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REVIEW ARTICLE

Research ethics aspects of experimentation with LSD on human subjects: a historical and ethical review

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Abstract
In this paper our aim is to examine whether research conducted on human participants with LSD-25 (lysergic acid diethylamide) raises unique research ethical questions or demands particular concerns with regard to the design, conduct and follow-up of these studies, and should this be the case, explore and describe those issues. Our analysis is based on reviewing publications up to date which examine the clinical, research and other uses of LSD and those addressing ethical and methodological concerns of these applications, just as some historical examinations of this subject. The first chapters of the paper give an overview regarding the history of LSD-research with human participants, healthy volunteers and patients alike. The remaining chapters have a focus on questions regarding the potential ethical issues of such human trials in the contemporary research ethics framework. We also consider briefly political and regulatory issues regarding this substance that possibly affect its clinical and research applications.

Keywords Research ethics · Clinical trial · Lysergic acid diethylamide · LSD research · Psychedelic research

Introduction

> If people did not sometimes do silly things, nothing intelligent would ever get done.
>
> Ludwig Wittgenstein.

From popular magazines' leading articles to in-depth reviews in renowned medical journals, a growing number of reports could be found on the (re)emerging interest in researching the so-called "psychedelic drugs"—a group of substances that include lysergic acid diethylamide (from now on: LSD) as well. New studies are investigating LSD's applicability and effects on different conditions and with various populations. For example, in 2016 alone more than 10 experiments were reported that involved LSD administered to human subjects. At the same time, however, there has been little reflection on the research ethics issues involved in this subject. One of the few papers to discuss such issues noted that, "to date, the ethical factors involved in research using controlled drugs have not been well described, recommendations have not been well developed, and there is almost no evidence-based guidance on how to assess these factors and proceed" (Andreae et al. 2016, p. 42).

In this paper we examine whether research conducted on human participants with LSD raises unique research ethics questions. In what sense do these studies demand particular attention with regard to the design, conduct and follow-up of these studies and what kind of special research ethics issues must be considered? Beginning with an overview of the exciting history of such research, we will provide a general assessment of research with LSD with human participants. In this second part we are following the ethics framework provided by Emanuel et al. which was developed for the assessment of major research ethics questions raised by clinical trials.ű.

The history of LSD research

The studies with LSD on human participants from the beginning of the 1950s include randomized and other controlled trials, experimental therapeutic uses, or close empirical observations without a control group, and informal experiments—a part of these being conducted on healthy

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volunteers, another part on patient populations. The number of such trials up to this date is estimated to be around 200, with several thousand publications explaining or describing those, not involving the numerous uncontrolled, but experimental applications, with tens of thousands of participants (Das et al. 2016; Passie et al. 2008; Sessa 2018).

The first documented—famously non-voluntary—experiment with LSD was conducted by Albert Hofmann on himself after he unintentionally synthesized it for the first time in 1938; this followed numerous animal experiments (Hofmann 1979). Scientific discussion on LSD first were published in scientific papers in 1943, and Joel Elkes conducted the first psychiatric experiment with LSD in 1951 (Dyck 2015B). The next decade witnessed widespread and diverse research interest in investigating this compound. Between 1951 and 1966 roughly 1000 clinical publications described the experimental uses of LSD, most of them concerned *psychedelic assisted psychotherapy*, with approximately 40,000 patients involved (Grinspoon and Bakalar 1981). These studies included about 120 LSD trials that were conducted with more than 1700 subjects and sponsored by the Federal government in this period with $4,000,000 of Federal financial support (Pollan 2015).

These experiments and therapeutic research were diverse in terms of their areas of interest and methodology: some researchers, like Joel Elkes, following Hofmann's trail, began by conducting self-experimentation (Dyck 2015B; Novak 1998). Besides the basic researches addressing the fundamental questions of safety, toxicity, pharmacological and pharmacokinetics issues, professionals conducted a large number of applied, therapeutic studies with LSD. Abramson put forward his *model psychosis* theory that regarded LSD-states as models of *chemically induced psychosis* (LSD labelled and explained as "schizotoxic" compound) that might be revealing in understanding mental disorders through such biochemical means. Other studies were performed to test recall and abstraction and to produce improved insight. Experimentation on patients with mental disorders included studies investigating the psychologically therapeutic potential of the substance that might even contribute to considerable emotional ventilation in schizophrenics (Das et al. 2016, p. 216–217). In this respect, the most widespread application of LSD was—and remains to be—its usage as an *adjunct psychotherapy*, i.e. as an adjuvant substance to assist psychotherapy of various sorts. Two dominant forms were most frequent (actually, so widespread that Stanislav Grof alone between 1956 and 1968 was present at 1.100 LSD and psilocybin sessions (Oram 2014)):

