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# Stakeholders' Views on Barriers to Research on Controlled Substances

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## ABSTRACT

Many diseases and disease symptoms still lack effective treatment. At the same time, certain controversial Schedule I drugs, such as heroin and cannabis, have been reputed to have considerable therapeutic potential for addressing significant medical problems. Yet, there is a paucity of U.S. clinical studies on the therapeutic uses of controlled drugs. For example, people living with HIV/AIDS experience a variety of disease- and medication-related symptoms. Their chronic pain is intense, frequent, and difficult to treat. Nevertheless, clinical trials of compassionate management for their chronic symptoms, which should be a research priority, are stymied.

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We employed qualitative methods to develop an understanding of the barriers to research on potential therapeutic uses of Schedule I drugs so that they might be addressed. We elicited the perspectives of key stakeholder groups that would be involved in such studies: people living with HIV/AIDS, clinicians, and members of institutional review boards. As we identified obstacles to research, we found that all of the stakeholder groups arrived at the same conclusion, that clinical research on the therapeutic potential of these drugs is ethically required.

## BACKGROUND

Certain controversial controlled drugs can have considerable therapeutic potential. Heroin, cannabis, and other illegal drugs are potent analgesics, some prescribed routinely in Europe.<sup>1</sup> Experiments with animals, as well as clinical data and trials, suggest that cocaine, ketamine,<sup>2</sup> and methylenedioxy-methamphetamine (MDMA)<sup>3</sup> may have a role in the treatment of a variety of physical and mental illnesses and ailments. Randomized controlled trials and systematic reviews have documented therapeutic benefits of heroin, cannabis, ketamine, and cocaine for selected indications, even for children, women in labor, and the elderly.<sup>4</sup> Some have hypothesized that cannabis or ibogaine might even have therapeutic benefits as treatment of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS).<sup>5</sup> Yet the evidence is sparse; there is a paucity of studies conducted in

the United States on the therapeutic uses of controlled drugs. Clearly, we need more high quality studies to assess the efficacy of these drugs and determine the risks that would be associated with their medicinal use.<sup>6</sup> The limited literature examining barriers to such research suggests that strict regulations, fear of legal consequences, stigma associated with abuse and the populations using illicit drugs, and lack of funding could act as barriers to research on controlled drugs.<sup>7</sup> Indeed, in the U.S., drugs such as heroin and cannabis are classified as Schedule I drugs, which defines them as having “no currently accepted medical use in treatment.”<sup>8</sup> Research on the therapeutic potential of Schedule I drugs has therefore been difficult, even though pain and other symptoms remain undertreated. The regulatory roadblocks, coupled with the need for effective treatment, create problematic situations. For example, off-label use has recently increased. Although ketamine may be a promising drug for the treatment of depression, we still lack rigorous evidence of its efficacy and the risks associated with sustained use.<sup>9</sup> Although the conduct of clinical studies with controversial controlled substances may raise unique ethical issues,<sup>10</sup> these impediments are barriers to developing effective treatments to alleviate chronic suffering and exploring harm reduction, and thus have significant implications for clinical ethics.<sup>11</sup>

People living with HIV/AIDS illustrate the effects of today’s restrictive policies regarding research with Schedule I drugs. They experience a variety of symptoms related to their disease and the long-term use of prescribed medications. Their chronic pain is intense, frequent, and difficult to treat.<sup>12</sup> The chronic pain associated with HIV/AIDS affects one-third of the HIV-positive population, a significant disease burden.<sup>13</sup> Chronic pain persists despite attempts at management with opioids, nonsteroidal anti-inflammatory drugs (NSAID), anti-inflammatory agents, tricyclic antidepressants, and pain modifying therapies.<sup>14</sup> In addition to pain, people living with HIV/AIDS (PLWHA) endure multiple chronic, systemic, neurological, oral, respiratory, musculoskeletal, ophthalmological, dermatological, genitourinary, and psychological symptoms.<sup>15</sup> The symptoms of many of these patients do not respond to currently available treatments. When legal drugs are ineffective, PLWHA often self-treat with illicit drugs that can produce medical complications and involve a risk of transmitting the disease.<sup>16</sup> It therefore seems reasonable to conclude that research on compassionate management and effective treatment for the chronic symptoms of this population should be a research priority, even if the potentially effective

agents include substances that we now classified as Schedule I.

To explore the actual social, ethical, legal, or regulatory barriers that inhibit such research on the effectiveness of Schedule I drugs, we elicited the perspectives of the key groups of stakeholders who would be involved if studies were to be undertaken. Because of the relevance of such studies to PLWHA, we selected them to represent the viewpoints of potential research participants. In addition, we sought the input of clinicians working with PLWHA, and members of institutional review boards (IRB).

Our pilot study had three immediate goals. One was to develop the tools for identifying actual and perceived barriers to clinical research with controversial Schedule I drugs and to pilot our methodology. Another was to enable a rational discussion of permissible research with such drugs and elicit stakeholders’ views on the core issues that would be raised by such studies. Our broader aim was to use the insights from our study to develop an empirical basis for reform of drug research policy and practical guidance for the future design of research. Most specifically, we wanted to elicit stakeholders’ opinions and experiences related to two key issues:

- Do the risks of physical harm associated with controlled substances constitute an insurmountable barrier to research on their medicinal value?
- Are social stigmas associated with controlled drugs, drug users, and/or PLWHA critical barriers to research?

## METHODS

### Study Design and Recruitment

To distinguish contrasting stakeholders’ views on standardly prescribed and illicit drugs, we chose heroin, marijuana, and gabapentin as examples of possible study drugs for treatment of symptoms associated with HIV/AIDS. Gabapentin, heroin, and cannabis differ in their legal status, addiction potential, and associated stigma. Gabapentin, our “inert comparator,” is approved by the U.S. Food and Drug Administration (FDA) as a medication to control seizures, and is used off-label to treat nerve pain. No stigma is associated with its name, and its addiction potential is generally dismissed.<sup>17</sup> Cannabis may be neither highly addictive nor harmful.<sup>18</sup> Support of research and legalization of medicinal and recreational cannabis use is becoming more popular as public perceptions of marijuana shift. The FDA still, however, classifies marijuana as a Schedule I drug. Heroin is also a Schedule I drug, with a high street value and a high potential for abuse.

Using purposive sampling, we enrolled participants for this study from three groups of stakeholders:

- PLWHA were recruited at inner city clinics serving predominantly under-resourced patients in New York City. They are potential research participants and beneficiaries of new therapeutics.
- Clinicians who treat PLWHA were recruited at an HIV update conference. They can appreciate the need for new therapies. They also have medically informed concerns about research on Schedule I drugs and potential obstacles to their use in the community.
- Members of IRBs were recruited from an annual bioethics meeting. IRB members serve their institutions by determining whether proposed studies comply with federal and institutional guidelines. They have a distinct perspective on concerns in the research process.

