International Journal of Drug Policy 108 (2022) 103816

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

Research Paper

Inconsistencies between national drug policy and professional beliefs about psychoactive drugs among psychiatrists in the United States

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ARTICLE INFO

Keywords:
Drug abuse
Drug harms
Drug benefits
Drug policy
Legal classification of drugs
Psilocybin
Alcohol
Ketamine
Survey

ABSTRACT

Background: Evidence points to an incongruence between international drug policy and expert opinion about safety, abuse potential, and therapeutic potential of specific drugs. However, no prior studies have directly explored psychiatrists' attitudes about the current drug schedule. Therefore, we examined whether American psychiatrists' perceptions of four psychoactive drugs differed from those indicated by their schedules.

Methods: A quasi-experimental online survey of a convenience sample of psychiatrists in the United States (N=181; Mean age=48.7; Female=35%). Participants were randomized to receive 1-of-4 vignettes, each depicting a depressed patient reporting relief from symptoms after non-prescribed psychoactive drug use (i.e., psilocybin [Schedule I], methamphetamine [SchedII], ketamine [SchedIII], or alprazolam [SchedIV]). Participants responded to questions related to this clinical scenario and then rated the safety, therapeutic, and abuse potentials of these four drugs and alcohol.

Results: There were significant differences by vignette condition in mean likelihood ratings of: warning against engaging in drug use again ($p<.01$), being concerned about developing a new psychiatric problem ($p<.001$), being concerned about increased suicide risk ($p<.01$) and being supportive of further use of this drug as part of the treatment plan ($p<.001$). Overall, non-prescribed use of methamphetamine and alprazolam was rated more concerning and less acceptable than non-prescribed use of psilocybin and ketamine. Compared to psilocybin and ketamine, participants rated methamphetamine and alprazolam as less safe ($p<.001$), having less therapeutic potential ($p<.001$), and having more abuse potential ($p<.001$). Mean ratings of safety and abuse/therapeutic potential of alprazolam and methamphetamine were equivalent to that of alcohol, and all three were rated more harmful than psilocybin and ketamine.

Conclusion: American psychiatrists' perceptions about safety and abuse/therapeutic potentials associated with certain psychoactive drugs were inconsistent with those indicated by their placement in drug schedules. These findings add to a growing consensus amongst experts that the current drug policy is not scientifically coherent.

Introduction

National and international drug policies strictly control the use of a large proportion of psychoactive drugs in recreational, clinical, and research settings. In Title II of the Comprehensive Drug Abuse and Control Act of 1970, otherwise known as the Controlled Substances Act (CSA), the United States (US) created five "schedules" with the aim of organizing harmful drugs from most to least dangerous (Schedule I-V) (Controlled Substances Act, 1970). However, these scheduling decisions were largely made in the absence of any clear pharmacologic, neuroscientific, or psychiatric evidence (Nutt et al., 2013). As a result, they did not accurately reflect the harms or therapeutic benefits of the various drugs (Nutt et al., 2013; Nutt et al., 2010). For example, drugs in lower, less restrictive, schedules are supposed to have progressively lower abuse potentials, accepted medical uses, and less potential for physical and psychological dependence. However, many drugs in lower schedules have greater potential for harm than those in higher schedules. For example, benzodiazepines, Schedule IV drugs commonly prescribed for the treatment of anxiety, are the third most commonly misused illicit or prescription substance in the US, with benzodiazepine overdose-related deaths increasing 400% from 1996 to 2013 (Votaw et al., 2019). Similarly, methamphetamine, which has been recalled in multiple formulations due to concerns for abuse and limited medical use, remains a Schedule II drug (Logan, 2001; Smith & Crim, 2011).

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https://doi.org/10.1016/j.drugpo.2022.103816

Conversely, several Schedule I drugs purported to be dangerous and of no medical value, including psilocybin, 3,4-methylenedioxy methamphetamine (MDMA), and cannabis (marijuana), have shown therapeutic potential (Baker et al., 2003; Griffiths et al., 2016; Hosking & Zajicek, 2008; Mitchell et al., 2021; Mithoefer et al., 2018, 2019) and low rates of misuse, addiction, or physical harm (Nutt, 2012; Nutt et al., 2010). In recent clinical studies, psilocybin and MDMA have both shown promise in the treatment of depression (Davis, Barrett et al., 2021), Post-Traumatic Stress Disorder (PTSD) (Mithoefer et al., 2019), tobacco use disorder (Johnson et al., 2014), alcohol use disorder (Bogenschutz et al., 2015), and end-of-life anxiety and depression in cancer patients (Griffiths et al., 2016). Indeed, the FDA has granted breakthrough therapy status to three separate trials of Schedule I compounds within the last five years: psilocybin for treatment-resistant depression and Major Depressive Disorder (MDD), and MDMA for PTSD, positioning these drugs for possible FDA approval within the next 2-4 years. Taken together, this body of research contradicts the placement of many drugs in their current schedules, yet little has been done to rectify these inconsistencies. Additionally, due to the existence of three United Nations treaties and the outsized influence of the US in determining international drug policy (Attia, 2021), the FDA classification system is effectively mirrored across global laws and regulations (Nutt et al., 2013). For example, the UK Misuse of Drugs Regulations classifies psilocybin, MDMA, and cannabis in the equivalent of US Schedule I, as do the current United Nations Conventions (Nutt et al., 2013).

There are several consequences to these incongruencies remaining in the drug schedule. Drugs in Schedule I are limited by stringent controls that make them difficult to study in both basic science and clinical settings. Obtaining regulatory approval to study a Schedule I drug can be a multi-year process, and even after approval is obtained, there are significant infrastructure-related requirements that deter investigators, grant-making organizations, and university ethics committees. Perhaps the best evidence for the significance of these deterrents is the effect of Schedule I status on psychedelic research. Between the years 1950 and 1965, there were six international scientific meetings and more than a thousand clinical papers published on psychedelics (Pollan, 2018). After the 1970 Controlled Drugs Act, research dwindled to a near standstill until the 2010s (Rucker et al., 2018). Even with this recent resurgence, most studies have been funded by charitable donations or for-profit companies due to continued hesitancy on the part of grant-making organizations such as the National Institutes of Health (Nutt et al., 2013). In fact, from the years 2006-2020, there were zero NIH funded grants directly funding psychedelic-assisted therapy clinical trials (Barnett et al., 2022), leaving much to be learned about their underlying pharmacologic mechanisms, long term safety profiles, drug-drug interactions, and therapeutic potential.