> One emphasized the mystical or conversion experience and its after effects; the other concentrated on exploring the labyrinth of the unconscious in the manner of psychoanalysis. Psychedelic therapy, as the first of these was called, involved the use of a large dose of LSD (200 μg or more) in a single session and was thought to be helpful in reforming alcoholics and criminals, as well as in improving the lives of normal people. The second type, psycholytic (literally, mind-loosening) therapy, required relatively small doses (usually not more than 150 μg) and several or even many sessions; it was used mainly for neurotic and psychosomatic disorders. (Grinspoon and Bakalar 1981, p. 275)

These LSD assisted psychedelic and psycholytic psychotherapies addressed several psychological problems, ranging from—as it was called then—"obsessional neurosis" through major depression, generalized anxiety and even psychotic conditions. One particularly promising field within this area of therapeutic application was the adjuvant use of LSD combined with counseling to reduce anxiety, depression, and pain in patients with advanced cancer. These studies involved more than one hundred patients, and this use of LSD was shown to be safe in this population (cf. Das et al. 2016; for a general outline and overviews—contemporary and recent alike—of these psychedelic and psycholytic LSD assisted therapies, see also Dyck 2015a; Passie 1997).

Humphrey Osmond coined the term "psychedelic" to denote and emphasize the mind-expanding, mystical experience-evoking capability of LSD and other, related psychotropic substances. He and his team used LSD assisted psychotherapy in treating chronic alcoholics, which was one of the most researched areas of LSD usage for therapeutic purposes together with the above mentioned application in anxiety of terminal patients. More recent reviews suggest that this could be regarded as a general success, both in terms of efficacy and having a very good side-effect profile at the same time (Das et al. 2016; Dos Santor et al. 2016; Krebs et al. 2012). A surprising fact—mostly from the perspective of a research ethics focused article—is that even Henry Beecher was involved as a principal investigator in one of these early experiments on healthy volunteers (von Felsinger et al. 1956).

Sydney Cohen, a leading figure in LSD (and psychedelic) research at that time has drawn the following conclusion regarding the overall—somatic and psychological—safety of LSD's controlled usage: he computed that the number of suicides was 0.4/1000, thus concluded that complications were, "*surprisingly infrequent*", and that, when given in a medical setting, "*LSD and mescaline were safe*" (Novak 1998, p. 23). These claims, based on the exploration of the first decades of LSD research on the relative safety of LSD itself and its application as an adjuvant substance are backed by Das et al.'s thorough and up-to-date review, as it summarizes safety issues: "Classic hallucinogens have very low physiological toxicities, with no evidence of resulting

organ damage or neuropsychological deficits even at very high doses. (…) For the large majority of participants, the most relevant safety concern is the potential for dangerous and erratic behavior resulting from the intense subjective experiences with these drugs." However, underlining, at the same time that "(…) the absolute contraindications of LSD use are physical conditions precluding marked excitement (e.g. cardiovascular disease), pregnancy, epilepsy, paranoid personality, overt psychosis, organic-toxic cerebral disorder, and so on." (Das et al. 2016, pp. 221–222).

Having overviewed these historic literature data, we consider these results as rendering risks associated with LSD experimentation on human subjects identifiable, which seem to be manageable and adequately minimizable in a properly controlled clinical or otherwise monitored research and therapeutic environment and follow-up design. We find it, however, particularly important to emphasize that given the subjective psychological effects being so profound, often burdensome and discomforting and also highly dependent on the above mentioned *set* and *setting*, LSD's experimental usage demands a thoroughly overthought design and carefully conducted on-going monitoring of these factors, thus to minimize the chance of participants encountering such negative experiences during and after the study.

In the frame of this historic review, it is worthy taking into consideration some methodological issues of this period. The experiments prior to 1962 could be characterized as primarily consisting of close empirical studies on small numbers of patients, frequently without a control group, and the included population were usually coming from the severely ill and treatment resistant patients (Oram 2014, 2016). Assessing the post-1962 period, medical historian Matthew Oram focused on the pivotal question whether, to what extent and with what limitations the "gold standard" RCT design was suitable for exploring and assessing psychedelic assisted psychotherapy. He argues that the novel regulation of proof of efficacy (the so-called Drug Amendments of 1962) resulting in a change in the design of LSD trials—though indirectly, yet practically required by the FDA and the professional community—had contributed to several false-negative outcomes of experiments on the efficacy of LSD resulting from ill-designed RCT trials out of the following reasons: The "golden standard" RCT design—(double) blinded, placebo controlled trial, focusing on examining the direct biological action of an agent—was hardly tailorable for LSD used as a means of psychedelic assisted psychotherapy. In fact, no research had been done on the general physiological effects of LSD and other psychedelics up until recent times. A peculiar aspect of the old and the new *Psychedelic Renaissances* (Sessa 2018) is that both have been almost exclusively focusing on the psychotherapeutic implications neglecting detailed investigations into the biological component.

