Journal of Addiction Science

https://doi.org/10.17756/jas.2022-057

Review article

Open Access

Could Psychedelics Treat Personality Disorders?

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Received: August 24, 2022
Accepted: December 01, 2022
Published: December 03, 2022

Citation: Iliff J, Moslehi S. 2022. Could Psychedelics Treat Personality Disorders? *J Addict Sci* 8(1): 10-19.

Published by United Scientific Group

Abstract

In this paper we review the existing historical literature on the use of classical psychedelics to treat personality disturbance and disorders. We address the findings and major limitations of that dataset. Finally, we ask which, if any, personality disorders are most suitable for further investigation and whether this is worthwhile. There are significant theoretical risks and difficulties but considering the clinical burden further investigation, including preliminary trials, is indicated.

Keywords

Personality disorders, Schizotypal, Paranoid, Personality, Emotionally Unstable, Antisocial

Introduction

Personality disorders (PD) are defined as "a pervasive pattern of maladaptive traits and behaviours beginning in early adult life, leading to substantial personal distress or social dysfunction, or both, and disruption to others" [1]. Researchers have suggested that the core disability in this phenomenologically varied group are problems in relationships [2] with the consistent features between the PDs being "substantial impairment of interpersonal function, identity problems, and recognizable social dysfunction. [3]. People with PDs suffer have increased incidence of suicide and homicide [4], and comorbid mental health conditions [5-7]. The financial cost to society is high, including high frequency and intensity of healthcare needs, frequent institutionalization, lost working hours and the cost of interventions [1, 8, 9].

Cost-effectiveness of current therapeutic interventions remains dubious [10, 11]. Evidence for pharmacotherapies is poor [3, 12] while psychotherapies have a stronger evidence base [13]. Dialectical behavior therapy and psychodynamic therapy are effective for reducing certain elements, such as suicidality and self-harm, in emotionally unstable PD [14]. Cognitive and psychodynamic therapies are useful for cluster C PDs [15].

Overall, there is no convincing evidence that measures of the core domains of the diagnosis, or functional measures of impairment in work and social settings, are rectified with existing treatments [3, 16, 17]. There is significant demand for novel treatment options for PDs.

Classical psychedelic drugs are partial serotonergic agonists including psilocybin, dimethyltryptamine (DMT), d-lysergic acid diethylamide (LSD), and mescaline. Administration produces multi-faceted changes in the subjective ex-

perience of individuals including perception, mood, intensified emotions, and at higher doses, dissolution of the sense of self and hallucinations [18, 19]. They do not have direct dopaminergic action, which likely explains their low dependence liability [20].

The mechanism of these effects remains poorly understood. Classical psychedelics act primarily through the 5HT2A receptor, with additional agonism at the 5HT2C, 5HT1A, 5HT4, 5HT5, 5HT6, and 5HT7 receptors [21]. Activation of these receptors activates signaling pathways that alter brain function as measured by fMRI and BOLD imaging techniques. There is a global increase in cortical functional connectivity [22] as well as reduced functional connectivity and blood flow in regional networks including the salience network and default mode network [23, 24].

While psychedelics' effects are mediated predominantly via the 5HT2A receptor agonism, as demonstrated by selective 5HT2AR antagonism with Ketanserin that blocks the psychoactive effects, they also have dopaminergic and glutamatergic effects [25].

Psilocybin does not bind with dopamine receptors directly, but it does upregulate dopamine in the striatum [26]. In addition, LSD interacts with dopaminergic receptors directly [27, 28]. At higher doses LSD stimulates dopamine D_2 receptors, as well as D_1 and D_4. This appears to underpin the more stimulated subjective effects reported in LSD use compared with psilocybin. Dopaminergic effects likely contribute to the psychotomimetic effects of classical psychedelics, and indeed LSD administration has been a model for psychosis since its invention.

By the middle of the 1960s over 40,000 trial participants had been administered LSD and thousands of scientific articles had been published [29]. Most of the trials reported efficacy of the drug for a range of mental health conditions including neuroses, addiction, and PDs [30]. However, outcomes of patients with psychotic disorders such as schizophrenia were reported as highly variable and often worsened. All studies were highly lacking by comparison with modern, rigorous trial requirements, including absence of controls, blinding, report of adverse outcomes, statistical analysis, and follow up of participants.