As this is a formative study based in qualitative methods, we formed homogeneous focus groups discussion (FGDs) with six to 13 participants in each.<sup>19</sup> FGDs allowed us to elicit the views of members of the predominant groups and to identify novel and unexpected perspectives. In FGDs, participants are able to challenge each other on controversial topics and analyze ideas together. We also conducted four in-depth interviews to triangulate the data and check for differences between responses in the group discussions as compared with private interviews.<sup>20</sup> All of the participants gave their verbal consent to participate and be recorded. We compensated participants with cash: \$100 for clinicians and IRB members, and \$40 for PLWHA (a restriction imposed by the outpatient clinics). The study was approved by the Icahn School of Medicine at Mount Sinai IRB.

### Data Collection and Management

Without existing models in the literature that were compatible with our research goals, we devised our own moderator guides, survey instruments, and clinical vignettes. We piloted them in one group and revised them after the pilot group discussion. To ensure anonymity, we did not request or record identifying data beyond those used for the purposes of analysis. We observed similar participant contributions from the FGDs and individual interviews.

Before the discussions began, participants in each FGD and the individual interviews completed identical anonymous surveys. The surveys collected basic demographic information, information related to personal experience, and opinions about illicit substances and HIV. At the end of each survey, par-

ticipants were asked to list barriers to conducting research testing Schedule I drugs as treatment for HIV symptoms and complications.

Interviewers and focus group facilitators were trained to frame open-ended questions to limit their impact on respondents. Note takers were trained to identify other unspoken or unintentional influences during the FGDs.<sup>21</sup> FGD note takers were also instructed to record descriptions of interactions and personal characteristics that would not be captured by the audio recorder. Because group discussions can tend to discourage dissent, facilitators were trained to challenge opinions in order to evoke further conversation. We also chose to keep the groups homogeneous, to insure that the dialogues could delve into specific experiences, and so that PLWHA were not identified outside of their clinic.

For the group and individual interviews alike, we asked the same foundational questions, albeit with more focus on personal information in the latter. Questions elicited respondents' experiences with HIV, views on the need for research, and opinions on participant willingness to participate in research using Schedule I drugs. Respondents were also asked about how the drug histories of study participants would impact their ability to provide informed consent. Finally, all stakeholders were asked for their opinions on measures to enable the study of therapeutic uses of Schedule I drugs and the necessary social or legal changes that would be needed for those trials to proceed.

All FGDs were audiotaped and professionally transcribed verbatim, including emotional expressions, pauses, emphasis, and laughter.<sup>22</sup> Researchers reviewed the transcripts and recordings to ensure accuracy of the transcribed data.

### Coding and Analysis

Using inductive and deductive coding, six members of our research team independently read through at least one transcript from each stakeholders' group and each individual set of interviews to formulate the codes based on relevant, emergent themes that participants mentioned (we only had FGD data for PLWHA). The six researchers discussed codes to find consensus, grouped themes, and generated axial codes.<sup>23</sup> Once a codebook was finalized, we applied it to the remaining transcripts and embedded comments and memos to highlight key sections, codes, and quotations. We used multiple coders for a representative sample of the data to ensure interrater reliability. We extrapolated a comprehensive codebook from the data and used it as our conceptual framework to analyze data from the FGDs.

Using a grounded theory approach, we developed themes and uncovered important new constructs from the data. We performed qualitative thematic analysis based in a critical realist epistemological position—the understanding that our findings, while real, are affected by situational variables and the observer’s perspective.<sup>24</sup> We compared data from individual interviews and FGDs to triangulate the data and discern whether speaking in a private interview significantly altered responses.

To analyze the free-list exercise at the end of the survey, we combined similar responses and generated a condensed, comprehensive list of reported barriers to research. We measured the frequencies and Smith’s Salience Index (SSI) for each listed barrier.<sup>25</sup>

## RESULTS

### Participants’ Characteristics

We interviewed two clinicians and two IRB members. For the FGDs, we recruited two groups of IRB members (seven to eight participants in each),

two groups of clinicians (six to eight participants in each), and four groups of patients (nine to 13 participants in each), for a total of 15 IRB members, 14 clinicians, and 40 PLWHA. More than 60 percent of the PLWHA respondents did not complete the free-listing exercise. In total, we collected free-listing data from 14 IRB members, 13 clinicians, and 15 PLWHA.

### Survey Data

Tables 1 and 2 present demographic data from the surveys conducted at the FGDs by the 69 participants who completed them. The average ages were similar between groups, but most other characteristics were different. The overwhelming majority (73 percent) of PLWHA were Black, while clinicians and IRB members were predominantly White (56 percent and 93 percent respectively). All (100 percent) clinicians and IRB members had graduate school level educations, while most (66 percent) PLWHA achieved no more than high school level. The clinicians and IRB members had comparable average reported annual incomes of greater than \$100,000, while the average patient reported income

**TABLE 1.** Demographic characteristics of respondents in study about barriers to researching highly controlled substances for HIV, 2014

Characteristic	Patient (n=40)		Clinician (n=14)		IRB member (n=15)		Total (N=69)	
Age (years)	54.9		46.2		49.8		50.3	
Income (average)	\$18,528		\$120,714		\$134,666		\$91,303	
	n	%	n	%	n	%	n	%
<b>Sex</b>								
Male	13	33	1	7	7	47	21	30
Female	16	40	10	71	6	40	32	47
N/a	11	27	3	22	2	13	16	23
<b>Race</b>								
Black	29	73	1	7	1	7	31	45
Black/Latino	1	3	1	7	14	93	2	3
Black/Native American	2	6	1	7	0	0	3	4
White	2	6	8	56	0	0	24	35
Latino	5	13	2	14	0	0	7	10
Latino/Native American	1	3	0	0	0	0	1	1
Asian	0	0	1	7	0	0	1	1
<b>Education</b>								
<High school	5	13	0	0	0	0	5	7
Some high school	12	30	0	0	0	0	12	17
High school	9	23	0	0	0	0	9	13
Some college	13	33	0	0	0	0	13	19
College	1	3	0	0	0	0	1	3
Graduate school	0	0	14	100	15	100	29	42

was less than \$20,000 annually. The self-described political affiliations of the groups also differed. IRB members and PLWHA described themselves as predominantly liberal (70 percent and 45 percent respectively) and clinicians as moderate (42 percent).