On the one hand, LSD in itself, that is, only through direct biological action was not responsible for the therapeutic benefits often described by earlier researchers and therapists. These benefits could only have been achieved by means of applying LSD as an adjuvant, viz. as an organic part of a much "broader" psychotherapy. (Here it might be noted that psychotherapies per se are at least very difficult to be tested by means of blinded RCT-s; nevertheless, LSD still was a candidate molecule—just like "magic bullet"-like drugs, e.g. antibiotics—whose efficacy and safety must have been tested according to these standards.) On the other hand, the profound and overwhelming effects of the LSD—both as experienced by the participant and seen by the investigators—rendered blinding and placebo-usage almost impossible (Oram 2014).

However, a turn towards the RCT type of LSD research could be understood in a more plural manner, that is, not only as a process that put obstacles or methodological restraints on the research, rather as much as a factor that have positively contributed to the continuation of LSD experimentation—even in the era of the political and legal change of the substance's status. The historical shifts and changes in the policy environment of LSD research are well described in Oram's analysis:

> During the 1960s, LSD psychotherapy research transformed rather than died. Instead of the government prohibiting research due to concerns over its non-medical use, the FDA evaluated applications to conduct research according to rules put in place under the Drug Amendments of 1962. (…) While the smaller number of researchers using LSD can give the impression that research was in decline, the studies that remained were significantly more methodologically sophisticated than previous studies. They therefore had the best chance of producing convincing proof of treatment efficacy, as needed to potentially turn the drug into an approved pharmaceutical. (Oram 2016, pp. 302–303)

Some comments might be necessary on two set of experiments from this period that became infamous for a variety of reasons: namely the MKUltra project, and Timothy Leary's and Richard Alpert's experimentation. The MKUltra project was the CIA's secret project to explore drugs such as LSD for mind control, as adjuvants to hypnosis, as supposed "truth serums", and for various sorts of military and intelligence uses. Beginning in the early 1950s, when the risks and basic safety issues of LSD were not yet properly assessed, the "volunteers" consequently were often under-informed, even unknowing. The most infamous instance of this was the case of the biologic warfare scientist Dr. Frank Olson, who

in 1953, killed himself after being unwittingly dosed with LSD at a CIA-sponsored party (Mashour 2007).

Timothy Leary and Richard Alpert, both psychotherapists and lecturers at Harvard, beginning from 1960, were allegedly providing psychedelic substances—most commonly *Psylocibe* mushrooms and LSD—to their students as well. Though in that period LSD was legal and legally accessible for clinical and experimental applications, this was problematic for several reasons. Since the effects and safety of these compounds were not satisfactorily explored by that time, and these "experiments" were often "conducted" in the course of informal events—during parties or gatherings—and not in a proper, clinically controlled setting, these conditions raised issues regarding scientific validity and (non)adequate risk-assessment. Recruiting volunteers for such experimentation from the circle of their students ran the risk of undue inducement and coercion as well. Also, the aims of these experimental session's—therapeutic, research, recreational and political/activist purposes—were often intentionally and/or carelessly mixed, rendering the methodological adequacy of them highly questionable. (Dyck 2015a).

"Subsequently the number of research programs dropped from 70 to nine" (Oram 2016, p. 290) until 1975. Some commentators regarding this dearth of trials are prone to claim that scientific LSD-research was dropped *mainly* because of these political and societal concerns and fears regarding the recreational/street use of the substance: "Historians and other commentators have primarily explained the decline in LSD psychotherapy research in the USA in the 1960s, towards its complete demise in the mid-1970s, as an outcome of the government backlash against the non-medical use of LSD" (Oram 2016, p. 291). However, Oram's explanation, which we share and rely on in our own analysis (see the following section), the process might have been slightly different and multi-casual: "Rather than a deliberate government initiative, the reduction in research reflected the formalization of pharmaceutical research and development engendered by the Drug Amendments of 1962, and was further influenced by the actions of Sandoz Pharmaceuticals" (Oram 2016, p. 292). Besides, aiming to understand this "drop" one should also keep in mind—as mentioned above—, that the quantitative drop harbored a qualitative improvement.

After the above mentioned dearth of researches from the 1970s till the end of the 1990s, in the new millennium we are witnessing a renewal of interest in studying the therapeutic potential of LSD on human participants (Dyck 2015a). Many recent studies are aiming to provide "a clearer characterization and definition of their principal effects on the mind and brain" (Das et al. 2016, p. 218), all of them different from the "historical" ones in terms of much more stringent—ethical and methodological—design, oversight and assessment measures applied onto them.