Since 2006 a second period of trials administering psychedelics, almost entirely psilocybin, to humans has begun. These trials come as part of a reconsideration for psychoactive medications that are illegal in the recreational sphere for use in the treatment of mental illness, including 3, 4 methylenedioxymethamphetamine; and ketamine, the NMDA-R antagonist, with possible nicotinergic or dopaminergic antidepressant activity, now licensed for depression [31].

Classical psychedelics pilot studies have demonstrated preliminary safety and hinted at efficacy of psilocybin to treat anxiety in end-of-life care [32-35]; obsessive-compulsive disorder [36]; alcohol dependence [37] with effects sustained at 36 weeks; tobacco addiction [38], with effects sustained at 12 months [39]; and treatment resistant depression [40], with effects sustained at 6 months [41]. Three studies have also shown preliminary safety and possible efficacy of the DMT containing brew Ayahuasca for depression [42, 43], including a randomized controlled trial [44].

All trials since 2006 have reported psilocybin to be psychologically and physiologically safe during its acute effects and after initial follow-up. In the 175 patients on whom data has been published to date, adverse events have included headaches, transient anxiety and transient nausea with effects more common at higher doses. There have been no serious adverse events. Physiological effects are mild and transient [38, 45]. Trials of ayahuasca report similar side effects plus vomiting in around 50% [42-44]. The long-term effects of psychedelics remain unstudied although safety remained high at 6-12 months (37, 38, 41, 46). Psychedelic use is not associated with increased incidence of mental health conditions [47]. Psychedelic drugs have a low abuse liability [48-52].

Methods

The MEDLINE database was searched using the terms LSD, lysergic acid diethylamide, psilocybin, psychedelic, hallucinogen and personality disorder, PD, schizoid, schizotypal, paranoid, histrionic, borderline, emotionally unstable, obsessive compulsive, dependent, avoidant, narcissistic, antisocial. Combinations of the above terms were used as appropriate. Where original papers were inaccessible the Multidisciplinary Association for Psychedelic Studies (MAPS) psychedelic trials database was used [53]. This contains a complete index and access for studies investigating therapeutic use of psychedelics between 1931 and 1995. Bibliographies of all relevant studies were manually searched. The search was conducted between 02/01/19 and 01/10/19. Only clinical trials and studies conducted on humans with PDs were included. 5 published clinical trials and one unpublished study, documented in a Newsletter to MAPS, were included as per this method. Synthesis of these studies here is highly simplistic - taking aggregates of outcomes for patients where comparable (e.g., benefit, no benefit or harm, harm) between studies, as well as qualitative reports of historical researchers that inform the overall conclusion.

Results

The use of psychedelics to treat personality disorders

Introduction and general criticisms

Five studies from the first phase of psychedelic research reported having treated PDs with classical psychedelics (see Table 1. They are of varying degrees of quality and suffer from many of the faults of research from their era (1958-1967). Presented here are some general criticisms that apply to all papers. Small numbers of PD patients were tested, making aggregate analysis of limited value and meta-analysis impossible. Moreover, diagnostic terminology and patient descriptions were often imprecisely applied and otherwise differ significantly from modern classifications used. Where possible this has been adjusted for by a comparison between diagnostic criteria of the time and present day. In all papers simplified and subjective metrics of outcomes without validated measures were used, and there is an absence of statistical analysis. As such the con-

Table 1: Summary of historical studies.

