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Research with Controlled Drugs: Why and Why Not? Response to Open Peer Commentaries on “An Ethical Exploration of Barriers to Research on Controlled Drugs”

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We thank the Open Peer Commentary authors for their support for our project and for their insightful and helpful comments on our paper, “An ethical exploration of barriers to research on controlled drugs”. We appreciate their concurring opinions that research on the therapeutic uses of controlled substances is needed and that, within reasonable constraints, it should be allowed. We also found the commentators discussions and their own insights on this issue to be informative and useful. They identified issues that we did not address in our manuscript and which clearly warrant further exploration.

Danton Char (2016), Dominic Sisti and Andrea G. Segal (2016), identify additional consequences of the regulations that impose draconian limitations on research with controlled drugs. Pointing to the rise in overdose deaths around the country by people who self-medicate with prescription painkillers and with illicit substances, Char made a strong case for the importance of harm reduction research and the need for substitution studies that involve different populations. He echoed our concern for the avoidable harms that are

experienced by desperate people who have no effective treatment for their chronic pain. His views also resonate with our appreciation of investigators' need for access to safe standardized products for their studies. Sisti and Segal describe the wide-scale off-label use of drugs, such as ketamine, that is promoted by market forces. In sum, several commentators concur with us that clinical research would expand the evidence base for therapeutic use of controlled drugs and make those found to be effective more accessible to patients who need them.

Andrew Plunk and Paul Harrell (2016), Ruth Macklin (2016), and Jay Brenner (2016) all agree with us that attitudes, political and economic reasons, and biases constitute barriers that impede research with controlled drugs. Plunk and Harrell share our awareness that research with controlled drugs involves consideration of both the risks and the possible benefits of their use. They remark that the use of some substances “might confer benefit relative to non-use at some level, even though there are harms associated with misuse.” (p.2, l.51) They also explain how some barriers are intentional whereas others are “unintended consequences of poorly implemented policy.” (p.2, l.42) Their conclusion resonates with ours. As they put it, “we should regulate research using the most dangerous drugs more tightly, but the added difficulty of those regulatory requirements should also be proportionate to the risks involved. In the context of the current discussion, policy should minimiz[e] ... barriers to research that are not justified.” (p.3, l.12) We are aware that imagined and real barriers should be explored empirically to substantiate or refute the need for constraints on research. As we explained in our paper, to address barriers to research we need to study them.

In addition to those barriers that we had envisioned, Macklin and Brenner noted that regulatory agencies appeared to be averse to anything that may support the use of drugs for recreational purposes. Macklin pointed out that even the name “National Institute on Drug Abuse” marks the mission of that NIH institute as clearly opposing drugs that are psychoactive and have pleasurable side effects. She also reminds us of two articles, one by Gerald L. Klerman published in 1972 and the other by Robert Michels published in 1984, which identify the Calvinist tone of U.S. drug policy and entrench the view that drugs which produce pleasure are inherently evil.

In their comments, “Justice and Research on Controlled Substances with HIV+ Persons,” Leslie P. Francis and John G. Francis (2016) agree that “[b]uilding the case for research improving pain management in HIV patients is an urgent matter.” (l.38) They then go on to identify relevant demographic factors such as the African-American burden of disease and some research related to risks for potential subjects. We concur that these issues warrant further exploration. They point out that restrictions on making data available, uncertainty about the protection of research confidentiality, and stigma associated with being in a study all need to be considered particularly because of the possible effects on minority groups. These complex considerations will have to be explored and taken into account in order to assure that study designs conform to standards of justice.

In the especially informative commentary, “Research on controlled drug use: a paradigm for public health research in sustainable health,” Evert van Leeuwen (2016), explains how the

sort of goals that Francis and Francis laid out were actually accomplished in The Netherlands. Recognizing the need for “evidence-based programs for people in vulnerable situations, like those suffering from addiction” (p.2, l.15) and the difficulty of developing them in the context of current research regulations that are designed for idealized populations and a narrow range of circumstances, van Leeuwen cautions that it is important to confront “undue political constraints in performing research” with vulnerable populations. (p.3, l.7) He maintains that an ethically responsible approach will involve developing a comprehensive understanding of all of the issues involved including justice, compassion, respect for persons, risks of harm, and harm reduction, as well as the likely results for the affected communities and society at large. He describes a process of support and oversight that was employed in a study that compared Heroin Assisted Treatment (HAT) with Methadone Maintenance Treatment (MMT). To accomplish that project, the committee empowered by the Dutch Ministry of Health set aside “the prejudices and other barriers in society regarding long-term chronic heroin addicted people.” (p.4, l. 47) Their guiding principle was that “groups with special vulnerability are taken seriously as human beings with a need for sustainable health.” (p.5, l.23) The outcome of the study was “better quality of life, better health and a reduction of crime and other harms on a societal level.” (p.4, l.9) We are committed to these aims and we sincerely hope that our future efforts will help to produce similar advances in sustainable health.

Although we do largely agree with our commentators, we respectfully disagree with Plunk and Harrell, who do not consider classification of a controversial drugs as Schedule I to be an “unsurmountable barrier” and posit that most barriers we described pertain solely to “[m]arijuana in its unrefined form”. Yet this form is most used recreationally and by patients. For that reason, it should be the focus of research, both regarding potential benefits and harms, and also to better inform the debate on legalization for medicinal and recreational use.

We also respectfully disagree with Drs. Char and Brenner's notion that outside the legal pharmaco-therapeutic industry “it is unlikely that any more than small additional direct therapeutic advantages will be found” by investigating controversial controlled substances. The industry is focused on investigations that will reward their investment. Indeed, as Drs. Segal and Sisti wrote, “because ketamine is generic and inexpensive,” and as Drs. Plunk and Harrell noted, “when [cannabis] can be grown by almost anyone,... who is going to fund large scale studies”? The therapeutic potential of cannabis as a treatment for the HIV-virus proper(1,2) and for epilepsy (3) were identified through studies that were not conducted by the pharmaceutical industry. The concern about the misalignment of industry goals and the public good may be even more valid when it comes to assessing the risk of controversial drugs on a population basis. That theme came up in the commentaries by van Leeuwen and Plunk, and the needs of resource poor populations that are greatly afflicted by the HIV virus was pointed out by Francis and Francis. As an aside, we would like to clarify that we emphasized randomized controlled trials (which Francis and Francis criticized) because it will be important to provide convincing evidence for therapeutic potential. We do, however, echo their concerns about “issues like enrollment bias, bias in study design, or analysis.”

We are happy to report that our paper, “Stakeholder Views on Barriers to Research on Controversial Controlled Substances,” which describes the unexpected but informative findings of our pilot study on these issues is forthcoming in *The Journal of Clinical Ethics* (Rhodes 2016). With much more work still to be done, we will surely take direction from the points made by the OPC authors and are grateful for their attention and their insights.

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