These range from novel neuro-imaging studies (Carhart-Harris et al. 2016a) through basic pharmacokinetical and functional ones (Dolder et al. 2016 and; Roseman et al. 2016, or; Strajhar et al. 2016) to experiments on more particular neuroscientific questions (Family et al. 2016; Kapócs et al. 2016; Komete and Vollenweider 2016; Kaelen et al. 2016a, b). Basic research in the field of psychiatry and psychology are also carried out. These "measures included psychometric scales, investigator ratings, prepulse inhibition (PPI) of the acoustic startle response, autonomic, endocrine, and adverse effects" (Das et al. 2016, p. 219). Placebo-controlled trials were conducted on healthy volunteers to assess the general psychological effects of LSD (Carhart-Harris et al. 2016b; Terhune et al. 2016 and; Lebedev et al. 2016), the mystical-type experiences (Liechti et al. 2016) and the so-called "ego dissolution" (Tagliazucchi et al. 2016) it might bring about, or even more specific psychological aspects it produces (Speth et al. 2016).

Other recent studies are examining—in line with the most dominant LSD-usage form (psychedelic assisted psychotherapy) previously mentioned—the beneficial effects of LSD used as an adjunct to psychotherapy with conclusive, though small-scale results (Dolder et al. 2015). The two most promising fields within this research area (as they were in the'60-s as well) are the following: Studies investigating LSD assisted psychotherapy in treatment for anxiety associated with life-threating diseases and—based on a broad corpus of studies in the past and growing number of present investigation—and as addiction interrupters of various dependencies, most prominently alcohol (Das et al. 2016, p. 217, 220).

According to conclusions of current, thorough reviews of these fields "recently completed trials investigating the utility of psychedelics in psychotherapy have demonstrated safety and impressive efficacy in treating anxiety related to terminal diseases" (Das et al. 2016, p. 219) and "a single dose of LSD, in the context of various alcoholism treatment programs, is associated with a decrease in alcohol misuse" (Krebs et al. 2012, p. 94). [Another, also very important article—though focusing on "underground therapies", and not on (controlled) trials, but likely bearing heavily on the issue of maximizing participant safety—in this respect is Sessa's and Friederike's exciting analysis (2016)].

What makes clinical research with LSD ethical?

In the second part we attempt to provide a general assessment regarding the ethics issues LSD clinical trials potentially raise. For this purpose we apply the seven dimension model put forward by Emanuel et al. (2000). These dimensions are suggested as a systematic framework aiming to

synthetize traditional codes, declarations and professional literature that are regarded as established sources to provide an ethical guidance for clinical research with human participants. Our discussion will follow these 7 dimensions by focusing on whether LSD experimentation raises or demands particular ethics concerns or considerations regarding them.

Value of the research

Based on the robust body of research findings outlined in the previous sections, we can conclude that clinical LSD research is valuable from medical, psychological and public health perspectives as well. Therapeutic applications—mostly as adjuvants to psychotherapy, foremost as addiction interrupters and to alleviate anxiety of terminal patients—LSD shows promising results based on past and recent clinical and psychological experiments, conducted in well controlled clinical/research environments and conditions, with acceptable risk/benefit profile.

Besides the clinical and psychological therapeutic uses, seen from a public health perspective, acquiring clinical and psychological results could assist public health professionals to develop and implement more effective strategies and policies for preventive and harm reduction purposes with regard to the recreational forms of LSD usage—an aspect we consider to be important regardless of the legal status of LSD: Should it fall under total prohibition, be accepted for therapeutic applications, or be decriminalized for recreational purposes, from a harm reduction perspective, the more we now about the substance clinically, the more we could help prevent and ameliorate harms stemming from its usage.

Consequently, if the scientific community agrees on that it is important to conduct more LSD research, then we risk drawing the following normative conclusions: New studies are needed to test novel hypotheses, to replicate studies, and to carry out studies that were formerly conducted on small populations with greater number of participants and with more robust methodology. Research should be conducted to further assess possible, clinical and social harms and benefits, to assess new therapeutic potentials and purposes [only to mention a fresh, interdisciplinary approach, see Horváth et al.'s research (2017)], and to provide a foundation for policies regulating LSD's medical and recreational usage.

Scientific validity

As a general remark on the value of more recent scientific evidences we should highlight that the majority of these experiments were carried out on a small number of subjects. Therefore, to produce more valid and robust outcomes, these trials ideally should involve a greater number of participants—healthy volunteers and patients alike.

Moreover, we believe that the questions of methodological constraints discussed above concerning the experimentation of the post-1962 period might be worth of consideration recently as well. Should and could the "golden-standard", double-blinded, placebo controlled RCT design be used to test the efficacy of LSD applied as an adjuvant to psychotherapy? If the answer is negative, what other methodologically robust trial-designs should be applied? This is an important matter both to assess—by means of meta-analysis and historical control—past research findings and to design prospective experiments. It could shed light on whether and how past RCT trials were appropriate for testing the efficacy of adjuvant LSD therapy. Consequently, we would have a better understanding of whether and to what extent past experiments provide relevant and adequate data. With a better grasp of this question researchers will be able to design and implement more appropriate studies.