Table 2 presents the range of personal experiences and opinions that respondents associated with illicit substances, PLWHA, and vulnerable populations. All questions that asked about familiarity defined it as having personal experience or knowing someone who fit the category. We asked the questions in this way to encourage participants to feel comfortable in answering. PLWHA and clinicians treating PLWHA indicated having familiarity with people who were HIV positive (93 percent and 86 percent respectively), but only one-third of IRB members reported personal experience with PLWHA. The overwhelming majority (71 percent) of participants indicated familiarity with recreational drug use: Smoking recreational drugs was

the most frequent form of familiarity for all stakeholders. Few participants reported personal experience with injection-drug use of any kind (16 percent), but many referenced first- and secondhand experiences during the discussion. Three-quarters of participants (75 percent) responded that they would support the legalization of marijuana.

### Free-List Reports of Barriers to Research

Table 3 provides data from the free-listing exercise. Of the 70 participants—25 of the 40 PLWHA, one of the 14 medical providers, and one of the 15 IRB members—did not complete the free-list exercise. Those participants were excluded from the frequency and salience analysis of the free-list exercises. We noted marked differences in the lists by stakeholder groups. Reporting bias was the most salient barrier identified by the PLWHA group (SSI=0.43). In their words, they were concerned that study participants would display a “lack of honesty”

**TABLE 2.** Experiences and opinions of respondents for study on barriers to researching tightly controlled substances for HIV, 2014

Experience*	Patient (n=40)		Clinician (n=14)		IRB member (n=15)		Total (N=69)	
	n	%	n	%	n	%	n	%
HIV								
Yes	37	93	12	86	5	33	54	78
No	3	7	2	14	10	66	15	22
MSM								
Yes	13	33	13	93	9	60	35	51
No	27	67	1	7	6	40	34	49
Transgender								
Yes	11	27	10	71	5	33	26	37
No	29	73	4	29	10	66	43	63
IVDU								
Yes	10	25	10	71	6	40	26	37
No	30	75	5	29	9	60	43	63
Drug use								
This month	11	27	3	22	4	27	18	26
Past—regularly	12	30	3	22	2	13	17	25
Past—rarely	6	16	5	34	3	20	14	22
Never	3	8	3	22	5	33	11	16
None of your business	7	18	0	0	1	7	8	11
Legalize?								
Yes	32	80	9	64	12	80	53	75
No	4	10	2	14	0	0	6	10
No opinion	2	5	3	22	3	20	8	12
N/a	2	5	0	0	0	0	2	3

\* Experienced by participant or someone close to participant.

and that “most people just want the money.” They predicted that participants would lie about their comorbidities or consumption habits in order to gain access to the Schedule I drug (for personal use or sale). Few clinicians mentioned dishonesty as a salient barrier, and none of the IRB members included it on their lists. Clinicians most frequently listed legal (SSI=0.43), reputational, and political barriers. IRB members also listed legal and reputational barriers, but they ranked ethical concerns most frequently (SSI=0.33), including issues such as informed consent, undue inducement, decisional capacity, and protecting vulnerable populations. Neither the clinicians nor the PLWHA listed any of these research ethical concerns as barriers to research.

### FGDs and In-Depth Interviews

The interactive and dynamic conversations in each interview and discussion group suggested that there was a comfortable rapport between the discussion leader and the participants in each group. Our analysis of the data revealed concordant and discordant perspectives among stakeholders; groups and some unanticipated perspectives. The most prominent themes were the need for research, barriers associated with physical risk and stigma, personal biases, and predicted study complications. We

also examined the pattern of how views evolved during the FGDs.

We found that each stakeholders’ group agreed on the need for research, but expressed distinct concerns associated with undertaking, approving, or participating in an actual study. Employing the Social Ecological Model to analyze the noted barriers, we identified dilemmas and a fundamental problem in the structure of drug policy.

*The need for research.* All stakeholders’ groups ultimately indicated that there is a need for research because of the clinical implications of developing additional treatment for pain. Clinicians and PLWHA agreed that neuropathy lacks adequate treatment. IRB members compared research on controlled drugs with studies on other potentially harmful drugs that provide valuable evidence of their safety and efficacy, suggesting that studies of Schedule I drugs could similarly prove informative.

In one discussion, clinicians described refractory pain and medications with undesirable side-effects as indicators of the need for improved treatment. One clinician remarked, “What I really want is a better toolbox. . . . What I’m looking for, certainly, is something with a longer half-life, less sedation, less side-effects.” Another clinician declared, “I’m not saying I agree or not with marijuana use,

**TABLE 3.** Free list of barriers to researching tightly controlled substances for HIV in the U.S., 2014

Barrier *	Patient (n=15)		Clinician (n=13)		IRB member (n=14)	
	Frequency	SSI**	Frequency	SSI**	Frequency	SSI**
Legal/regulatory	1	0.07	6	0.35	5	0.32
Stigma	1	0.07	7	0.22	4	0.22
Politics	0	0.0	6	0.29	1	0.07
Ethics (informed consent, undue inducement, capacity, vulnerable population)	0	0.0	1	0.6	6	0.33
Reporting bias (dishonesty, drug/money seeking behavior)	7	0.43	3	0.17	0	0.0
Biomedical risk (addiction, drug interaction, disease transmission)	4	0.23	5	0.29	2	0.01
Confidentiality	2	0.1	2	0.15	3	0.15
Funding	1	0.07	2	0.08	0	0.0
IRB approval	0	0.0	0	0.0	3	0.15
Post-trial issues	0	0.0	0	0.0	3	0.07
Investigator/institutional reluctance	0	0.0	1	0.8	3	0.13
Ignorance	2	0.09	0	0.0	2	0.08

\* Reported responses with >3 respondents

\*\* Smith’s Saliency Index

but if it's going to help people that are ill and it's going—to help them with the pain and suffering, right, I think that is something that definitely needs to be studied and measured and managed.”

Clinicians agreed that the current pain management medications are insufficient and that substances like marijuana could manage pain that other medications do not ameliorate. They also mentioned the absence of evidence to support prescribing decisions. In addition, they wanted research into non-narcotic pain management options without burdensome side-effects.

During one FGD, PLWHA expressed the need for more effective neuropathy treatment. One remarked, “I get angry because I say ‘You mean to tell me you got all this medicine, technology . . . and you can't give me anything to alleviate this so that I can function as a regular human being?’” Another PLWHA expressed, “I had neuropathy too. I don't know what my doctors give me, but it wasn't working. I used to have to get up and have to put my feet on the cold floor. And it'd go away for about 10 minutes and then come back.”

Others who had AIDS neuropathy were dissatisfied with their current treatments, but resigned to tolerate it. One explained, “My T-cell [count] was completely zero. And it was like that for a year [*sic*]. [My doctor] right now, is more concerned about building my T-cell count up . . . sometimes I just have to do deal with the side-effects. There's nothing I can do about it.”

Most IRB members had little to no experience with neuropathy or its treatment, and their responses indicated an entirely different perspective on the need for research than that of clinicians and PLWHA. When asked why research on Schedule I drugs should be pursued, they focused on intellectual justifications, such as to simply better understand the drug itself. Nevertheless, they acknowledged that information is required to make and implement informed decisions about prescribing strictly controlled drugs.