Study	Subjects	Positive outcome	Positive outcome proportion	Diagnosis	Treatment	Adverse effects	Frequency of adverse effects	Sessions
Cohen and Eisner, 1958	17	12	0.7	PD or trait	LSD and two other variants (25 mcg - 250 mcg)	Anxiety and depression	Not reported	1 to 16
Chandler and Hartman, 1960	110	93	0.85	Anxiety, depression, PD/ trait and Schizophrenia	LSD (25 - 150 mcg)	1. Transient state of panic. 2.Paresthesias to pain	Not reported	1 to 26
Whitaker, 1964	100	65	0.65	Psychoneuroses, Sexual disorders, PDs and Schizophrenia	LSD (100 - 200 mcg) and Nicotinic acid (200 mg)	Transient increased distress	0.14	Not reported
Baker, 1964	150	100	0.6	PD (Paranoid PD was excluded)	LSD (2000 mcg)	Not reported	Not reported	Not reported
Savage, 1967	243	118	0.49	PD/ trait	LSD (200 - 300 mcg) +/- Mescaline, 70/30 O_2 and CO_2	Worsened symptoms (unclear)	2 out of 243	Not reported
Gasser, 1994-95	121	69	0.57	PD and other psychiatric diseases	LSD (100 - 400 mcg) and MDMA (125 mg)	Unclear	Not reported	LSD (1 to 16); MDMA (1 to 4)

clusions that can be drawn are highly limited. In all papers except one, by Savage et al. [54], concurrent psychotherapy was used as a conjunction to therapy and is a potential confounder to the effects of the drug's administration alone. Concurrent talking therapy was used in all but one study [55]. The length and nature of follow-ups to assess progression over time differed significantly between papers and within papers and was in some cases not documented.

Cohen and Eisner, 1958

22 patients were reported as treated by Cohen and Eisner [56] with LSD as well as two variants. The patients had a number of different diagnoses ranging from "neurotic depressions, anxiety states, and character disorders to borderline schizophrenia". They were treated weekly, although intervals were extended for those with more treatment sessions. An initial dose of 25 mcg, taken orally, was given rising subsequently in increments to 100 - 150mcg. 1-acetyl-d-lysergic acid diethylamide and 1-methyl-d-lysergic acid diethylamide were also used on 5 and 1 occasions respectively with effects estimated by the authors at equivalent to 200 - 250 mcg of LSD. Between 1 and 16 treatment sessions took place for individual patients, with an average of 4.6 per patient.

During the drug session somatic symptoms are reported in cases, as well as anxiety which was "excessive" in some instances. Heightened anxiety and depression were reported in the post-drug period in some patients. Frequency of adverse effects was not reported. No episodes of drug induced psychosis were reported in this study, however the author reported a separate case of a compulsive personality disordered patient who had a response to LSD (50 mcg and 100 mcg) "resembling paranoid schizophrenia" in which, although there was no functional impairment "delusions in the religious area and surrounding the drug persisted".

Follow-up ranged from 6 - 17 months with "continuing success in behavioral adaptation" being the crucial criteria for improvement. Improvement itself was defined as 'objective evidence of a better situational adjustment' as judged by the patient, a close companion and two doctors.

A group of 17 subjects with PD or traits who did not have comorbid contraindications for psychedelics, such as schizophrenia, were reported. 12 out of 17 were judged to have improved where confounding comorbidities are included (7/12 when comorbidities are excluded). Two had narcissistic PD but their major indication was a depressive reaction so the efficacy for PD traits in these patients remains unclear. Four patients had passive-aggressive personality, which is no longer in the DSM and does not align with any modern classification, of which all four were judged to have improved [1, 57]. Of this conversion "reaction" was comorbid in one and chronic anxiety with alcoholism in another - both of which could confound suggestions of efficacy for PDs in these patients. Both patients with emotionally unstable PD showed improvement. Further, one patient described as having a "depressive reaction in an emotionally unstable person" was described as unimproved. Three patients with 'compulsive personality' were all reported as improved. Of two patients described as having 'hysterical personality' one has improved. Hysterical personality was replaced by histrionic in the DSM-III [58] and the criteria remain broadly similar between DSM-I and V, although the wording has changed. two patients with inadequate and schizoid personalities were reported with neither showing improvement and this despite having 16 and 5 drug sessions respectively. one person with paranoid personality, which features in the DSM-I and is comparable to modern DSM-V criteria, was trialed with no improvement.

The general criticisms of these historic papers apply. In this study there are problems with diagnostic terminology. For example, 'narcissistic personality' which is not part of the

DSM-I and cannot be compared to modern criteria, is used to report results.