Although the effects of the drug schedule on research has been well documented (Nutt et al., 2013, 2015), little is understood about its effect on physician attitudes and behaviors. There is some evidence that drug policy directly affects the prescription habits of physicians and therefore clinical outcomes (Kalaria & Kelly, 2019). For example, despite over forty years of research demonstrating the superior efficacy of medication-assisted treatments for opioid use disorder, only an estimated 12.5% of patients with opioid use disorder receive buprenorphine (Schedule III) or methadone (Schedule II) therapy due in part due to the strict regulatory requirements associated with their respective schedules (Alford et al., 2011; Haffajee et al., 2018; Wakeman et al., 2020). It is also possible that physicians systematically underestimate the risks associated with drugs in lower schedules. For example, Xanax (alprazolam), a Schedule IV drug, has been shown to be more reinforcing and more toxic in overdose than other benzodiazepines and to have a more severe withdrawal syndrome, yet it was the most commonly prescribed benzodiazepine as of 2018 (Ait-Daoud et al., 2018; Juergens, 1991). In contrast, there is evidence that physicians perceive the harms and benefits associated with specific drugs and adjust their behaviors accordingly, even in the absence of scheduling changes. For example, from 2013 to 2018, there was a gradual decrease in the prescribing of benzodiazepines in the US, perhaps reflecting a growing awareness of the associated risks (Esechie et al., 2021). Additionally, prescriptions of methamphetamine peaked at 31 million in 1967 and, in the setting of growing concerns for abuse liability, were down to 8,000 as of 2019, despite methamphetamine maintaining its Schedule II status (Lindquist, 2019; Office of National Drug Policy, 2022). Similarly, off-label prescriptions of ketamine have increased significantly in the last decade as evidence for therapeutic efficacy for depression has emerged (Wilkinson et al., 2017).

Given the pending approval of several Schedule I drugs for medical use and the escalating problems of abuse of several drugs in lower schedules, there is a growing need to understand physician attitudes and behaviors surrounding the apparent contradictions in the drug schedule. It is possible that physicians rely on the schedule to inform their opinions and prescribing habits, in which case we would expect an overall agreement with the drug scheduling categories for specific drugs. It is also possible that they engage in a more nuanced assessment of drugs based on clinical experience, research and other factors, in which case we would expect to find contradictions between their opinions and those implied by the drug schedule.

As specialists in the prescription and abuse of psychoactive drugs, psychiatrists are an ideally positioned physician subspecialty to evaluate the risks and benefits associated with scheduled drugs. However, no prior studies have investigated these perceptions or psychiatrists' overall views of the drug schedule. Therefore, to explore whether there are inconsistencies between psychiatrist perspectives and current drug scheduling placements, we conducted a national quasi-experimental survey study of American psychiatrists. Using a series of 4 clinical vignettes, our first aim was to assess the attitudes and beliefs about a depressed patient's non-prescribed use of 1 of 4 psychoactive drugs (one drug from each schedule I-IV). This approach forced psychiatrists to consider drugs in the context of a clinical risk/benefit analysis and allowed us to elucidate the specific, practical implications of psychiatrists' views in these clinical vignettes. Next, we examined psychiatrists' general perceptions about the safety, abuse potential, and therapeutic benefits of 4 psychoactive drugs (and the unscheduled drug alcohol) in the absence of a clinical vignette. This approach allowed for a direct comparison of psychiatrists' views to those indicated by the CSA. Lastly, we explored qualitative perspectives about the impact of drug policies on psychiatry training and psychiatrists' attitudes/beliefs about psychoactive drugs. Elucidating psychiatrists' perceptions and attitudes in these three areas would represent a critical first step in understanding the interaction between the drug schedule and physician attitudes and behaviors.

Methods

Participants and procedure

This study involved the recruitment of a national convenience sample of psychiatrists in the US. Recruitment occurred via two psychiatrist emailing lists purchased from marketing companies, email listservs from the APA, and personal networks (snowball sampling). Active recruitment occurred from April 7, 2021 to May 2, 2021. Potential participants received an email invitation which contained information about the study, the basic inclusion criteria (i.e., board certified psychiatrists or psychiatry residents in the US who can read, write, and speak English fluently), and the option to click a secure web link (hosted by www.qualtrics.com) to read more about the study and to participate if they chose to do so. The participants were presented with a consent form, and once completed, they could begin the survey. This study was determined exempt from the Institutional Review Board at Ohio State University. The full survey is available from the corresponding author.

Measures and quasi-experimental conditions

The survey for this study included questionnaires assessing participant demographics and other background information (e.g., age, sex, gender, education, religion, professional training and work history). Participants were then randomized to view one of four variations of a vignette (see Vignette in Supplemental Document) depicting a patient who wanted to incorporate one of the following drugs in treating their severe depression: A) psychedelic mushrooms (i.e., psilocybin; a Schedule I drug), B) Desoxyn (i.e. methamphetamine; a Schedule II drug), C) ketamine (Schedule III drug), or D) Xanax (i.e. alprazolam; a Schedule IV drug). Participants were then asked to rate the likelihood of and/or their level of agreement with a series of clinical decisions and projected future outcomes of the vignette. Although each of these drugs have well established anti-depressant properties (Davis et al., 2021b; Griffiths et al., 2016; Krystal et al., 2019; Murrough et al., 2013; Rasmussen, 2008; Srisurapanont & Boonyanaruthee, 1997; Stotz et al., 1999; van Marwijk et al., 2012; Warner et al., 1988), none are currently FDA approved for the treatment of major depressive disorder, although an intranasal formulation of the ketamine enantiomer, Spravato (esketamine), was recently approved for treatment-resistant depression (see Supplemental Table 1, Rationale for Drug Selection in Supplemental Document for further details).