### Physical Risk

All stakeholders initially responded that the risk of physical harm would be a barrier to research with human subjects using Schedule I drugs. When queried about our three comparator-drugs, most did not know what gabapentin was. Participants accepted research on its therapeutic uses. The absence of reservations suggested that there was no stigma associated with it. The clinicians and PLWHA who were familiar with gabapentin remarked that it had little street value and did not allow users to get high.

Across the groups, stakeholders perceived marijuana to be associated with less risk than heroin. Participants from all of the groups also mentioned their concern about the risks of addiction, misuse, and diversion (that is, persons who are legally prescribed a drug would transfer it to others for illicit use). As the discussions progressed, however, participants began to question their original presumptions about risks and to see the risk of physical harm as less of a barrier to research than they had originally assumed.

PLWHA almost unanimously agreed that the risks associated with heroin are barriers that would make them reluctant to participate in any trials. Many of the PLWHA described their firsthand experience with addiction. In the FGDs they offered stories from their own lives and the lives of family members and friends as reasons to resist exposure to heroin. Explaining his reluctance to participate in a study with heroin as the study drug, one PLWHA explained, “Especially if it's a substance I know I can get addicted to, because I've done a lot of drugs, and I've been addicted to a lot of drugs. And right now, at this point in my life, I'm too old to get another habit. So . . . no.” Another worried, “It's such an addictive drug. I know too many people that that drug has taken out.” But most PLWHA expressed openness or positive opinions about participating marijuana trials.

Several clinicians and IRB members also expressed rather strong concerns about addictive potential. Two IRB members opined, “The enslaving effect, of course, is a side-effect, which we cannot control,” and, “I think particularly if you're talking about an illegal substance, there's that automatic presumption that addiction is a problem, period.” A clinician expressed a similar fear in these words, “My worry with these particular drugs, heroin, is the addiction and the CNS [central nervous system]-related HIV problems.”

Others, however, viewed the risk of addiction as something to control, rather than a reason to prevent such research. As one IRB member explained, “I honestly wouldn't be terribly concerned that in my trial that they were going to become addicted. . . . I assume that we would be looking for risk protections the same way we would for any drug.” All of the stakeholders' groups also mentioned the potential for harm to nontrial participants. Clinicians and PLWHA focused on the risk of diversion and concern that participants might sell their medications. Some PLWHA confessed that they would participate in a trial so that they could profit by selling the drug. One offered, “She [my doctor] can prescribe

it [heroin] to me 25 times and I'm going to be on the next corner selling it to the next dope fiend. So she ain't going to give me that. I don't want it. That's going to cause me to go to jail, because I'm going to find a way to hustle with it." PLWHA also predicted allowing people to consume heroin legally would have dire effects on their communities. One predicted, "They [are] going to become addicted. Then they're going to be bootlegging and stealing out the stores. And 125th Street is going to be on fire."

### Stigma

IRB members and clinicians frequently mentioned stigma associated with illicit substances and drug users. One IRB member said, "There's this presumption on IRBs . . . of people who are known active illicit substance users, you always have the worst image of them and the assumption that they are all in the trial for the money so they can get their next fix. But I think it speaks to what is an inherent bias among a lot of IRB members as well as clinicians—that addiction is the worst possible thing." Other IRB members elaborated and expressed similar concerns: "If somebody sees your prescription for heroin, or if your boss finds out you're on heroin versus . . . oxycodone, I don't know how an employer would feel about having an employee that they know is receiving marijuana or heroin or something like that on the job," and, "We already know in the states where medical marijuana has been legal, people have been fired—even though they have a legitimate prescription for it."

IRB members and clinicians also expressed the view that the stigma associated with drugs and drug users would create barriers to research by making investigators reluctant to conduct trials involving these substances. IRB members remarked about the institutional risks. One declared, "I think of the stigma around the use of an illicit substance and what it implies both for the participants of the study but, more importantly, the institution. [Institutions are] afraid of the public backlash and how it would affect them as an institution and their fundraising activities and PR and everything else." Another IRB member noted, "There's the politics involved. [The] last thing you need is the *New York Times* saying how the Department of Health is giving people heroin."

IRB members and clinicians were also aware that conducting this type of research could tarnish the reputation of a clinician, an IRB member, or an investigator. One clinician remarked, "I would totally, about five or 10 minutes ago, [have] said that I would definitely help accomplish some cannabis research.

But now that I'm thinking about it, if your name gets tarnished . . . the price is powerful." Another offered, "Maybe it's not such a good idea for me to be pioneering just because you wouldn't—I wouldn't want to set anything back by being considered less reputable. I certainly wouldn't stake my next academic degree on that being my thesis." An IRB member added, "I think that there is always the concern, particularly following some of the trials that have gone bad. IRB members think about the potential risk for them should it go wrong because IRBs are under increasing scrutiny particularly when you have a severe adverse event."

IRB members and clinicians identified specific systems and institutional arrangements that would obstruct research with controlled substances. IRB members mentioned possible intervention by institutional risk managers. Clinicians mentioned their worries about IRB review committees. None of the PLWHA mentioned reputational risks as relevant barriers to research.

### Personal Perspectives

The FGDs initiated a deliberative process that allowed clinicians and IRB members to notice how their own perspectives skewed their opinions. One IRB member even suggested using a fictitious name for the study drug while accurately ascribing its relevant risks in proposals for studying heroin. This strategy was proposed as a way to avoid the name-associated bias.

In each FGD with PLWHA, some participants voiced negative opinions about research with human subjects and researchers. The widely shared attitude toward participation in research was expressed by one PLWHA who declared, "I would do them as long as you're talking to me, I'm on the computer. But when it comes to clinical trials, I'm not too enthused about doing anything—me being a guinea pig for anybody." Several participants shared the view that they were part of a targeted population. As one explained, "A lot of people of color, Black people, don't enter studies like that. Look at Tuskegee. [Nods of agreement.] You look back at places like that and see what they did to people in the study. They're people of minorities; you know, they needed money. . . . Years after, people didn't even know about it. I did some research on it. Most Black people [are] scared of studies." Whether or not the story was accurate, one PLWHA shared this anecdote, which expressed the group's trepidations about research participation: "Listen, we know someone who did this study. . . . She went in. She did the study. She sat there. They gave her all the

crack she wanted. . . . But when she came out— . . . she was so messed up that she immediately went to a long-term rehab. Long-term.”