The issue of scientific validity is further complicated by social circumstances. Andreae et al. put forward in their article commenting on the obstacles to research on controlled substances that trials with such compounds are often facing barriers that directly or indirectly inhibit these investigations—in our understanding, LSD-research is vulnerable to all of the obstacles that the authors identify. These obstacles include overly strict regulations, fear, stigma and financial barriers (Andreae et al. 2016). They stem from numerous different, yet interrelated sources. As we have mentioned in the previous section, it is disputed by medical historians and ethicists whether and to what extent the political/societal happenings and regulations of the past contributed to a significant drop in LSD research for almost 40 years (cf. See Dyck 2015a, b; Smith et al. 2014). The classification of LSD as a Schedule 1 drug places LSD research into an extremely challenging regulatory environment. We agree with Andreae et al. that the result is a sort of "catch 22" scenario that creates a challenge to the scientific validity of clinical LSD trials. The catch 22 produced by U.S. drug policy could be characterized as such (EU's controlled substances' regulations being pretty the same in this respect): The policy defines controlled substances in Schedule 1 as having no "accepted medical use"—in that way, by the same, the scheduling itself obstructs efforts to investigate whether or not it actually has medical uses (Andreae et al. 2016).

Two remarks we would like to make here: First, it is worth noting that being placed on Schedule 1 does not *ban* research with LSD. That is, it is not an "absolute" obstacle, these laws and regulations do not explicitly prohibit such research to be carried out. However, it is beyond dispute that this scheduling might contribute to the subtle obstacles such as fear of stigma in the eyes of colleagues or the general audience, lack of funding, the very high costs of these substances, difficulties in obtaining the substances. Secondly, no justification explains treating stigmatized drugs such as LSD

differently than other similarly dangerous—but differently scheduled—drugs like cocaine, oxycodone, or Ritalin. What could be the reason for such differences? Is it simply the different history of research and medical and/or "recreational" use? These questions might be addressed not only by policy makers and regulatory bodies, but could be considered by the broader scientific community as well.

Having considered all these factors from a historical and contemporary perspective as well, we believe that besides and together with the above mentioned obstacles, today the most significant obstacle is the dearth of researchers who are interested in the field for various reasons. This, in turn, is neither solely a scientific, nor a political problem—it is simply a matter of choice in a set of cases. Naturally, we do not want to call into question that some researchers are actually discouraged by the formerly described obstacles. Nevertheless, it seems evident that the more professionals will join this field, the easier it will be to re-schedule these substances—thus overcoming many of these obstacles—and examine whether they are indeed as beneficial as professional voices suggested decades ago. As a final remark to this aspect, we also find it important to emphasize that if researchers—in the manner of evidence based medicine—would like to clarify concerns surrounding such research, they should primarily stick to non-activist, non-ideological notional and methodological means, and better not mix these aims (and should put aside the possibilities of regulatory and "cultural" changes their researches might (in)directly contribute to).

Fair subject selection

We find fair subject selection not to be a particularly important LSD-related issue. As mentioned above, LSD assisted psychotherapy applied as an addiction interrupter shows promising results, most prominently with regard to alcohol addiction. Therefore, more and broader research is needed to further assess this application form.

At the same time, if alcohol-addicts are treated as a vulnerable population in virtue of their impaired decision-making capacity, researchers must consider the general research ethics concerns about the inclusion of such patient populations. On the one hand, "over-protecting" this population (or patients suffering from other serious substance addictions) because REC members might raise concerns about such patients' capacity to consent into such research, could result in excluding patients. This might end up causing them harm by not allowing them to take part in research that might possibly be beneficial for them. On the other hand, underestimating the risk their impaired decision making capacity also could subject these participants to risks (Emanuel et al. 2000).

One certain challenge regarding the follow-up period is the unavailability of the substance for participants once the study has ended. This is so because LSD is accessible only in the frame of experiments due to its legal status in every country. That is, should a participant found the experiences beneficial therapeutically, they are denied to access it. The more it is problematic in case of patients whose conditions are regarded as therapy-resistant, who, at the same time, found ailment in this experimental therapy. We consider it an issue of justice in researches conducted on patients worth of further considerations.

Favorable risk–benefit ratio

Could the potential risks to individual subjects be minimized and well managed in prospective LSD trials? As mentioned above, according to the robust body of data, the addictive potential of LSD is minimal (Nutt et al. 2010; Das et al. 2016), the toxicity associated with dosages used in therapies being also negligible. However, the subjective experiences could be truly terrifying and disturbing:

> The effects of LSD are remarkably unpredictable. The effects are due to interruption of the normal interaction between the brain cells and serotonin. The usual mental effects are delusions, visual hallucinations, distortion of sense of time and identity, impaired depth and time perception, artificial sense of euphoria or certainty, distorted perception of the size and shape of objects, movements, colors, sounds, touch and the user's own body image, severe, terrifying thoughts and feelings, fear of losing control, fear of death, panic attacks, and so on. (Das 2016, p. 215).