Next, all participants were presented with a series of questions about the safety, therapeutic potential, and abuse potential of psilocybin, methamphetamine, ketamine, alprazolam, and alcohol, in the absence of any clear clinical guidelines. Specifically, participants were asked to, "Please rate each of the following substances in terms of their **perceived safety/therapeutic potential/abuse potential** if used properly or as directed." Therefore, participants were presumably making their ratings based on a variety of intersecting factors including the influence of national drug policy, their own knowledge of the scientific literature and the pharmacological action of these different drugs, and their individual clinical experiences, though these specific factors were not directly assessed in these questions. Drugs were presented with both their generic and brand names (when relevant) throughout the survey but are referred to by their generic names throughout this paper, given this journal's international readership. Finally, a series of qualitative questions were included to directly explore perspectives about the impact of drug policies on psychiatry training and participant attitudes/beliefs. Participants were required to complete the survey in one sitting for their data to be stored and used. Participants had the option to enter a raffle for a chance to win one of 14 $100 gift cards and one of 30 $50 gift cards. Overall, 282 people clicked a link and were presented with the informed consent document. All of these participants passed the bot detection and relevant fraud detection indices in Qualtrics. Of these, 185 consented to participate, were randomized to a vignette condition, and completed all questions after the vignette. An additional four participants were excluded because they did not complete the remaining questionnaires in the survey. Thus, the final sample was 181 participants.

Analytic strategy

We began by calculating summary statistics of all demographic characteristics and comparing demographic characteristics by vignette groups using a series of chi-square (sex, region of residence, residency training status, license status, fellowship training, common diagnoses treated in practice, psychotherapy in practice, training in and primary theoretical orientation used in practice, practice setting, and whether they have dedicated research time) and one-way ANOVAs (age, years practicing as a psychiatrist, number of peer-reviewed publications, number of research presentations). Post-hoc tests of mean wise comparisons (ANOVAs) and z-tests of comparing proportions (chi-square), with Bonferroni correction, were used to explore specific group differences in demographic characteristics. Next, using a series of one-way ANOVAs, we examined whether psychiatrists' perceptions about the acceptability, potential harms and therapeutic benefits of different psychoactive drugs differed as a function of the drug's schedule in the US (using vignette group as a proxy for drug schedule). Post-hoc tests of mean wise comparisons were used to explore specific mean group differences. Repeated measures ANOVAs were then used to examine whether mean ratings of safety, therapeutic potential, and abuse potential differed as a function of drug type (i.e., psilocybin, methamphetamine, ketamine, alprazolam, alcohol). Next, post-hoc tests of mean wise comparisons were used to explore specific mean group differences. To determine whether randomization to clinical vignettes had influenced ratings of safety, therapeutic potential, and abuse potential, a one-way ANOVA was conducted comparing mean ratings across the vignette groups (there were no statistically significant finding; data available upon request). A p-value of .05 was used to determine statistical significance, and effect sizes (Phi for chi-square and eta-squared for ANOVA) were used to interpret strength of any statistical differences in each quantitative analysis. Analyses were performed using SPSS v 28 (IBM, 2021).

Next, we explored perspectives describing the impact of drug policies on psychiatry training and psychiatrists' attitudes/beliefs about psychoactive drugs using qualitative content analysis. The guide for qualitative data analysis and coding steps described by Casterlé et al. (2012) was used in this analytic process. We started with the preparation of the coding process (e.g., reading all text-entry responses, generating list of themes, refining themes), and then followed with the actual coding process (e.g., use themes to generate concepts to define each theme and then assign themes a numerical value for coding) (Dierckx de Casterlé et al., 2012). All coded responses were tracked under each theme within each open-ended question, and a calculation was conducted for the proportion of responses out of the valid responses to each question. After the actual coding process, a randomly selected 20% of valid responses from each open-ended question was used to examine inter-rater reliability. Responses were independently coded without any prior exposure to the specific qualitative data and coding process for each question. The inter-rater reliability was good (81% for question one, 89% for question two, and 82% for question 3; mean IRR = 84%).

Results

Participant characteristics

As Table 1 shows, participants were primarily middle aged (M=48.7, SD=16.2) male (65.2%) psychiatrists with an average of 16.2 years (SD=15.3) of practice after residency. The sample was geographically diverse, with similar proportions from the Southern (26.0%), Western (25.4%), Midwestern (26.5%), and Northeastern (21.0%) US. Table 1 also presents demographic information of participants as a function of each of the four vignettes. The four vignette groups did not statistically differ in any of the demographic variables.

Ratings of drug harms and benefits in randomized clinical vignette scenarios

Table 2 presents responses to the four vignettes. As a function of which drug vignette was presented, there were significant differences in mean likelihood ratings of: warning the patient against engaging in drug use again, $F(3.0, 46.7) = 5.92$, $p<.01$, $\eta_p^2=.09$, being concerned about the patient developing a new psychiatric problem, $F(3.0, 52.9) = 8.33$, $p<.001$, $\eta_p^2=.12$, being concerned about increased suicide risk, $F(3.0, 32.8) = 4.92$, $p<.01$, $\eta_p^2=.08$, and being supportive of further use of this drug as part of the treatment plan, $F(3.0, 95.9) = 12.7$, $p<.001$, $\eta_p^2=.18$. Post-hoc tests of mean pairwise comparisons revealed that participants were more likely to warn against the repeated, non-prescribed use of methamphetamine (M=1.13, SD=1.45) and alprazolam (M=1.36, SD=1.34) than that of psilocybin (M=0.22, SD=1.70) or ketamine (M=0.24, SD=1.91). Additionally, participants were more concerned about the development of a new psychiatric problem following the non-prescribed use of methamphetamine (M=1.06, SD=1.14)

Table 1
Demographics.