### Study Complications

Participants in the FGDs raised concerns about possible deception by participants in research that could undermine the validity of a clinical trial. For example, one clinician offered this prediction: “If you give too much [incentive], you’re looking at a bunch of folks who are looking for that. They call and say they have terrible pain and they want \$200.” An overwhelming majority of PLWHAs shared this view. One expressed the concern with particular clarity: “One of the biggest barriers in this entire problem is how honest the client is going to be. Because, most of us, if you tell us you’re going to pay us \$2,000 to do something, we’ll lie, steal, and cheat to get that money.” Clinicians and PLWHA also predicted that research participants would drop out of studies once they received the drugs or money. For example, one clinician remarked, “They might not finish the research because they’ll get high or use the money to get [high].” And one PLWHA said, “Most of the time, the barriers to a study is that most people only do it in the beginning, just to get the initial incentive and the money. And then once they get it, they’re all getting high again and they’re not going to complete the study.”

Because of their disease, PLWHA are vulnerable to a number of harms related to their immune-compromised physical condition and the social stigma associated with the illness. Participants from all groups expressed these concerns. A PLWA noted, “When you’re on enough drugs already, and you’re already consuming enough, to try something, not knowing the outlook or the outcome—I think it’s enough. You take enough drugs already.” Another PLWHA said, “Because we got a whole lot of things going on, . . . issues with us. My liver [is] fucked up already. I don’t know what’s going—I mess around with some research and [I may] be done.” One clinician said, “I don’t know if we are specifically talking about studying this in the HIV positive population, but I think that’s like a very interesting subject to consider and makes it a lot more complicated and maybe not the place to start.” Another said, “What I’m trying to say is start with the least controversial population. . . . I mean, there’s a lot of people with neuropathy out there.” One of the IRB members noted, “What would have to change though is that you’d have to have some studies that weren’t done on some of these diseases . . . that already have that stigma.”

### Evolution of Views

As the discussions progressed, clinicians and IRB members identified inconsistencies in their own opinions about issues related to research on controlled substances and began to challenge each others’ statements. As their comments indicate, the participants displayed reflection, insights, and willingness to revise unfounded beliefs. Late in each FGD, comments such as these, by clinicians, were made: “Am I having a hard time with this because it is a drug that I think of as illicit? . . . Maybe the answer is just give people informed consent and you let them know. We do invasive surgeries. We do chemo. Am I sitting here, swimming through stigma in my own head right now? Maybe you just give them consent,” and, “I sort of almost feel neutral about it. But the more I think about it, why not study it? . . . Because there’s so much politics and maybe some of this, like, really old school sort of sheltered . . . stigma that research—I mean, smoke it, eat it, you know, extract the different. . . . —So let’s research it.”

Upon reflection, members of the groups noticed that their initial views on the risks of heroin were based on presumptions rather than evidence. To that affect, one clinician asked, “If we can get rid of those problems with the heroin and treat pain with heroin, what I would be questioning [is], What’s the difference between heroin and morphine, or heroin and oxycontin?” An IRB member showed a similar recognition, stating, “I honestly wouldn’t be terribly concerned that in my trial that they were going to become addicted. I mean heroin is addictive, but it’s not like one dose, I mean, that you’re suddenly addicted in any physiological sense. I assume that we would be looking for risk protections the same way we would for any drug in terms of phase-in and phase-out.” Another IRB member remarked, “We looked at a lot of nicotine drugs in schizophrenics—and you know you give nicotine, because they do better on it, but you know it is addictive.” Another IRB member responded, “Now what? I feel like I’m talking out of both sides of my mouth because really we didn’t have any trouble with the nicotine studies,” and another IRB member expressed that insight saying, “We kind of walked through it while we sat here and there’s not a real good reason to say no to this kind of research. [Laughing.]” Within the span of a 90-minute discussion, both the IRB members and the clinicians came to recognize that their unsupported beliefs had affected their previous attitudes towards the risk of providing heroin in research. Seeing that transformation in group after group was unanticipated, startling, and encouraging.

### Participants' Insights

Across the groups of stakeholders, participants began to identify gaps in their knowledge about the therapeutic effects of Schedule I drugs such as heroin. Their ignorance appeared to make participants feel uncomfortable. The discomfort seemed to foster critical reflection, and that, in turn, led the participants to identify their ignorance as a barrier to research. A few even mentioned that their ignorance was a reason to pursue research because knowledge gained from studies would be the grounds for evidence-based practice in the future. Ultimately, nearly all of the clinicians and IRB members reached the conclusion that, with appropriate study design and considerable caution, the risks of physical harm involved in studying heroin or marijuana as a possible treatment for HIV symptoms were surmountable. Some granted that symptom relief, even with addictive consequences, could be a significant benefit for people living with extreme, refractory pain. An IRB member referenced the "benefit ratio," implying that addiction may be an easier ailment than living with unremitting pain, thereby benefiting the patient. An IRB member said, "So what if a person becomes addicted to a prescription painkiller? If they're in unremitting pain, so . . . ?" Other group members added that offering heroin at HIV clinics could reduce harms associated with illicit drug self-medication, spreading infection with shared needles, and risking legal and social penalties. It could also provide the benefits that come with accessing the healthcare system. In sum, one clinician remarked, "I'm sure we'll have a lot more patients coming into the clinic [if we offer heroin]. And it would be more like the safe injecting rooms in Vancouver and Switzerland and New Zealand where people could be observed using in a safer setting, where overdoses could be identified more quickly and prevented. I mean I think there are tangible health benefits to the user or the participant."

### DISCUSSION

The findings from this qualitative pilot study reveal the impact of unexamined beliefs and attitudes on studying the therapeutic potential of Schedule I drugs for the management of HIV symptoms. The FGDs, in-depth interviews, and free-listing exercise data demonstrate similarities and differences in the initial views of each group of stakeholders.

The participants' initial opinions as recorded in the free-listing exercise suggest that stakeholders in each group have distinctive concerns. These groups also have little awareness of the perspectives of other

interested parties. Clinicians and IRB members expressed concerns with their own and their institution's reputations, and PLWHA expressed concern with dishonesty. This finding makes it easy to appreciate just how different their perspectives are. The FGDs and interviews further confirmed these divergent perspectives.

### Evolution of Views in FGDs

During the FGDs, participants expressed their views on the various topics. In all of the discussions, it was clear that most of the participants had not previously considered the medicinal potential of the Schedule I drugs. Yet, each conversation led participants to become skeptical of their initial qualms, challenge their initial views, and recognize them as reflections of unsubstantiated bias. In every group, and in instance after instance, open discussion led participants to confirm the need for research on controlled drugs to explore their potential for alleviating serious medical problems associated with HIV.

Although we did not begin with a commitment to any particular philosophic method, the *sui generis* result that we observed in the FGDs is compatible with deliberative democracy theory.<sup>26</sup> Deliberative democracy is an approach in contemporary moral philosophy embraced by theorists known as "contractarian constructivists." Amy Guttmann, Dennis Thompson, Leonard Fleck, and other proponents of this approach to resolving challenging ethical issues maintain that democratic deliberations allow people to discuss their differences in understanding and opinion. According to these theorists, the agreements that result from such a process represent conclusions about what justice requires.