Moreover, as the harm-reduction site, Erowid adds:

> LSD can precipitate strong, temporary changes in an individual's experience of life and reality. Even in low doses, it is a powerful psychoactive that can be significantly affected by experiences, set and setting. Recent experiences, especially strong ones, can have a substantial effect on a trip. Physically or psychologically unsettling events in the days before an LSD trip can blossom into more serious distress and trauma while tripping. (Erowid 2017)

This is certainly a big challenge that must be taken very seriously at all stages of the trial: at design phase, during the trial and through the follow-up period.

As a general remark, the harms stemming from the overwhelming nature of the subjective experiences could be reduced by providing a safe and supporting *set* and *setting*, i.e. adequate preparation and research environment for the participants. According to research findings addressing the potential mental harm triggered by LSD, the subjective

experience of the research participant is dominantly affected by the *set* and the *setting*. *Set* stands for the mindset—viz. the disposition, mood, actual thoughts, recent traumas, etc.—that will shape the experience from the within. This could be "set" to an appropriate form by an adequately designed psychotherapeutic/psychological predispositioning of the participants by mental health professionals. *Setting*, complementarily, denotes the outer environment—ranging from the color, arrangement, clothing of furniture of the trial site through the sound-system the site is equipped with, to the music played during the "trip" (cf. the following studies and sources in this respect: Carhart-Harris et al. 2016b.; Das et al. 2016; Erowid 2017; Gasser et al. 2015; Grof 1980.; Hofmann 1979; Kaelen et al. 2016a, b; Richards 2016).

A particular harm could stem from the fact that "individuals with a family history of schizophrenia or early onset mental illness should be extremely careful because LSD is known to trigger latent psychological and mental problems" (Erowid 2017). This possibility demands even more careful attention—the more in Phase I studies, recruiting healthy participants. If the study is to involve participants with such family history, the trial design should include on-going psychological monitoring and assessment, and compelling scientific evidence must be presented to justify the deliberate inclusion of such "risked" participants. Relatedly, as a result that people with addiction, suffering from mental disorders and the terminally ill potentially are at a higher risk of being harmed by the LSD caused mental experience, the importance of designing and providing a safe and supporting set and setting, one minimizing the potential psychological harms (often referred to as 'bad trip') should be stressed even more in case of trials involving such patients. For instance, the Gasser et al. (2015, p. 57) and Krebs and Johansen (2012, p. 997) articles offer actual examples of what actual measures were taken to mitigate such harm.

From the aspect of these mental risks, more particularly resulting from the unpredictable nature of the experience, the question could be asked: are LSD users (regular or occasional ones) or non-users subject to greater risks (cf. Andreae et al. 2016, p. 44)? Non-users might be at risk because of their lack of former experiences—by the same token, regular users might underestimate the risk based on their past experiences. Also, importantly, media (mis)information could distort the risk assessment of individuals as well, having the capacity to make LSD users and non-users over- or underestimate the risks. Consequently, a carefully designed and conducted informed consent process—one that may apply audio-visual vehicles as well, or personal accounts of user experiences to make future subjects with all means possible ready—might be applied to prepare participants for such experiences.

All in all, regarding the clinical and psychological risk-profile of LSD one could find numerous, evidence-based, methodologically robust sources—yet only concerning its usage in a controlled, clinical and/or experimental environment. However, given the fact that from the early 1960s LSD had become a widely used drug of recreation and continues to be available as a street drug, these clinical and experimental findings might be (and we believe: should be) complemented by data on health risks of its non-controlled, street usage (even if our paper is aimed to explore ethical issues of LSD research in a *controlled, clinical* environment). At the same time, gathering such information—or at least proper approximations and estimations about it—by means of e.g. epidemiological surveys might confront with the following methodological constrain: LSD being an illicit substance for recreational use in all countries around the world, the harms encountered by recreational users could be underreported.

This could be so because users, presumably out of fear of possible legal consequences, might be more hesitant to report to the medical professionals that their somatic or psychological symptoms are caused by their taking an illicit drug. If, in turn a hospitalized patient's such symptoms health care workers do not link to LSD intoxication (because the patient do not inform them about it, and they are not able to trace LSD's presence in the body, for instance), then on several occasions adverse effects of non-clinical LSD usage *might* remain unnoticed and un(der)reported. Therefore, clinically important information about LSD related harms might be unreachable by the community of health care professionals.

Independent review

Research ethics committee oversight is needed in these experiments for all the general reasons Emanuel et al. lists in their article. REC oversight might be a safeguard in the eyes of sponsors and policy-makers. It might help to overcome stigmas and address the fears, mis-information, and misunderstandings thereof. At the same time, in theory at least, the special legal status of the substance might incline REC members to fall prey to prejudices and biases towards LSD experimentation. Ideally, however, this will not take place.

