across different psychedelic substances.

Although life-threatening reactions to psychedelics are rare in the community, accidents and other iatrogenic harms can occur, but they appear to be largely preventable in therapeutic applications by managing increasingly well-understood risk factors (e.g., cardiovascular illness, history of psychosis, failure to educate and prepare patients for what to expect, and high doses) (Nichols and Grob, 2018; Le Dare et al., 2020; Yaden et al., 2021). Much of this has been recognized since the 1960s, along with the advice provided by Hoffmann and other early leaders in psychedelic medicines development (Hofmann, 1992; Griffiths et al., 2006; Johnson et al., 2008; Belouin and Henningfield, 2018; Belouin et al., 2022).

REMS are a key component on the path to approval for psychedelic medicines because they are an evidence-based approach to minimizing inappropriate prescribing, use, and access, and to mandating conditions expected to mitigate risks. The surveillance and monitoring components of REMS also provide a basis for their evolution to more effectively minimize risks and contribute to positive therapeutic outcomes, while reducing burdens to the patient and healthcare system (e.g., restrictive prescribing rules) that may be a deterrent to their use by providing a basis for evidence-based evolution and modification of the REMS. A major challenge in both REMS elements and how they are implemented in healthcare settings is to minimize risks without being so burdensome as to reduced access to patients who could benefit from these medicines. In this regard, the diversity of patients with respect to where they live (e.g., rural versus urban), ethnicity, and other demographic factors that contribute to healthcare disparities are vital to consider in REMS approaches.

Table 6
Examples of REMS elements that might be considered for psychedelic medicines.

Education, registration and training of providers, therapists, and prescribers
Controlled drug distribution programs, including reverse distribution systems
Patient registries to enable long-term monitoring of health outcomes and reduce the risks of inappropriate prescribing
Approaches to prevent and detect off-label prescribing and use
Surveys of patients and prescribers to assess knowledge and to ensure compliance with safe use conditions
Elements to Assure Safe Use (ETASU), including required prescribing behaviors, follow-up procedures, and patient pre-screening

Table 6 provides a few examples of potential REMS elements that may be considered by FDA in discussion with a drug sponsor and with input from external FDA Advisory Committees that will likely be convened to advise FDA on the approvability of psychedelic medicines and other issues that may be posed by FDA. Every one of these elements are influenced by the evidence-based abuse related risks of concerns, e.g., how to manage them (first element), concerns about medication diversion (second element),and long term abuse related risks including potential psychedelic substance use in patients that had no such prior histories (third element).

\10.1. *How should psychedelic-based new drug products containing schedule I substances be rescheduled?*

Despite the social and political controversies that have accompanied psychedelics since the 1960s, the accumulated scientific, medical, and public health evidence provides a basis for some thoughts on how LSD, psilocybin, MDMA, and other psychedelic drug products might be rescheduled, if approved by the FDA. These and other classic psychedelics have been the most thoroughly studied, and we can also draw on several decades of data from national surveys.

As implied by the CSA requirement to consider its eight factors in scheduling recommendations, scheduling is based on far more than pharmacology, though pharmacological characterization including evaluation of rewarding effects, dependence, and withdrawal are fundamental and guided by factors 1–3 and 7. However, scheduling also includes public health risks and benefits, as addressed by factors 4, 5, and 6, in an effort to strike an appropriate balance between protecting the public from uncontrolled access to drugs with serious abuse-related risks, but not so overly restrictive that drugs with great potential will be underutilized. From a regulatory perspective, CSA scheduling and REMS are distinct protections, but both have implications for patient safety and access. Additionally, it is important that these key regulatory tools also consider their potential impact on existing health care disparities, as is discussed by Belouin et al. (2022) in this special issue.

For psilocybin, although some abuse-related data are yet to be collected based largely on adverse event reporting in ongoing clinical trials, we do not expect that this will substantially alter the characterization of psilocybin from the preliminary 8FA that was published in 2018. In that review Johnson et al., concluded as follows: "All 8 factors and other lines of evidence taken together indicate the profile of a substance that is characterized by some level of abuse potential and potential risks. However, the findings do not support placement more restrictively than Schedule IV." (Johnson et al. (2018), p. 19). Whether FDA and DEA agree with this assessment will not be known until FDA approves a psilocybin-containing product and makes its scheduling recommendation. Regardless of FDA and DEA's determination, other countries that approve psilocybin containing products are not obliged to follow the US scheduling approach.