It has, however, been noted that the focus group process can produce a convergence of views. Our finding is remarkable because all eight of our FGDs reached the same conclusions on a set of related issues. This consistent, overlapping consensus, across all groups of stakeholders and expressed concerns, could not have been produced by a single dominant voice.<sup>27</sup> Figure 1 illustrates the evolution of views within all eight of the FGDs on the core question about the risk of physical harm as a barrier to research on controlled drugs. Participants provided similar reasons for concluding that the risk of physical harm should not be a barrier to research during the discussion of each of the potential barriers that they had identified. We labeled these reasons for rejecting the potential barriers (1) exceptionalism, (2) benefit, (3) knowledge, and (4) harm reduction.

*Exceptionalism* refers to a participant's realization that the risks of research with heroin and mari-

juana were not greater than the risks of other studies with interventions such as chemotherapy, oxycodone and nicotine, which could also involve a risk of harm to subjects. *Benefit* refers to the appreciation of the potential for marijuana and/or heroin to provide effective, affordable, and accessible treatment for refractory pain and other symptoms. *Knowledge* indicates the information that would result from studies of the safety and efficacy of the drugs. That information would allow physicians to consider whether or not to administer them in future treatment decisions. *Harm reduction* refers to the potential benefit that the legal provision of a controlled substance can provide to mitigate other risks, such as improper self-medication, avoidable illness, or crime.

Through their deliberation, the clinicians, IRB members, and PLWHA systematically refuted many of their own previous opinions of barriers to research on controlled substances. They concluded that further research should be considered, and in some cases that it was even ethically required. PLWHA, however, persisted in expressing strong reservations about studies that would provide heroin. They continued to assert that participation in heroin trials was inconceivable for them or their loved ones. Personal experiences with addiction and intimates who had overdosed were pervasive, and those experiences had a powerful effect on their views. The deliberation that produced these four arguments led the FGD participants from all three stakeholder-groups to conclude that the risks of physical harm from research should not constitute a barrier to research. Our FGDs modeled how a deliberative democratic process can be effective in disabusing participants of their biases and helping them to revise their attitudes toward research on controlled substances. With discussion, participants in each FGD reached agreement on the most pressing issues. Where they disagreed, their differences were explicitly revealed. Further deliberations may help us to refine our understanding of genuine barriers to research with controlled substances and to identify the legitimate limits for conducting such research according to the highest ethical standards.

### Existing Literature

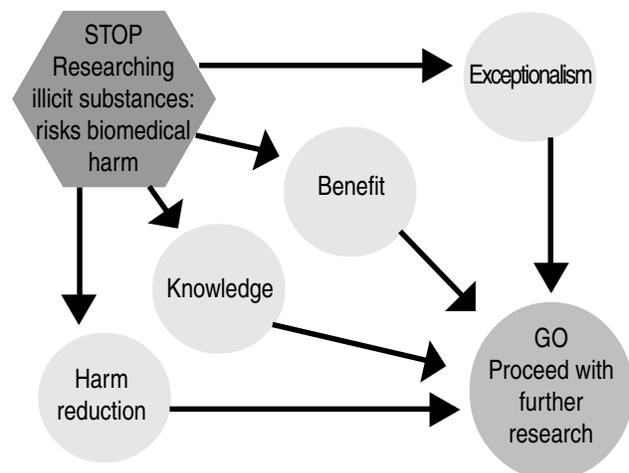
We have only identified a few studies that investigated potential barriers to research with illicit substances in the U.S.,<sup>28</sup> and an article by Bell and Salmon was the only study that explored the ethical bias of a review committee against illicit drug users. It found that assumptions about users' incapacity to participate in trials were unwarranted.<sup>29</sup>

Our study findings are consistent with theirs in that we also noted that IRB members were skeptical that individuals who used substances would be unable to provide informed consent and adhere to a study protocol. At the same time, PLWHA reported that they would refuse to participate in a clinical trial with heroin out of concern for the risks. Their responses indicate their ability to distinguish between greater and lesser risks, and therefore suggest that they do have the capacity to make responsible decisions about participation in research studies.

### Strength and Limitations

The uniqueness of this study lies in its three groups of stakeholders. We gained invaluable insights about the differences in their perspectives, as well as the similarities in the conclusions that they reached. Comparing and contrasting the perspectives that they revealed in their responses to the same questions illuminated the similarities and differences in the experiences of each group of stakeholders and how those differences led them to perceive research with controlled substances. The inclusion of PLWHA who have experience with addiction was an especially innovative and valuable feature of our study, because the PLWHA contributed voices from the population of potential participation in controlled substance studies.

Because of the small sample size, the purposive sample, and the limited range of participants' demographics, our pilot study was not representative of the groups of stakeholders at large. The IRB members were all recruited from a bioethics conference, and most described themselves as liberals. The cli-



**Figure 1.** Evolution of participants' positions on risks versus benefits of therapeutic research on controlled substances for PLWHA

nician group was drawn from the New York area, and a significant majority were women. Some clinicians voiced strong antipathy toward narcotics and Western medicine, which limited the scope of the conversation about research with controlled substances.

The group discussions involving PLWHA were conducted in two clinics that included only patients with limited education and low socioeconomic status, as demonstrated in the demographics survey responses. In some cases, the educational limitations of these participants may have prevented them from completing the survey. Several either expressed or demonstrated their inability to read or write. This factor may have accounted for why only 40 percent completed the free-listing exercise. All of these limitations make it difficult to draw strong, generalizable conclusions.

Before conducting the FGDs, we anticipated that in-depth interviews would be necessary for respondents to be willing to share personal, sensitive, and potentially compromising information and views on controversial topics. From our experience, however, we learned, to the contrary, that the participants were at least as forthcoming in groups as they were in private conversation. The data from the in-depth interviews were consistent with the data from the FGDs. Furthermore, the FGDs allowed participants to challenge each other and gain insight into the validity of their previously unexamined views on research with illicit drugs. Although we found that FGDs were a suitable tool, in our future work we plan to incorporate more varied study vignettes, based on actual clinical trials, to allow us to delve more deeply into the thorny issues of research ethics that could present barriers to research on controlled drugs. We will need to sample more geographically and demographically diverse populations.

## CONCLUSIONS

By including the voices of clinicians, IRB members, and potential research participants, our work adds significantly to the small body of prior research on barriers to controversial drug research. The inclusion of all three groups of stakeholders is especially valuable because it allowed us to compare their perspectives and identify their limited awareness of the perspectives of the other stakeholders. We were also able to identify the strong influence of their personal experiences and the impact of bias and stigma on their opinions. All of these factors constitute considerable barriers to research on the

therapeutic benefits of controversial controlled drugs.