Chandler and Hartman, 1960

Chandler and Hartman [59] reported treating 110 patients with a range of diagnoses. This included those with anxiety, depressive and schizophrenic 'reactions', and a significant proportion with "PD/trait", who were treated with 690 LSD administrations at a range of doses that increased from as little as 25 mcg to 150 mcg (typical first dose of 50 mcg). Across all patients the nature of the therapy varied substantially. Broadly a 'psycholytic model' (lower dose, psychotherapeutic structure) was used with concurrent non-drug psychotherapy alongside sessions in which LSD was administered. Sessions upon administration of LSD ranged from totally unstructured to more structured sessions with oriented patients, although analytical and intellectual language was minimized. These drug sessions lasted for between 4 - 4.5 hours before the effects were terminated with secobarbital or chlorpromazine. The intervals between drug sessions also varied, from twice a week to approximately once a month, with a typical interval of 2 weeks between which several psychotherapy sessions would be administered. Patients had between 1 and 26 drug sessions with an average of 6.2 sessions. Adverse effects reported included a transient state of panic at higher doses as well as a range of transient somatic symptoms from paresthesia's to pain. The incidence of either was not reported.

Measurement of outcomes were subjective assessments made by the therapist. In total 4 patients showed 'outstanding improvement' (numerically rated +5); 20 showed 'Marked improvement' (+4); 25 showed 'considerable improvement' (+3); 23 showed 'some improvement' (+2); 15 showed 'slight improvement' (+1); 19 showed 'little or no change' (+0); 3 were 'slightly worse' (-1) and 0 were 'definitely worse' (-2). There was no control group.

Of these there were 25 with PD who showed 'some improvement' (+2) on average. 10 of these were diagnosed with schizoid PD with an average of improvement of +1.9 (+2 equated to some improvement). Three were diagnosed with Paranoid PD with an average of improvement of +1 (equated to 'slight improvement'). Eight patients were diagnosed with compulsive PD, which is not found in the modern DSM-V but maintains broad similarity with the modern-day Obsessive-Compulsive PD, with an average of improvement of +2 (equated to 'some improvement'). Four patients with Cyclothymic PD were described with an average of improvement of +3 (equated to 'marked improvement'). This is also not found in the modern DSM-V, and the DSM-I description bears comparison only to the emotional lability seen in Borderline or Emotionally Unstable PD.

Eleven patients with 'personality trait disturbance' were reported whose outcomes were rated +1.3 (between slight and some improvement) on average. One patient with emotionally unstable personality trait was reported with +2 (equated with 'some improvement'), this DSM-1 'trait disturbance' is the diagnostic equivalent of the DSM-V emotionally unstable PD, although the criteria is more behaviorally focused and lacks symptomatic criteria. 7 'passive-aggressive' and Three 'inadequate' personality trait patients were reported with averages of +1.3 (between slight and some improvement) and +2 (some improvement), respectively. Three patients with Antisocial reaction, which falls under the umbrella term of sociopathic personality disturbances, were reported with an average of improvement of +2 (equated to 'some improvement'). This diagnosis broadly aligns with the DSM-V classification of antisocial personality disorder.

There was no further analysis either of each of these PDs and trait disturbances or as a group, other than the outcomes as averages shown above. The exception to this is some subjective reports. The authors noted that "We have found that the patients with character trait disturbances do most poorly. The immature, generally unstable, inadequate, or passive-aggressive personalities do not appear to do well with the drug". They also noted that "This is in keeping with the findings of Cohen and Eisner". Regarding PDs more specifically they concluded that "the subgroup that did best was that of the cyclothymic personalities" and that "The emotionally labile person is better able to make use of the LSD-25 experience than the more rigidly defended person". They also described that "With LSD as an aid, it has been possible to 'reach' and work with patients who are otherwise unresponsive to psychotherapy. This includes a number with severe characterological defense systems of the obsessive compulsive and acting out type".