Johnson et al. summarized additional considerations that also appear to remain valid:

> "The 8-factor analysis contained in this review should be considered an abbreviated assessment of abuse potential as compared to what

would be required by the FDA to accompany the submission of an NDA for approval of a psilocybin containing drug product. Furthermore, considerable additional study will yet be required to support the submission of a complete and reviewable NDA and its abuse potential assessment …. In contrast to Schedule III drugs and even to many drugs placed in Schedule IV, the reinforcing effects in preclinical studies are marginal. There is no clear evidence of physical dependence and withdrawal in preclinical or clinical studies, or among those who chronically used illicit products. Euphoriant effects can occur under limited circumstances but appear attenuated by dysphoric effects. The doses that pose a risk of acute poisoning death ('overdose') appear to be approximately 1000 times the likely highest clinical dose to be marketed, psychological dependence resulting in daily use appears rare, and all major drug surveillance systems reviewed in Factors 4, 5, and 6 of this analysis indicate rates of abuse, emergency department reports, and treatment seeking in youth and adults that are substantially lower than are evident for many Schedule IV drugs. It is possible, of course that subsequent study with larger populations and different designs in animals and humans, would yield different outcomes, but this review suggests that psilocybin would be appropriately placed in Schedule IV of the CSA if the FDA approves a psilocybin NDA." (Johnson et al. (2018), pp. 19–20).

Also consistent with the foregoing analysis is the approach and conclusions of the American Psychiatric Association (APA) Diagnostic and Statistical Manual, 5th Revision (DSM 5) (American Psychiatric Association, 2013) as pertains to "Other Hallucinogens" which includes LSD, psilocybin, and MDMA (but not PCP). For example, in contrast to most Schedule II, III, and IV drugs, "Withdrawal symptoms and signs are not established for hallucinogens, and so this criterion does not apply [to Other Hallucinogen Use Disorder]" (APA (2013), p. 523). Consistent with this, Substance Withdrawal is not included as a diagnosis associated with Other Hallucinogens (APA (2013), p. 482).

Substance Use Disorder for hallucinogens is recognized as a potential diagnosis in the DSM 5. However, APA's discussion of prevalence states "Of all substance use disorders, other hallucinogen disorder is one of the rarest. The 12-month prevalence is estimated to be 0.5% among 12 to 17-year-olds and 0.1% among adults age 18 and older in the United States." (APA (2013), p. 525).

It is important to note that tolerance to hallucinogens, including LSD, MDMA and psilocybin has been well documented in human and animal studies (Isbell and Jasinski, 1969; Nichols, 2004; Parrott, 2005; Rosenberg et al., 1963b; Wolbach et al., 1962a), which suggests that some degree of physiological dependence is possible, but, if so it is apparently rare and has not been accepted as a meaningful effect by the American Psychiatric Association.

In addition to the low prevalence of substances use disorders associated with classic psychedelics, it is noted that peyote, which contains the classic psychedelic mescaline, and ayahuasca, which contains the classic psychedelic (DMT), have been used in ceremonial contexts by indigenous peoples for generations, with evidence that participation in such ceremonies may confer a number of mental health benefits (Johnson et al., 2019). Furthermore, more recent studies suggest that lifetime classic psychedelic use may be associated with a reduced likelihood of several types of mental and physical health problems. A series of population risk studies based on the nationally representative Substance Abuse and Mental Health Service Administration (SAMHSA) National Survey on Drug Use and Health (NSDUH) suggest that lifetime classic psychedelic use is associated with a reduced likelihood of psychological distress, opioid use disorders, and suicidal thinking, planning, and attempt, as well as a reduced likelihood of hypertension, diabetes, obesity, cancer, and/or heart disease (Hendricks et al., 2015; Pisano et al., 2017; Sexton et al., 2019; Simonsson et al., 2021a, 2021b, 2021c). Analysis of NSDUH data also suggests that lifetime classic psychedelic use is associated with a reduced risk of criminal behavior (Hendricks et al., 2018). Hendrix et al. are careful to discuss limitations, however, with their findings suggesting potential differences across psychedelic substances that merit further exploration. A more recent study that is also based on NSDUH data suggests that MDMA may also be associated with decreased risk of major depressive episodes (Jones and Nock, 2022), which was supported by exploratory findings in a recent MDMA clinical trial (Mitchell, 2021). Thus, although the foregoing findings need to be treated cautiously and merit further research, they suggests lower abuse-related risks with these psychedelic substances than those associated with the Schedule II opioids and stimulants.