We also witnessed how our FGDs eventually led participants to refute the exceptionalism of controlled substances research and to acknowledge the potential for benefit, knowledge, and harm reduction that could result from research with controlled substances. This transformation in attitudes provides some reasons to anticipate that, with an effort focused on understanding and addressing people's concerns, the existing policies that inhibit research on tightly controlled drugs can be reformed so that needed research may proceed. Additionally, diminishing the social stigma associated with Schedule I drugs will reduce the risks for IRB members and clinicians. Achieving such regulatory and social reform will enable investigators to undertake studies and IRB members to approve them, and thereby allow clinicians to fulfill their duty to their patients by providing drugs that are effective in meeting patients' medical needs.

While our work highlights specific areas of stigma and bias that affect science, it also reveals that there is more that we need to study. We need to inform our understanding of the nature of the risk of physical harm by eliciting the views of experts on addiction and the known effects of marijuana and heroin. Furthermore, it is important, specifically, to explore the research ethics issues of informed consent, vulnerability, undue inducement, and therapeutic misconception that will be especially complex in this context. Developing a detailed understanding of how these ethical concepts bear on the ethical conduct of research with controlled substances will be critical in formulating guidance on how such studies may be conducted, particularly in studies that propose to involve participants from vulnerable groups or people who may be current or past drug users. An informed perspective on these issues should be developed before leaping into clinical trials with controlled substances, which are clearly not without risks or adverse effects. For example, we are aware that cannabis use during adolescence may increase a subsequent risk to develop schizophrenia.<sup>30</sup> Further research with a greater diversity of stakeholders is necessary to develop a broader consensus on these ethical issues. Evidence-based recommendations, including input from relevant experts on controlled substances, need to be created so that investigators can employ that guidance on how clinical trials of controlled drugs may be conducted in accordance with the highest ethical standards. While this article was under review for publication, the momentum for medical cannabis

use has grown,<sup>31</sup> new indications for marijuana have been identified,<sup>32</sup> and off-label treatment with intravenous ketamine for depression has become widespread.<sup>33</sup> These developments emphasize the urgent need to address barriers to research, so that treatment choices can be informed by sound clinical evidence.

## NOTES

1. M. Gossop, F. Keaney, P. Sharma, and M. Jackson, "The Unique Role of Diamorphine in British Medical Practice: A Survey of General Practitioners and Hospital Doctors," *European Addiction Research* 11, no. 2 (2005): 76-82.

2. E.T. Kavalali and L.M. Monteggia, "Synaptic Mechanisms Underlying Rapid Antidepressant Action of Ketamine," *American Journal of Psychiatry* 169, no. 11 (November 2012): 1150-6; J. Li et al., "To Use or Not to Use: An Update on Licit and Illicit Ketamine Use," *Substance Abuse and Rehabilitation* 2 (2011): 11-20; M.G. Roback, J.E. Wathen, T. MacKenzie, and L. Bajaj, "A Randomized, Controlled Trial of I.v. versus I.m. Ketamine for Sedation of Pediatric Patients Receiving Emergency Department Orthopedic Procedures," *Annals of Emergency Medicine* 48, no. 5 (November 2006): 605-12.

3. N. Sindicich, L. Degenhardt, and W. Hall, "The Use of MDMA for Therapeutic Purposes," *Health and Psychological Effects of "Ecstasy" (MDMA) Use* 12, no. 62 (2010).

4. A.E. Conlin and L. McLean, "Systematic Review and Meta-Analysis Assessing the Effectiveness of Local Anesthetic, Vasoconstrictive, and Lubricating Agents in Flexible Fibre-Optic Nasolaryngoscopy," *Journal of Otolaryngology—Head & Neck Surgery* 37, no. 2 (April 2008): 240-9; R. Elliott, C.T. Fischer, and D.L. Rennie, "Evolving Guidelines for Publication of Qualitative Research Studies in Psychology and Related Fields," *British Journal of Clinical Psychology/The British Psychological Society* 38, no. 3 (September 1999): 215-29; M. Iskedjian, B. Bereza, A. Gordon, C. Piwko, and T.R. Einarson, "Meta-Analysis of Cannabis Based Treatments for Neuropathic and Multiple Sclerosis-Related Pain," *Current Medical Research and Opinion* 23, no. 1 (January 2007): 17-24; J.M. Kendall, B.C. Reeves, and V.S. Latter, "Multicentre Randomised Controlled Trial of Nasal Diamorphine for Analgesia in Children and Teenagers with Clinical Fractures," *BMJ (Clinical Research Ed.)* 322, no. 7281 (February 2001): 261-65; M.E. Lynch and F. Campbell, "Cannabinoids for Treatment of Chronic Non-Cancer Pain; a Systematic Review of Randomized Trials," *British Journal of Clinical Pharmacology* 72, no. 5 (November 2011): 735-44; R.J. McInnes, E. Hillan, D. Clark, and H. Gilmour, "Diamorphine for Pain Relief in Labour? A Randomised Controlled Trial Comparing Intramuscular Injection and Patient-Controlled Analgesia," *BJOG: An International Journal of Obstetrics and Gynaecology* 111, no. 10 (October 2004): 1081-9; Roback et al., "A Randomized, Controlled Trial of I.v. versus I.m. Ketamine," see note 2 above.

5. E.M. Silva et al., "Anti-HIV-1 Activity of the Iboga

Alkaloid Congener 18-Methoxycoronaridine," *Planta Medica* 70, no. 9 (September 2004): 808-12; C.M. Costantino et al., "Cannabinoid Receptor 2-Mediated Attenuation of CXCR4-Tropic HIV Infection in Primary CD4+ T Cells," *PLoS ONE* 7, no. 3 (March 20, 2012).

6. L. French et al., "Early cannabis use, polygenic risk score for schizophrenia and brain maturation in adolescence," *JAMA Psychiatry* 72, no. 10 (2015): 1002-11; A. Dines et al., Euro-DEN Research Group, "Acute recreational drug and new psychoactive substance toxicity in Europe: 12 months data collection from the European Drug Emergencies Network (Euro-DEN)," *Clinical Toxicology* 53, no. 9 (2015): 893-900; S. Gibbons, "'Level highs'—novel and emerging psychoactive drugs: A chemical overview for the toxicologist," *Clinical Toxicology* 50, no. 1 (2012): 15-24.

7. D.I. Abrams, "Medical Marijuana: Tribulations and Trials," *Journal of Psychoactive Drugs* 30, no. 2 (1998): 163-9; P.J. Cohen, "Medical Marijuana: The Conflict between Scientific Evidence and Political Ideology: Part Two of Two," *Journal of Pain & Palliative Care Pharmacotherapy* 23, no. 2 (2009a): 120-40.