Informed consent

Concerning studies with healthy volunteers, we see the following problems: The first is a question related to informed consent that Andreae et al. also pose. "*Are current users, past users, or nonusers capable of providing informed consent for a study that involves their using a controlled drug?*" (Andreae et al. 2016, 44) We consider this question concerning LSD to be especially important because, unlike marijuana, LSD could hardly—if at all—be produced at home. It implies that present or prospective users of LSD outside of medically supervised uses could possess LSD

from the black market—a condition many users might regard as unsafe. Thus, in turn, both for those who have previous experiences or those who haven't but are seeking for one, a chance to take part in such a study might implicitly "promise" an opportunity to try clinical grade pure substances. This chance might put their voluntariness into question; one might even regard such an opportunity as a sort of *undue inducement*.

Relatedly, it could be asked, both in case of healthy volunteers and patients, whether former experiences or their absence require individualized informing processes. That is, should different informing processes be applied in case of former, present or non-users? This could be especially problematic with LSD. The subjective experiences could be profound, especially for LSD- (or generally illicit substance-) naïve users. The unique drama of the subjective experience may require a peculiarly detailed manner of eliciting informed consent that may have to involve special means (e.g., short videos) to explain what to expect. This may be especially necessary because the media often circulates incorrect information on LSD, possibly conveying false expectations about such experience. All in all, this problem could be summed as such: though it is always a challenge to provide a meaningful informing process—one that fulfills the epistemic criterion of preparing the participants fully and truly for what they might expect, but stemming from the peculiar nature of the mental experiences caused by LSD, and its rare nature in the general population, meeting this epistemic criterion might be more complicated than in case of other (psychoactive) substances. However, during the informing process, this hindrance might be honestly acknowledged and communicated towards the participants.

An additional issue is whether the effects of the substance affect the decision making capacity during the experimentation. If the answer is in the affirmative, should this effect be understood as temporarily rendering the participant lacking decision making capacity, therefore unable to give or withdraw consent? Research findings suggest that indeed this is the case. People under the influence of LSD do have an altered decision making capacity. As, for example, the Erowid entry suggests, people in this condition are likely be subjected to "profound, life-changing spiritual insights" and this could "affect their decisions" (Erowid 2017). This possibility is relevant from a research ethics aspect for the following reason:

Subjects might change their mind about participating in the study and withdraw their consent under the influence of LSD (suppose, for example, in the midst of the "peak experience"). What should researchers do in such a case? Should they—considering the participant's withdrawal of consent as valid—allow participants to exit the experiment, and leave the trial site—even if that would interrupt the actual LSD session? Based on the available empirical data, we believe that in this case a paternalistic stance is ethically justifiable. That is, unless participants are proven to be devoid of LSD's mental and physiological effects by the health care professionals supervising the experiment, even in case of participants' "deliberately" asking for allowance to leave the experimental site, they should not be granted this opportunity. Given the fact that LSD is generally considered to last for 12 h, participants should also be informed about and ask to accept a *no driving rule* for the day after the ingestion, as well as to avoid some other activities (e.g. operating heavy machinery) for that day. Naturally, the reason and purpose of this measure should be thoroughly explained both written (in the IC sheet) and orally to the participants, particularly describing how long they will have remain under supervision while the effects of the substance wear off totally. This is for the sake of their protection—i.e. in the lights of the relevant data, though subjects might subjectively have the (false) experience that they have a command over their actions and are in a sound mindset (e.g. they assume they could drive home from the research site), but they actually might still be under (heavy) psychological influence, thus potentially endangering themselves and others. Thus, we believe that such conditions justify a rather paternalistic take on this issue.

Respect for participants

Confidentiality is especially important with regard to LSD research, given the peculiar legal status of the substance and the social stigma surrounding it. For example, because subjects may be discouraged because of the illegal status of the substances, and even if they decide to take part in research, they might have a very strong interest in keeping their participation secret.

"Respect includes permitting subjects to change their mind, to decide that the research does not match their interests, and to withdraw without penalty" (Emanuel et al. 2000). As mentioned in the above section as well, this is particularly relevant because of the peculiar nature of the experience for those having that for the first time and even for those who are familiar with it. Since, according to numerous studies (e.g. Szabó et al. 2014) and personal accounts (e.g. EROWID Experience Vaults), experiences could be new and different even for long term users. Briefly, this means that the LSD experience seems to be unique and unpredictable for the first-timer and regular users as well—it is easily imaginable that if a regular, but recreational user decides to join a controlled study, where evidently the *set* and the *setting* could be quite different than the person got used to, one even might encounter an unexpected and uncomfortable experience.

Thus, the experience could be of such kind that they might want to withdraw from further participation (e.g. after

the first session of an LSD trial that is designed to have multiple session). This right should be emphasized in the informed consent process and repeated through to the end of the trial.

Conclusions

This analysis purposed to explore the nearly seven decades of research with Albert Hoffman's "problem child", LSD from a research ethics perspective. The history of this experimentation is not devoid of questionable research practices, even scandalous or tragic events—at the same time, as existing literature suggests, LSD research on humans has a non-negligible potential for achieving clinical benefits for some specific patients' groups. Currently the most promising therapeutic potential of LSD is its usage as adjuvant psychotherapy in treating chronic alcoholism (sometimes even in case of patients considered therapy-resistant) and in decreasing symptoms of anxiety in terminally ill patients.