With respect to MDMA, although the DSM-5 includes it with the indoleamines such as psilocybin and LSD with respect to potential clinical diagnoses, as discussed earlier it likely has somewhat higher abuse potential than the indoleamines. MDMA's distinction is illustrated by the findings that it appears to have stronger reinforcing effects than LSD in animal studies though still substantially lower than for Schedule II amphetamine and cocaine (Beardsley et al., 1986; Fantegrossi et al., 2002; Fantegrossi, 2008; Coker et al., 2021).

Taking the foregoing into consideration, Coker et al. (2021) concluded the following based on their preliminary 8FA of an MDMA drug product under development: "Although further analyses will be considered for the abuse potential assessment that will be submitted in the NDA, the current evidence does not suggest a high risk of abuse or dependence of MDMA in a clinical setting. This preliminary analysis supports the plausibility of recommendation for rescheduling as no more restrictive than Schedule III."

In summary, taking together diverse lines of evidence as have already been presented for psilocybin in a review article (Johnson et al., 2018), and MDMA in a presentations (e.g., Coker et al., 2021) we believe that based on available evidence, classic psychedelics including LSD and psilocybin, and the entactogen MDMA, warrant continued listing in the CSA., that Schedule V is likely not sufficiently restrictive.

For NCEs including substances with chemical structures that are similar to LSD, psilocybin, or MDMA, extensive study will likely be required and could reveal abuse potential profiles that are substantially higher or lower than the classic psychedelics since small chemical changes can result in substantial variation in pharmacological and toxicological effects as is evidenced by the so-called designer stimulants, cannabinoids, and opioids including fentanyl and FRS (Rannazzisi, 2013; National Institute on Drug Abuse, 2015; The White House, 2021).

11. Discussion and conclusions

Assessing the abuse potential of psychedelic substances is fundamentally the same CSA- and FDA-guided process as applied to other CNS-active substances and drug products. Put another way, in their review of regulatory perspectives on the evaluation of hallucinogenic drugs the FDA scientists concluded, "From the regulatory perspective, the same regulatory framework that applies to the development of any drug applies to the development of hallucinogens." (Calderon et al. (2018), p. 7). Thus, despite historical controversies concerning the risks and benefits of psychedelic substances, decades of scientific study, national surveillance, and FDA-advised medications development efforts provide a basis for a data-driven understanding and assessment of the abuse-related risks of psychedelics.

Our discussion of the abuse-related science and issues has been presented in the regulatory context of the CSA and the FD&C because that is the pathway for approval of new medicines and their scheduling and rescheduling in the CSA. Thus, scientific research, medical experience, public health impact, and legally binding federal laws are inextricably intertwined.

From a scientific perspective, abuse potential assessment involves determination of the degree of pharmacologic equivalence of the new drug (substance and/or product) to previously scheduled drugs (in Factors 1, 2 & 3 of the 8FA), how the public health risks and benefits compare to known recreationally used substances (in Factors 4, 5 & 6),

as well as evidence from studies and relevant medical use to related substance and products to help understand the potential of the drug to produce psychic and physiological dependence, i.e., a substance use disorder and withdrawal (in Factor 7).

In accordance with the CSA, drugs with sufficient abuse potential to merit CSA listing but without approved therapeutic use can only be placed in Schedule I, regardless of the actual level of abuse potential. Conversely, drug products that are in Schedule I during development must be removed from Schedule I and rescheduled if they are approved by the FDA before they can be marketed. The CSA and FDA provide a legally- and scientifically-based path for this process.

From the perspective of drug approval and labeling, the abuse-related studies and findings also inform section 9 (Drug Abuse and Dependency) of the FDA-approved drug label and other labeling that addresses potential side-effects, dosing, and safety. The abuse-related studies and findings also inform the risk management components, including elements [of treatment] to assure safe use (ETASU), which are included in a legally enforceable REMS for any drugs for which the FDA determines that risk mitigation measures beyond the labeling "are necessary to ensure that the benefits of the medication outweigh the risks" (U.S. Food and Drug Administration (2020b) [REMS Guidance], p. 2).