Characteristic	Total Sample (N=181)M(SD) or %	Vignette Group				F or X2	Effect Size
		Psilocybin M(SD) or %N=45	Methamphet amineM(SD) or %N=48	Ketamine M(SD) or %N=46	Alprazolam M(SD) or %N=42		
Age	48.7 (16.2)	46.6 (14.6)	49.0 (16.6)	49.3 (15.7)	49.9 (18.0)	0.36	0.006
Sex:						5.61	0.18
Male	65.2%	66.70%	77.10%	54.30%	61.90%		
Female	34.8%	33.30%	22.90%	45.70%	38.10%		
Region Residing:						9.57	0.231
South	26.0%	35.6%	16.7%	26.1%	26.2%		
West	25.4%	31.1%	20.8%	23.9%	26.2%		
Midwest	26.5%	17.8%	37.5%	26.1%	23.8%		
Northeast	21.0%	13.3%	22.9%	23.9%	23.8%		
Years practicing as psychiatrist	16.2 (15.3)	14.2 (13.1)	16.4 (15.6)	15.9 (15.0)	18.6 (17.4)	0.6	0.01
Number of peer-reviewed scientific publications	6.89 (19.0)	6.78 (20.6)	4.10 (14.6)	8 (18.3)	8.98 (22.5)	0.56	0.009
Number of academic research presentations	7.15 (19.2)	6.49 (18.6)	3.27 (11.8)	9.54 (21.6)	9.69 (23.2)	1.16	0.019
In Residency or Fellowship Training:	23.2%	22.2%	27.1%	19.6%	23.8%	0.78	0.066
Current Resident	20.4%	22.2%	22.9%	15.2%	21.4%		
Current Fellow	2.8%	0.0%	4.2%	4.3%	2.4%		
Licensed Psychiatrist (American Board of Psychiatry and Neurology)	79.0%	75.6%	77.1%	82.6%	81.0%	0.886	0.07
Degrees Additional to Medical Degree							
None	72.4%	71.1%	72.9%	63.0%	83.3%	14.1	0.285
PhD	5.5%	6.7%	8.3%	6.5%	0.0%		
Master's Degree	18.2%	17.8%	10.4%	30.4%	14.3%		
Other	3.9%	4.4%	8.3%	0.0%	2.4%		
Completed Psychiatry Fellowship (total)	40.9%	33.3%	50.0%	34.8%	45.2%	3.75	0.144
Addiction	6.6%	0.0%	8.3%	10.9%	7.1%	5.52	0.162
Child and Adolescent	13.8%	13.3%	20.8%	6.5%	14.3%	4.06	0.15
Forensic	3.3%	0.0%	4.2%	4.3%	4.8%	2.36	0.12
Geriatric	3.9%	2.2%	4.2%	6.5%	2.4%	1.41	0.09
Consult-Liaison	3.9%	4.4%	8.3%	0.0%	2.4%	4.18	0.161
Public	1.7%	2.2%	0.0%	2.2%	2.4%	1.62	0.078
Neuropsychiatry	1.1%	2.2%	2.1%	0.0%	0.0%	2.03	0.103
Other	11.0%	8.9%	8.3%	13.0%	14.3%	1.26	0.082
Most Common Diagnoses:							
Schizophrenia Spectrum and Other Psychotic Disorders	47.0%	51.1%	45.8%	45.7%	45.2%	0.417	0.048
Bipolar and Related Disorders	61.3%	62.2%	62.5%	60.9%	59.5%	0.105	0.024
Depressive Disorders	87.8%	91.1%	89.6%	80.4%	90.5%	3.223	0.133
Anxiety Disorders	78.5%	80.0%	79.2%	76.1%	78.6%	0.231	0.036
Substance Use Disorders	55.2%	46.7%	56.3%	56.5%	61.9%	2.14	0.109
Trauma and Stressor Related Disorders	54.1%	60.0%	54.2%	45.7%	57.1%	2.11	0.108
Feeding and Eating Disorders	3.3%	4.4%	2.1%	4.3%	2.4%	0.921	0.061
Obsessive Compulsive and Related Disorders	20.4%	20.0%	16.7%	21.7%	23.8%	0.767	0.065
Other	15.5%	13.3%	25.0%	15.2%	7.1%	5.72	0.178
Utilizes Psychotherapy in Practice	76.2%	75.6%	81.3%	71.7%	76.2%	1.19	0.081
1-25%	39.2%	40.0%	41.7%	32.6%	42.9%		
26-50%	21.5%	15.6%	22.9%	26.1%	21.4%		
51-75%	8.8%	8.9%	8.3%	10.9%	7.1%		
76-100%	6.6%	11.1%	8.3%	2.2%	4.8%		
Primary Theoretical Orientation:							
Psychodynamic/Psychoanalytic	44.8%	46.7%	58.3%	26.1%	47.6%	10.27	0.238
Motivational Enhancement/Interviewing	38.7%	48.9%	31.3%	34.8%	40.5%	3.45	0.138
Integrative/Holistic	13.8%	22.2%	14.6%	13.0%	4.8%	5.61	0.176
Acceptance and Commitment Therapy	8.3%	15.6%	8.3%	8.7%	0.0%	7.51	0.196
Cognitive-Behavioral Therapy	51.9%	46.7%	54.2%	52.2%	54.8%	0.732	0.064
Other Cognitive	3.9%	2.2%	4.2%	2.2%	7.1%	1.79	0.103
Other Behavioral	6.6%	6.7%	6.3%	2.2%	11.9%	3.23	0.137
Humanistic/Person-Centered Therapy	9.9%	11.1%	6.3%	8.7%	14.3%	1.79	0.099
Family Systems Therapy	6.1%	8.9%	2.1%	8.7%	4.8%	2.69	0.121
Dialectical Behavior Therapy	6.6%	6.7%	4.2%	6.5%	9.5%	1.15	0.076
Other	9.9%	4.4%	10.4%	15.2%	9.5%	2.94	0.128
Formally Trained in Primary Theoretical Orientation	21.0%	20.0%	16.7%	21.7%	26.2%	1.27	0.084
Research Conducted in Current Practice	29.3%	24.4%	27.1%	37.0%	28.6%	1.94	0.104
Percentage of Practice Dedicated to Research:						14.4	0.323
1-25%	18.2%	13.3%	16.7%	23.9%	19.0%		
26-50%	2.8%	8.9%	0.0%	2.2%	0.0%		
51-75%	6.1%	2.2%	4.2%	8.7%	9.5%		

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Total Sample (N=181)M(SD) or %	Vignette Group				F or X2	Effect Size
		Psilocybin M(SD) or %N=45	Methamphet amineM(SD) or %N=48	Ketamine M(SD) or %N=46	Alprazolam M(SD) or %N=42		
76-100%	2.2%	0.0%	6.3%	2.2%	0.0%		
Current Practice Setting:							
Outpatient Mental Health Agency	24.9%	31.1%	27.1%	15.2%	26.2%	3.4	0.137
Private Practice	25.4%	26.7%	29.2%	19.6%	26.2%	1.24	0.083
University Clinic (Outpatient)	31.5%	35.6%	25.0%	34.8%	31.0%	1.52	0.092
University Medical Center	23.8%	24.4%	25.0%	19.6%	26.2%	0.636	0.059
Research	10.5%	8.9%	14.6%	10.9%	7.1%	1.43	0.091
Community Hospital	14.4%	13.3%	12.5%	19.6%	11.9%	1.39	0.088
Outpatient Substance Abuse/Addiction Treatment Agency	8.3%	6.7%	8.3%	4.3%	14.3%	2.83	0.131
Residential Substance Abuse Treatment/Rehabilitation	2.8%	4.4%	0.0%	2.2%	4.8%	2.62	0.118
Other	13.8%	13.3%	12.5%	15.2%	14.3%	0.162	0.03

Note. There were no statistical differences in demographic characteristics between groups.