Generally, the scientific validity of studies needs to be improved in the future, both in terms of the number of participants and methodology, but there are some already existing good practices for the design, conduct and follow-up of ethically sound LSD trials. The classical, "golden standard" placebo-controlled and blinding designs for randomized controlled trials seem often hardly realizable with LSD that in turn could negatively affect, or at least limit the potential for improvements in the scientific validity of trials. Consequently, we suggest that further elaboration is needed to explore the limitations and potentials of different means of controlling LSD trials.

Fair subject selection does not seem to pose unique ethics issues and it highly depends on the aims of a given trial—e.g. depending on whether chronic alcoholic patients are considered as vulnerable population. However, for improving the risk–benefit profile of a planned study it is advisable to include patients' groups that might have a clinical benefit in participation, like studies did that focused on patients with serious alcohol addiction. The legal and regulatory status of LSD might also pose certain challenges in providing benefits to patients in case a study shew to be advantageous to participants and superior to already existing therapies—given that outside the study, LSD remains unavailable for such participants due to its illicit status. Thus, the ethical principle on the fair distribution of risk and benefits of a given human research study could be difficult to realize in the current regulatory environments.

In case of LSD clinical trials, the risk–benefit profile of the study could be influenced by individual characteristics, like the psychiatric profile of the individuals, thus the ethical design shall emphasize carefully developed eligibility criteria of research participants. According to the relevant literature, the physical risk profile of LSD in a controlled research environment is rather positive: the risk of significant physical symptoms, adverse reactions, toxicity and its addictive potential is very low. However, the psychological risk profile of LSD usage is considerable. Distress, mental discomfort, burdensome emotional experiences are frequently described phenomena, although rarely resulting in irreversible harm or trauma, particularly in an adequately supervised setting. These negative experiences and the mental risks are highly depending on the environmental and psychic disposition of the subjects, and shown to be controllable and minimalize for a significant degree. Both the environment and the researchers should be adequate to conduct such studies:

These psychoactive drug studies thus pose certain extra requirements on the infrastructure needs compared to a "traditional" a drug trial whose venue is usually a hospital or other clinical site. Minimizing the potential of emotional discomfort patients need to be mentally prepared and supported by a trained psychologist or psychiatrist (having *special* expertise in LSD and/or psychedelic assisted psychotherapy), and by constructing novel means of informing and even "entertainment" (see the above described importance of a proper and relaxing *setting*). Professionals need not only be knowledgeable, but at least as creative as well: For such means might range from audiovisual material designed by such health care, mental health, and harm-reduction professionals who indeed have an understanding of the "nature" of the LSD experience they want to prepare the participants for—e.g. because they have personal experiences with the substance—, and crafted by artists able to create such means reflecting the *psychedelic* experience; through the proper, supporting arrangement of clinical site furniture; to operating Hi-Fi systems with carefully selected music. These aspects are particularly important in case of experiments on LSD's adjuvant psychotherapeutic use.

It is ethically essential to achieve an advantageous risk–benefit ratio in such a study, therefore exclusion and inclusion criteria must be thoroughly considered by researchers and strictly monitored by RECs. Beyond some usually applied exclusion criteria for drug trials, like age limits and some serious somatic diseases, in case of LSD trials, people with known psychotic diagnosis (or in the family), people with bipolar disorder and some other psychiatric conditions (e.g. higher than low suicide risk) should, as a general rule, be excluded from study participation—never to be overruled in trials with healthy volunteers. This general exclusion criteria should be overruled only—evidently only in Phase II or Phase III studies—if compelling scientific evidence suggests that such participants are specifically sought for because the LSD trial is expected to provide benefits and be responsive specifically for these populations conditions and needs.

Having touched on the issue of justice with regard to the unavailability of LSD outside the trial, we believe that the indeed enormous changes—in its research, clinical, and jurisdictional aspects stemming from the former ones—the medical and political community witnessed with regard to (medical) marijuana might be apprehended as a parallel for such future of LSD.

Informed consent process should be tailored not just to participants needs, but also to study characteristic. Information provision should be continuous and embedded in ongoing psychological monitoring during and after the study. Research participants must be informed that their right to leave the study (immediately) will be suspended until they are assessed by the health care and mental health professionals to be totally devoid of the psychoactive effects. Confidentiality and data protection requirements should be carefully checked during the REC approval process, particularly as the peculiar legal and regulatory status of the substance necessitates an even stricter protection of participants' data.

All in all, we do consider the possible benefits, if carried out in a properly designed, conducted, overseen and carefully monitored manner, to outweigh the risks. What is more, in some areas—most prominently as addiction interrupters and in case of terminally ill patients—these benefits seem so promising, with few other therapies being able to reach the same effect, that the continuation of such research do seems imperative.

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