Whitaker, 1964

In 1964 Whitaker published a study of 100 patients treated with LSD with a range of conditions including psychoneuroses, sexual disorders, and schizophrenia [60]. A control group of sorts was implemented. This consisted of patients treated in the last few years, matched for diagnoses and durations, based on not wanting to deny suitable patients drug assisted treatment following positive initial results. Drug administration was preceded by 3 to 6 'interviews', extensive journalling, and preparation. The drug was given between 100 and 250 mcg IM or IV rather than orally with 200 mg nicotinic acid. The effects were terminated 5 hours later with chlorpromazine (100 mg) and amylobarbitone (100 mg). Interpretation and integration of the experience were encouraged. With regular psychotherapeutic sessions, also called 'interviews', between drug sessions. An average of 3.28 drug sessions were administered. Assessment of outcomes was by subjective agreement by the clinician and patient.

The paper's definition of 'successful' included "at least almost complete relief from symptoms, or cessation of abnormal or anti-social motivation in PDs, together with a comprehensive apparently consistent awareness of the psychogenesis." Recovered was defined as "complete freedom from symptoms and thoroughly complete understanding of themselves". Borderline was defined as "definite symptomatic improvement or comprehensive consistent awareness of the psychogenesis". Unsuccessful results included where patients were lost to follow-up, "unaffected by treatment" or had "doubtful improvement".

Taking the paper's results 47 patients had successful treatment, 18 borderline outcomes, and 35 failures. Patients in the control group also benefited with 12 patients successful, 30 patient's borderline, and 58 failures. Subgroup analysis is absent.

Of 100, 27 patients described as having PDs were treated with LSD, including 2 patients with anorexia nervosa. Twenty two patients had diagnoses consistent with modern classifications of which 17 showed improvement [61]. Of these 13 patients had hysterical PD: 1 of whom was recovered, 8 were much improved, 1 had doubtful improvement and 3 evaded evaluations. Nine other patients had 'Antisocial character' PD: 1 of whom recovered, 4 were much improved, 3 were improved and 1 evaded evaluation. Three patients with 'psychopathy personality' were also reported: 1 of whom had doubtful improvement and 2 of whom evaded evaluation. Despite not being recognized in the DSM-V, 'psychopathic personality' falls under the DSM-I term for Antisocial PD, 'Antisocial Reaction'.

Adverse reactions were reported for the cohort but not specifically for personality disordered patients. This included one case of 'abreaction and regression' after a treatment series without response to the drug. Fourteen cases were terminated prematurely with amobarbital due to uncontrollable acting out and intolerable distress, 6 of these showed no improvement in outcome and 4 evaded further treatment. The other most significant side effect was 'transient increased distress' between sessions reported in a third of patients. In one case a patient experienced "recurrence of the LSD effect" the subsequent day. No patients requested additional LSD beyond what was administered.

Baker, 1964

E. Baker [55], of Toronto, reported treating 150 patients with a range of non-psychotic diagnoses (unspecified). Doses of LSD up to 2000 mcg intramuscularly were used and improvement was reported in approximately 2/3rds of all patients. A selection of the 150 patients had PD. Of these only 'compulsive PD' falls close to the modern classification. Raw data, including number of PD patients and their improvements, is unavailable. Baker noted that the LSD allowed "Frequently enough, the patient [to come to] the core of his neurosis, or PD but that "Finding the problem is of course different from solving it." He also listed "paranoid personality" as a contraindication to use of LSD.

Savage, 1967

Published in 1967, Savage et al. [54] conducted a very large study of 243 patients at two locations in Baltimore in the United States. Preparations sessions over 1 - 2 months included interviews and use of a 70/30 mix of O_2 and CO_2 to familiarize the patient with altered states and engender trust within the setting and with the therapist. Drug sessions followed using between 200 and 300 mcg of LSD augmented in some cases by between 200 and 400 mg of mescaline. Morning sessions focused on introspectiveness and lying with eyeshades was encouraged while during the afternoons looking at external stimuli like relevant objects or art was encouraged. A 'Psychedelic' format (high dose and no attempt at interpretation or talking therapy) was used. Two therapists, one male and one female, including a doctor, were present for the drug sessions. Follow up interviews took place at one, two, four, eight and twelve weeks, and at six months. The first 113 of the patients were sent questionnaires as part of follow-up. Ratings were otherwise subjective reports along a 5-point scale by a team of clinicians, one of whom had seen the patient before and after therapy. The scale consisted of -1 - Worse, meaning "illness exacerbated by treatment"; 0 - No "clinical evidence of" improvement; +1 - some improvement meaning "a decrease in severity of symptoms without complete amelioration"; +2 - substantial improvement including "partial improvement of symptoms with significant attitude changes", and +3 - marked improvement meaning "No discernible pathology."