Table 2
Comparison of responses to vignette questions as a function of which drug vignette was presented (ie. psilocybin (Schedule I); Methamphetamine (Schedule II); Ketamine (Schedule III); Alprazolam (Schedule IV)).

Question	Vignette Group				F	Effect Size	Post-hoc [a]	Drug Schedule Comparison [b]
	Psilocybin M(SD) N=45	Methamphet amineM(SD) N=48	Ketamine M(SD) N=46	Alprazolam M(SD) N=42				
How likely are you to explore the patient's subjective experience for psychological insights into their depression?	1.89 (1.40)	1.65 (1.42)	1.93 (1.25)	1.81 (1.25)	0.42	0.007	NS	NS
How likely are you to warn against engaging in this behavior again?	0.22 (1.70)	1.13 (1.45)	0.24 (1.91)	1.36 (1.34)	5.92**	0.091^^	M=A>P; P=K	II=IV>I; I=III
How likely do you think it is that this experience was beneficial to the short-term treatment of the patient's illness?	1.44 (1.10)	0.85 (1.19)	1.52 (1.15)	1.12 (1.47)	2.94*	0.047^	NS	NS
How likely do you think it is that this experience will improve the long-term course of the patient's depression?	0.07 (1.47)	-0.48 (1.46)	0.28 (1.31)	-0.45 (1.69)	3.00*	0.048^	NS	NS
How likely are you to be concerned about the patient's safety?	0.73 (1.63)	1.15 (1.29)	0.76 (1.64)	1.05 (1.40)	0.88	0.015^	NS	NS
How likely are you to be concerned about the patient developing a new psychiatric problem (ie. Addiction, thought disorder, mood disorder)?	-0.22 (1.64)	1.06 (1.14)	-0.02 (1.63)	0.79 (1.37)	8.33***	0.124^^	M=A>P=K	II=IV>I=III
How likely are you to be concerned about this drug increasing suicide risk?	-1.04 (1.33)	-0.50 (1.56)	-1.00 (1.54)	0.02 (1.52)	4.92**	0.077^^	A>P=K	IV>I=III
How likely would you be to support use of this drug as part of your own treatment plan for the patient?	-0.87 (1.71)	-1.12 (1.47)	0.61 (1.73)	-1.14 (1.39)	12.7***	0.177^^^	K>P, K>M, K>A	III>I; III>II; III>IV

Range of scores are -3 (definitely not) to +3 (definitely)
*p<.05, **p<.01, ***p<.001
^ small, ^^ medium, ^^^ large
[a] P=Psilocybin; K=Ketamine; M=Methamphetamine; A=Alprazolam
[b] Each drug (i.e. P, M, K, A) represents a different Schedule as defined by the Controlled Substances Act (ie. Schedules I, II, III, IV). Alcohol (Alc) is not scheduled (i.e. Legal).

and alprazolam (*M*=0.79, *SD*=1.37) as compared to psilocybin (*M*=-0.22, *SD*=1.64) and ketamine (*M*=-0.02, *SD*=1.63). Post-hoc analysis also revealed that participants were most concerned about increased suicide risk following the non-prescribed use of alprazolam (*M*=0.02, *SD*=1.52) as compared to that of psilocybin (*M*=-1.04, *SD*=1.33) and ketamine (*M*=-1.00, *SD*=1.54). The most pronounced and statistically significant differences emerged in the ratings of the likelihood of use of the drug as part of their own treatment plan. In this measure, ketamine (*M*=0.61, *SD*=1.73) was rated as significantly more likely than any other drug to be integrated into the participant's treatment plan. Differences between psilocybin (*M*=-0.87, *SD*=1.71), methamphetamine (*M*=-1.12, *SD*=1.47), and alprazolam (*M*=-1.14, *SD*=1.39) did not reach the level of significance. Across each of the above items, the non-prescribed use of methamphetamine (Schedule II) and alprazolam (Schedule IV) were rated as more concerning and less acceptable than the non-prescribed use of psilocybin (Schedule I) and ketamine (Schedule III), in conflict with current drug scheduling (see Column in Table 2, "Drug Schedule Comparison").

Table 3
Comparison of ratings of safety, therapeutic and abuse potentials of four scheduled drugs (Schedules I-IV) and alcohol (N=181).

Variable	Psilocybin M(SD)	Methamphetamine M(SD)	Ketamine M(SD)	Alprazolam M(SD)	Alcohol M(SD)	F	Effect Size	Post-hoc [d]	Drug Schedule Comparison [e]	Implied Comparison as Defined by CSA [f]
[a] Safety	0.44 (1.61)	-0.67 (1.64)	0.73 (1.31)	-0.49 (1.49)	-0.63 (1.53)	45.24***	0.20^^^	M=A=Alc< P=K	II=IV=L<I=III	I<II<III<IV
[b] Therap-eutic Potential	2.35 (.998)	1.66 (1.01)	2.65 (0.79)	2.04 (0.86)	0.64 (0.70)	184.2***	0.51^^^	Alc<M<A<P<K	L<II<IV<I<III	I<II<III<IV
[c] Abuse Potential	1.76 (0.99)	3.34 (0.70)	2.32 (0.78)	3.37 (0.63)	3.33 (.64)	227.0***	0.56^^^	P<K<M=A=Alc	I<III<II=IV=L	IV<III<II<I

*p<.05, **p<.01, ***p<.001
^ small, ^^ medium, ^^^ large
[a] Range of scores are -3 (extremely unsafe) to +3 (extremely safe)
[b] Range of scores are 0 (no therapeutic potential) to 4 (very strong therapeutic potential)
[c] Range of scores are 0 (no abuse potential) to 4 (very strong abuse potential)
[d] P=Psilocybin; M=Methamphetamine; K=Ketamine; A=Alprazolam; Alc=Alcohol
[e] Each drug (i.e. P, M, K, A) represents a different Schedule as defined by the Controlled Substances Act (i.e. Schedules I, II, III, IV). Alcohol (Alc) is not scheduled (i.e. Legal). L=Legal.
[f] The CSA utilizes three criteria (safety, therapeutic potential, and abuse potential) to make scheduling decisions. Schedule I drugs are purported to have the highest potential for abuse, no accepted medical use, and are unsafe, even under medical supervision. The additional scheduled drugs (II-V) are purported have progressively lower abuse potential, higher therapeutic value, and higher degrees of safety when prescribed under medical supervision.