8. U.S. Drug Enforcement Agency, "United States Code (USC) Controlled Substances Act: Section 812. Schedules of Controlled Substances," United Office of Diversion Control, Drug Enforcement Administration, 2007, [www.gpoaccess.gov](http://www.gpoaccess.gov).

9. D.J. Newport et al., "APA Council of Research Task Force on Novel Biomarkers and Treatments Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression," *American Journal of Psychiatry* 172, no. 10 (2015): 950-66.

10. M.H. Andrae et al., "Inhaled Cannabis for Chronic Neuropathic Pain: An Individual Patient Data Meta-Analysis," *Journal of Pain* (September 2007).

11. Cohen, "Medical Marijuana: The Conflict between Scientific Evidence and Political Ideology," see note 7 above; Abrams, "Medical Marijuana," see note 7 above; G.G. Nahas and A. Greenwood, "The First Report of the National Commission on Marihuana (1972): Signal of Misunderstanding or Exercise in Ambiguity," *Bulletin of the New York Academy of Medicine* 50, no. 1 (January 1974): 55-75.

12. R.J. Ellis et al., "Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover Clinical Trial," *Neuropsychopharmacology* 34, no. 3 (February 2009): 672-80.

13. S. Ghosh, A. Chandran, and J.P. Jansen, "Epidemiology of HIV-Related Neuropathy: A Systematic Literature Review," *AIDS Research and Human Retroviruses* 28, no. 1 (January 2012): 36-48.

14. N.B. Finnerup, S.H. Sindrup, and T.S. Jensen, "The Evidence for Pharmacological Treatment of Neuropathic Pain," *Pain* 150, no. 3 (September 2010): 573-81.

15. M. Giles and C. Workman, "Clinical Manifestations and the Natural History of HIV," *HIV Management in Australasia* (2009): 125-32.

16. D. Elbrit and C. Bayon, "Neurocognitive Impairment, Depression, and Anxiety in HIV-1-Infected Patients across Western Europe and Canada: The Cranium Study -

- Ethnicity Analysis," *International AIDS Society* 15, no. 6 (2012): 18276; Giles and Workman, "Clinical Manifestations and the Natural History of HIV," see note 15 above; R.D. Harrington, J.A. Woodward, T.M. Hooton, and J.R. Horn, "Life-Threatening Interactions between HIV-1 Protease Inhibitors and the Illicit Drugs MDMA and Gamma-Hydroxybutyrate," *Archives of Internal Medicine* 159, no. 18 (October 1999): 2221-4; R. Klitzman, "From 'Male Bonding Rituals' to 'Suicide Tuesday': A Qualitative Study of Issues Faced by Gay Male Ecstasy (MDMA) Users," *Journal of Homosexuality* 51, no. 3 (2006): 7-32.; S.M. Kousik, T. C. Napier, and P.M. Carvey, "The Effects of Psychostimulant Drugs on Blood Brain Barrier Function and Neuroinflammation," *Frontiers in Pharmacology* 3 (2012): 121.
17. D.J. Nutt, L.A. King, and L.D. Phillips, "Drug Harms in the UK: A Multicriteria Decision Analysis," *Lancet* 376, no. 9752 (November 2010): 1558-65.
18. C.B. Bourgain et al., "A Damage/benefit Evaluation of Addictive Product Use," *Addiction* 107, no. 2 (February 2012): 441-50.; Cohen, "Medical Marijuana," see note 7 above; P.J. Cohen, "Medical Marijuana: The Conflict between Scientific Evidence and Political Ideology: Part One of Two," *Journal of Pain and Palliative Care Pharmacotherapy* 23, no. 2 (2009): 120-40.
19. K. Charmaz, *Constructing Grounded Theory: A Practical Guide through Qualitative Analysis* (London: Sage, 2006).
20. Ibid.
21. T.J. Rapley, "The Art(fulness) of Open-Ended Interviewing: Some Considerations on Analysing Interviews," *Qualitative Research* 1, no. 3 (1 December 2001): 303-23.
22. C.E. Hill et al., "Consensual Qualitative Research: An Update," *Journal of Counseling Psychology* 52, no. 2 (2005): 196-205.
23. Charmaz, "Constructing Grounded Theory," see note 19 above.
24. H.R. Bernard, *Research Methods in Anthropology: Qualitative and Quantitative Approaches* (Lanham, Md.: Rowan & Littlefield, 2011); Rowman Altamira; G. Guest, A. Bunce, and L. Johnson, "How Many Interviews Are Enough? An Experiment with Data Saturation and Variability," *Field Methods* 18 (2006): 59-82.; P. Liamputtong, *Focus Group Methodology: Principles and Practice* (London: Sage, 2011); S. Sofaer, "Qualitative Research Methods," *International Journal for Quality in Health Care* 14, no. 4 (1 August 2002): 329-36; C. Willig, *Introducing Qualitative Research in Psychology*, 3rd ed. (Berkshire, U.K.: Open University Press, 2013).
25. M. Quinlan, "Considerations for Collecting Freelists in the Field: Examples from Ethnobotany," *Field Methods* 17, no. 3 (1 August 2005): 219-34.
26. A. Gutmann and D. Thompson, *Why Deliberative Democracy?* (Princeton, N.J.: Princeton University Press, 2004); L.M. Fleck, *Just Caring: Health Care Rationing and Democratic Deliberation* (Oxford, U.K.: University Press, 2009).
27. J. Rawls, *Political Liberalism* (New York: Columbia University Press, 1993).
28. E.E. Anderson and S. Solomon, "Research Ethics Education for Community-Engaged Research: A Review and Research Agenda," *Research Ethics* (2012); K. Bell and A. Salmon, "What Women Who Use Drugs Have to Say about Ethical Research: Findings of an Exploratory Qualitative Study," *Journal of Empirical Research on Human Research Ethics* 6, no. 4 (December 2011): 84-98; Gossop, "The Unique Role of Diamorphine in British Medical Practice," see note 1 above.
29. K. Bell and A. Salmon, "Good Intentions and Dangerous Assumptions: Research Ethics Committees and Illicit Drug Use Research," *Research Ethics* 8 (2012): 191-9.
30. French et al., "Early cannabis use," see note 6 above.
31. C. McCall, "Momentum grows for medical use of marijuana," *Lancet* 24, no. 386 (2015): 1615-6.
32. D. Friedman and O. Devinsky, "Cannabinoids in the Treatment of Epilepsy," *New England Journal of Medicine* 7, no. 374 (2016): 94-5.
33. "Club Drug Ketamine Gains Traction as A Treatment For Depression," NPR.org, 2015, <http://www.npr.org/sections/health-shots/2015/09/28/443203592/club-drug-ketamine-gains-traction-as-a-treatment-for-depression>.