Although the regulatory framework for research, new drug development, approval, and regulation of psychedelic substances are the same as for other CNS-active drugs, the more highly hallucinogenic substances that fall under the psychedelic umbrella pose novel challenges to research regarding the scientific reliability and validity of study findings. The safety risks include disturbing visual perceptual effects, acute fear, anxiety, and panic. The risks of such adverse events have been very low in clinical trials (e.g., Griffiths et al., 2016; Ross et al., 2016; Griffiths et al., 2018; COMPASS Pathways, 2021; Mitchell, 2021; Ross et al., 2022) because the clinical trial designs incorporate risk mitigating protocols (see, also Griffiths et al. (2006); Johnson et al. (2008)).

The fact that serious risks that do exist for psychedelics can be mitigated and managed by the evidence base emerging from clinical trials that will be taken into consideration for both FDA approval and the rescheduling of Schedule I substances. Simply stated, it is difficult for the FDA to approve drugs with serious risks in which there is not an evidence base to guide risk mitigation. From a scheduling perspective, note that one of the three CSA criteria for Schedule I placement is "lack of accepted safety for use of the drug or other substance under medical supervision." (U.S. Drug Enforcement Administration, 2022a). In addition to supporting approval and contributing to scheduling and rescheduling, available and emerging clinical trial data will be critical in the development of warnings for labeling, advice to both healthcare providers and their patients to minimize and manage such risks, and the development of REMS as discussed earlier.

The need for dedicated animal and human abuse-related studies will likely vary widely across drug products: classic already well-studied drugs with decades of community experience will likely require the least amount of new abuse-related studies.Schedule V would seem to provide an insufficient level of control and Schedule II is not indicated by data from abuse-related pharmacology, clinical trials, or public health experiences, and would be a substantial barrier to use for many of the indications currently under development.

Novel drugs, whether minor variants or analogs of classic psychedelics or substantially different NCEs, will certainly merit extensive nonclinical and clinical research to fully characterize their abuse potential because there will not be real-world community experience to draw upon and because seemingly small changes in the chemical structure of a drug can confer substantial changes in safety and abuse potential. The potential pipeline of the drugs in this broad category could include some NCE's that do not merit scheduling, and others that merit Schedule II or other scheduling.

Although not generally considered a key consideration in drug scheduling and approval, the stigma and fear associated with drugs that are widely believed to carry high risks of abuse and overdose, like those of many Schedule II drugs, is important to consider. Stigma and misunderstandings of risks, abuse, and other safety-related effects could limit their acceptability to patients who could benefit from their use and health care professionals who will need to prescribe and oversee these medicines. In turn this could further fuel existing health care disparities in general, and possibly already vulnerable populations to a greater degree (Volkow, 2020; Belouin et al., 2022; Hendricks, 2022). These concerns also support the importance of NIDA, FDA, and other federal agencies working together to educate the general public about the evidence for abuse-related and other types of risks and benefits of psychedelic drugs, so that when these products are approved, access and utilization will be driven by medical need and desire of patients and their healthcare providers, and not suppressed by unfounded fear and stigma. These efforts should be part of comprehensive efforts to reduce longstanding disparities in healthcare.

In conclusion, decades of misunderstanding about the many abuse-related concerns posed by psychedelics, which have been reinforced by their Schedule I listing, is increasingly being addressed by research from the molecular level to Phase 3 clinical trials as well as by epidemiologic evidence. The research and advancement of scientific understanding of psychedelic drug effects, safety, and benefits is paving the way for potential FDA approval and appropriate CSA scheduling of future NDAs. As discussed elsewhere in this special issue (Belouin et al., 2022; Magar et al., 2022), this will be a crucial step for the realization of the potential promise of the medical and public health benefits of psychedelic-based medicines in the US and globally.

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Jack Henningfield and Marion Coe are employees of PinneyAssociates, Inc. which provides scientific and regulatory consulting support for new drug applications (NDAs) and risk management programs for a broad range of CNS active substances and drug products including psychedelic substances, new chemical entities, and alternative formulations and routes of delivery, as well as dietary ingredient notifications, cannabinoid assessment, and noncombustible tobacco/nicotine products for FDA regulation. Drs. Henningfield and Coe received no external financial support for writing this article and no external commercial interests had any input.

David Heal and Sharon Smith are shareholders and employees of DevelRx Ltd. DevelRx provides consultancy on drug discovery and development to treat psychiatric, neurological and metabolic disorders. They specialize in advising pharmaceutical companies on drug abuse and dependence evaluations and prepare regulatory submissions. DevelRx advises on the development and approval of cannabinoids and other natural products as novel foods or food additives. DevelRx, David Heal and Sharon Smith have received no external financial support for writing this article, and no external commercial interests had any input.

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Author roles and article development process

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