Ratings of drug harms and benefits in terms of Controlled Substances Act Criteria

Table 3 presents participant ratings of the safety, therapeutic, and abuse potential of the four drugs from the vignettes, as well as alcohol (as a comparison due to its unscheduled legal status). There was a significant main effect for drug type in the ratings of safety of the different drugs, $F(3.53, 312.4) = 45.24$, $p < 0.001$, $\eta_p^2 = 0.20$. Post-hoc tests of mean pairwise comparisons revealed that ketamine (M=0.73, SD=1.31) and psilocybin (M=0.044, SD=1.61) were rated to be comparable in safety, while alprazolam (M=-0.49, SD=1.64), alcohol (M=-0.63, SD=1.53), and methamphetamine (M=-0.67, SD=1.64) were rated to be comparably less safe. Additionally, there was a significant main effect for drug type in the ratings of perceived therapeutic value, $F(3.48, 440.2) = 184.2$, $p < 0.001$, $\eta_p^2 = 0.51$. Post- hoc tests of mean pairwise comparisons revealed that participants rated ketamine (M=2.65, SD=0.79) as having the highest therapeutic potential, followed by psilocybin (M=2.35, SD=0.998), alprazolam (M=2.04, SD=0.86), and methamphetamine (M=1.66, SD=1.01), which were all rated significantly different from each other. Alcohol (M=0.64, SD=0.70) was rated as having the least therapeutic potential of all the drugs. Finally, there was a significant main effect for drug type in the ratings of abuse potential of the five drugs, $F(3.19, 399.2) = 227.0$, $p < 0.001$, $\eta_p^2 = 0.56$. Psilocybin (M=1.76, SD=0.99) was rated as having the lowest abuse potential followed by ketamine (M=2.32, SD=0.78), while methamphetamine (M=3.34, SD=0.70), alprazolam (M=3.37, SD=0.63) and alcohol (M=3.33, SD=0.64) were roughly equivalent and were rated as having a higher abuse potential than both psilocybin and ketamine. Across all three parameters (safety, therapeutic and abuse potential), participant ratings were inconsistent with those indicated by the current drug schedule (see Columns in Table 3, "Drug Schedule Comparison" and "Implied Comparison as Defined by CSA"). Specifically, mean ratings of safety and abuse/therapeutic potential of alprazolam (Schedule IV) and methamphetamine (Schedule II) were equivalent to that of alcohol, a currently unscheduled legal drug, and all three were rated as more harmful than psilocybin (Schedule I) and ketamine (Schedule III).

Beliefs about the influence of US drug policy on psychiatry training

We asked participants to describe the influence of US Drug Policy on psychiatric training, psychiatric practice, and professional beliefs about certain drugs. As Supplemental Table 2 shows, our analysis of primary themes revealed that nearly one-fourth of the 181 responses reflected that US drug policy limits learning opportunities through increasing stigmatization. Another one-fourth of responses mentioned that policy influences psychiatry training through its impact on the prescription of and teaching related to controlled drugs (e.g. Benzodiazepines), and about one-fifth of responses expressed the idea that drug policy affects biases and attitudes amongst trainees towards drugs and drug users.

Beliefs about the influence of US drug policy on psychiatry practice

As Supplemental Table 3 shows, analysis of the primary themes revealed that nearly a third of all responses (the highest percentage) expressed that US drug policy increases the difficulty of prescribing controlled substances in psychiatric care. Similarly, approximately one-fourth of all responses reflected that US drug policy contributes to the demonization and/or punishment of substance use/substance use disorders, and about one-fifth believed that US drug policy increases the difficulty of treating such disorders.

Influence of US drug policy on professional beliefs about certain drugs

As Supplemental Table 4a shows, our analysis of primary themes revealed that around one-fifth of responses reflected that US drug policy had little or no influence on professional beliefs about certain drugs, with various justifications. However, 14% of responses described increased caution or skepticism around controlled substances, with benzodiazepines being the most common among responses that mentioned specific substances. Because almost three-quarters of responses did not directly answer the question about how US drug policy influences professional beliefs about certain drugs, responses were also coded into subthemes within the non-response category (Supplemental Table 4b). Among these, 28% reflected some form of criticism of US drug policy. For example, nearly a tenth of total responses stated that their professional beliefs are based on scientific evidence rather than US drug policy.

Discussion

This study aimed to assess psychiatrists' attitudes and beliefs about the use of 1 of 4 non-prescribed controlled substances in the treatment of a depressed patient and to examine the safety, abuse potential, and

therapeutic potentials of four controlled substances under the CSA and alcohol. To address aim 1, we utilized a randomized clinical vignette, and to address aim 2 we asked for a direct assessment using the three criteria outlined in the CSA (i.e., safety, therapeutic value, and abuse potential). Overall, our results from these analyses indicated that psychiatrists' perceptions of the acceptability, safety, abuse and therapeutic potentials of these drugs tended to conflict with those defined by their current schedule. Specifically, in our clinical vignettes, the non-prescribed use of methamphetamine and alprazolam (Schedule II and IV, respectively) were rated as more concerning and less acceptable than the non-prescribed use of psilocybin and ketamine (Schedule I and Schedule III, respectively). Similarly, in the direct rating questions, psychiatrists tended to rate psilocybin and ketamine (Schedule I and Schedule III drugs respectively) as safer, having less abuse potential and more therapeutic potential than alprazolam, methamphetamine, and alcohol (Schedule III, Schedule II, and unscheduled drugs respectively).

To our knowledge, this is the first survey study to date that directly assesses psychiatrists' perceptions of the relative harms and potential benefits of specific drugs in the terms outlined by the CSA. However, our findings are congruent with several recent analyses which attempt to categorize drug harms based on a more grounded scientific understanding of substance misuse and use disorders. These efforts began in 2007 with the development of a 9-criterion matrix of drug harms by Nutt and colleagues (Nutt et al., 2007) and have culminated in the development of a 16-criterion scale which takes into account individual and societal harms and weights each category in terms of its relative significance (Nutt et al., 2010). Utilizing this approach, expert panels in the United Kingdom, Australia, and European Union have since converged on rankings of drug harms which closely correlate with our findings (Bonomo et al., 2019; Nutt et al., 2010; van Amsterdam et al., 2015). Although these studies did not ask specifically about psilocybin, they did ask about 'magic mushrooms', which contain psilocybin, and lysergic acid diethylamide (LSD), a synthetic psychedelic compound with similar pharmacologic properties. Thus, with regard to the drugs in our survey, these three analyses also rated alcohol, methamphetamine, and benzodiazepines as more harmful than ketamine, and psilocybin containing 'magic mushrooms'.

Interestingly, our results also overlap substantially with several recent surveys of drug users. Our study extends prior analyses by asking about both perceived harms and therapeutic potential of specific drugs. Several patterns emerge in these surveys, including the consistent ranking of alcohol as one of the most harmful drugs, and of psilocybin as the least harmful and most beneficial (Carhart-Harris & Nutt, 2010, 2013; Morgan et al., 2013). Interestingly and in contrast to our study, drug users generally ranked psilocybin as more beneficial than ketamine (Carhart-Harris & Nutt, 2010, 2013). Our sample's rating of ketamine as having more therapeutic potential than psilocybin may reflect the currently more extensive body of research pointing to ketamine's effectiveness in treating depression, and the recent FDA approval of esketamine for treatment-resistant depression (Krystal et al., 2019; Murrough et al., 2013). However, considering the growing body of research surrounding psilocybin and its potential for longer acting therapeutic effects (Gukasyan et al., 2022), it is possible that psilocybin will surpass ketamine in terms of perceived therapeutic potential in the coming years.

It is worth noting that, although all drugs in the clinical vignettes have some evidence for efficacy in the treatment of depression, many of the studies investigating benzodiazepines and psychostimulants for depression were published in the 1990s (see Srisurapanont & Boonyanaruthee, 1997; Stotz et al., 1999), while ketamine and psilocybin are under active investigation for the treatment of depression. It is likely that psychiatrists are more familiar with this recent literature and, therefore, more likely to view ketamine and psilocybin as therapeutic in this context. Even with this caveat, our results, and other recent surveys, point to a growing realization among mental health clinicians of the potential of psilocybin in treating psychiatric disorders. For example, in two recent surveys, one of psychiatrists and one of psychologists, a majority of each sample (81-85%) felt that psilocybin deserved further research, and nearly half (43-47%) felt that psilocybin showed promise in treating psychiatric conditions (Barnett et al., 2018; Davis et al., 2021a). In a more recent survey of addiction specialists (about two-thirds of whom were psychiatrists), 64% strongly agreed or agreed that psychedelics show promise in the treatment of substance use disorders and 82% agreed they show promise in treating psychiatric disorders overall (Anderson, 2021). In our sample, psilocybin was rated as having high therapeutic potential, second only to ketamine.

Additionally, our sample found psilocybin to be safer and more acceptable than indicated by previous surveys. For example, in Barnett et al.'s (2018) survey of psychiatrists, 64.9% of the sample felt that the use of classic hallucinogens, which include psilocybin, increased the risk for a subsequent psychiatric disorder and 47.8% felt their use increased the risk for long-term cognitive impairment (Barnett et al., 2018). Our participants reported more concern about the development of a new psychiatric disorder and an increased risk of suicide following the non-prescribed use of methamphetamine and alprazolam as compared to psilocybin. Given that Barnett's survey asked only about psilocybin and ours was a comparative analysis, it is difficult to draw firm conclusions from these differences. However, our findings do provide further context in the realm of psychiatric clinical decision making and risk assessment.

In Davis et al.'s (2021a) survey of psychologists, about three-quarters of participants indicated that they would warn their client about the risks associated with the non-prescribed use of psilocybin while, in our survey, psychiatrists were more likely to warn against the non-prescribed use of methamphetamine and alprazolam. Additionally, in the psychologist survey, participants rated psilocybin as comparable in safety to alcohol, while in our survey, participants rated psilocybin as safer than alcohol, methamphetamine, and alprazolam and as having the lowest abuse potential of all drugs in our questionnaire. When accounting for these differences, it is important to note that about one-quarter of our sample reported working in a medical center compared to only 15% of the psychologist sample. Alcohol and benzodiazepines account for more than five and ten times as many emergency department visits in a given year, respectively (Brown, Crane, & Naeger, 2018), as all hallucinogens combined, suggesting that psychiatrists working in the hospital setting are more likely to have encountered their harms. Similarly, emergency department visits due to stimulants are about five times the number of those due to hallucinogens, with visits due to methamphetamine doubling from 2003-2011 (Brown, Crane, & Naeger, 2018; Richards et al., 2017).

Additionally, there are several harms more highly associated with psychostimulants and benzodiazepines which are particularly likely to result in inpatient psychiatric hospitalization and therefore particularly salient to psychiatrists, namely: psychosis, overdose, and suicide attempts. Compared to other drugs, methamphetamine-related visits to the emergency room are more likely to present with psychosis and to result in involuntary psychiatric holds (Brown, Crane, & Naeger, 2018; Johnson et al., 2018). Even when appropriately prescribed, the rate of stimulant-induced psychosis and mania is estimated to be 1.48 per 100 person-years, a non-trivial risk which psychiatrists are likely to encounter in practice (Mosholder et al., 2009). Furthermore, from 2015 to 2019, overdose deaths related to psychostimulants other than cocaine (ie. methamphetamine) increased by 180% (Han et al., 2021) and those associated with benzodiazepines increased by 400% from 1996 to 2013 (Votaw et al., 2019). Overall, benzodiazepines are implicated in one third of overdose and suicide attempts (Ait-Daoud et al., 2018), a fact which psychiatrists seemed to acknowledge in their high level of concern with alprazolam and suicide in the clinical vignette. Of note, there is a small, but growing, body of case reports highlighting treatment-emergent suicidal behaviors associated with ketamine and esketamine (Cusin et al., 2020; Gastaldon et al., 2021; Weleff et al., 2022). These findings do not appear to have entered the realm of psychiatric clinical

decision making as of yet but may shift psychiatrists' opinions if they persist.

Given the recent publication of several studies demonstrating the therapeutic efficacy of psilocybin, including one double-blind, and one open label, randomized controlled trial of psilocybin-assisted therapy in the treatment of depression and a phase 3 trial planned for 2022 for treatment-resistant depression (Carhart-Harris et al., 2021; Compass Pathways, 2021; Davis et al., 2021b), it is likely that a New Drug Application (NDA) will be submitted for psilocybin within the next 2-5 years. If approved, psilocybin will need to be rescheduled as required by the CSA. A recent review of psilocybin, based on the CSA's 8 factors of abuse potential, suggested that it would be appropriately placed in Schedule IV (Johnson et al., 2018). Given that psychiatrists in our survey ranked psilocybin as having a lower abuse potential and an equivalent safety profile to ketamine, a Schedule III drug, it is likely the they would agree with the placement of psilocybin in Schedule IV.

However, as discussed above, psychiatrists seem particularly concerned with serious adverse events resulting in hospitalization. As the estimated lethal dose of psilocybin is approximately 1000 times the effective dose, overdoses requiring hospitalization are likely to remain minimal (Johnson et al., 2018). Additionally, there have been no cases of prolonged psychosis reported in modern trials with psilocybin (Rucker et al., 2018), and lifetime psychedelic use has been associated with reduced odds of past year suicidal planning, thinking, and suicide attempt (Hendricks et al., 2015). However, it is important to note that modern trials are conducted in a controlled, therapeutic environment and have thus far excluded participants at high risk for psychosis and suicidal behaviors (Johnson et al., 2018). It is therefore likely that, as the treatment is expanded to a broader population, more adverse events will emerge. For example, there have been some concerns for emergent suicidal behaviors in the recent Phase 2 clinical trial of psilocybin (Compass Pathways, 2021). Given these concerns, it is likely that psychiatrists would favor rescheduling psilocybin in the context of a Risk Evaluation and Mitigation Strategies (REMS) plan to closely monitor and track adverse outcomes and assure compliance with the proper administration of the drug (ie. in a setting with psychological support and trained staff).

Overall, perhaps the most striking pattern to emerge in our findings and in previous surveys (Barnett et al., 2018; Bonomo et al., 2019; Davis et al., 2021a; Nutt et al., 2010; van Amsterdam et al., 2015), is an incongruence between the opinions of mental health professionals and those indicated by the current drug schedule. The causes of this divide would require additional research to fully elucidate, however, it does suggest that, rather than relying on the drug schedule to make decisions, psychiatrists engage in a more nuanced assessment of drugs based on the relevant research, clinical experience, and other factors. This is consistent with our qualitative analysis, in which nearly one-third of respondents expressed skepticism towards the drug policy and one-fifth reflected that the drug policy had little to no effect on their professional beliefs. An interesting area of future research would be to determine the degree to which psychiatrists' opinions and behaviors are directly affected by a drug's schedule, perhaps through examining changes in prescription rates or attitudes following a rescheduling event. One interesting possibility, supported by both prescribing patterns and our survey, is that psychiatrists make initial decisions based on a drug's schedule and then adjust their behaviors over time based on clinical experience and emerging research. If this is the case, it is important that a drug's initial scheduling reflect its actual risks and benefits and that rescheduling is accompanied by close monitoring for adverse events.

As a cross-sectional internet survey, this study suffers from a number of limitations. Given that this was a convenience sample, there is the possibility of selection bias. Specifically, it is possible that, given the areas of interest of the authors and the topic of the study, the respondents were more likely to view psychedelics favorably than a general population of psychiatrists. Additionally, given that we used a variety of recruitment approaches (ie. Snowball sampling, listserves), we were unable to calculate response rates. In terms of our measures of drug harms, more sophisticated approaches (as utilized by Nutt et al., 2007 and 2010) have been developed, however, we specifically chose to ask participants about the criteria for drug scheduling used by the CSA, as this was congruent with our primary aim.

Our findings add to a growing consensus among experts in addiction and mental health that the current drug policy is not scientifically coherent with regard to specific drugs. In our sample of American psychiatrists, this discordance was especially pronounced with regard to the Schedule I drug, psilocybin, which was rated as having a high therapeutic potential and low abuse potential, as well as with respect to alcohol, which was rated as the most harmful drug across multiple measures, despite its unscheduled status. Furthermore, in a clinical scenario, our sample rated the non-prescribed use of methamphetamine and alprazolam, Schedule II and IV drugs respectively, as more concerning and less acceptable than that of psilocybin and ketamine. Consistent with emerging research, participants in our sample rated ketamine as the most therapeutic of all drugs and the most likely to be integrated it into their own treatment plan. Of note, participants rated psilocybin as the second most therapeutic drug but were not likely to utilize it as part of their hypothetical treatment plans, possibly due to its current legal status. Overall, these findings suggest that psychiatrists evaluate drugs based on a variety of factors beyond the drug schedule and might support efforts to bring the schedule more in line with the clinical and scientific evidence.

Credit author statement

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Funding

Funding for the study was provided by the Drug Enforcement and Policy Center, Moritz College of Law, The Ohio State University. AKD is also supported by funding from Tim Ferriss, Matt Mullenweg, Craig Nerenberg, Blake Mycoskie, the Steven and Alexandra Cohen Foundation, and by the Center for Psychedelic Drug Research and Education in the College of Social Work at Ohio State University, funded by anonymous private donors. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Ethics approval

The authors declare that they have obtained ethics approval from an appropriately constituted ethics committee/institutional review board where the research entailed animal or human participation.

Declarations of Interest

AKD is a board member of Source Research Foundation. This organization was not involved in the design/execution of this study or the interpretation or communication of findings.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2022.103816.

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