One hundred and eighteen patients had PDs or 'personality disturbance', in all 94 had improvement, 22 had none, and 2 worsened. Of 7 with 'schizoid personality': 2 worsened, 2 saw no improvement; 2 saw some improvement, and 1 had substantial improvement. Of 5 patients reported with 'paranoid personality' all 5 had no improvement. Of 42 who had 'immature personality', 8 were reported as having no changes, 15 had some improvement, 12 had substantial improvement and 7 had marked improvement. This is not a classification found in the modern DSM-V but is a nonspecific umbrella term used in the DSM-I that remains inconsistent with the modern classification. Of 7 patients with 'emotionally unstable personality' 2 saw no improvement, 3 had some improvement, 1 had substantial improvement and 1 had marked improvement. Of 26 patients with 'compulsive personality' in 2 no improvement was seen, in 11 some improvement was seen, in 8 substantial improvement was seen and in 5 marked improvement was seen. Of 11 people with 'hysterical personality', 2 saw no improvement, 2 saw some improvement, 4 saw substantial improvement and 3 saw marked improvement. Three patients with 'antisocial personality' were reported, 1 of whom had some improvement, 1 of whom had substantial improvement and 1 of whom had marked improvement. Those in the category of 'personality disturbance, other' included 17 patients, is also included, 1 of whom had no improvement, 10 of whom had some improvement, 3 of whom had substantial improvement and 3 of whom had marked improvement. This DSM-I group is a catch all for diagnoses that do not fit traditional categories and is no longer in use.

Gasser, 1994-95

A newsletter of the Multidisciplinary Association of Psychedelic Studies by Gasser in 1994-95 [62] reports a follow-up study on the use of LSD, and 3, 4 methylenedioxymethamphetamine (MDMA), to treat PDs. It collected data on 121 patients of all diagnoses followed up after treatment conducted between 1988 and 1993. A 'psycholytic' model was used (described here as low dose to medium dose, group setting and continuous verbal therapy) with periods of silence that reflected other 'psychedelic' paradigms (described here as high dose, use of music and silence). Of three therapists involved two used MDMA (3 - 4 sessions of 125 mg), a non-classical semi-psychedelic, in combination with LSD (100 - 400 mcg). The other used MDMA alone. The average duration of ther-

apy was approximately three years but ranged from as little as one session to over nine years. There were an average 70.3 concurrent non-drug sessions. Drug sessions varied from 1 to 16 with an average of 6.3 sessions, or 1 every 5 months. The treatments were reported to be safe, with negative feelings frequent within sessions, but only one patient having them recur after the event. None were hospitalized during their treatment period, although 1.6% were hospitalized after.

Results were gathered by means of a questionnaire after a follow-up period of on average approximately two years - although this length was highly variable. 90.9% of patients reported subjective improvement after treatment. 64.5% said the sessions were important emotionally, and 56.2% said they were important for interpersonal relations. Eighty-one percent reported improved relationships with family and 3.3% reported worse.

Thirty-eight percent of the 121 had a diagnosis of PD and borderline PD was diagnosed "rather often" within this group. The author notes that psycholytic treatment with psychedelics was "well suited" to treatment of borderline and narcissistic PD. However no raw data or further analysis of subgroups is available. Ultimately however this paper is not peer reviewed and as the author notes does "not offer objective proof of the efficacy of psycholytic therapy" due to the design of the study.

Aggregate analysis

Between all papers 184 PD patients were reported. Raw data was not available from Chandler and Hartman [59]. Taking a total from Savage, Whitaker and Cohen and Eisner's papers 125/159 had improvement (78%) while 2 worsened and 4 were lost to follow-up. Within those DSM-I classifications analogous to DSM-V classifications this number drops to 69/94 improved (73%) (Table 2). Taken together there is more evidence to suggest psychedelics might be useful in Cluster C and Cluster B but not Cluster A disorders.

Looking at Cluster A, in the papers discussed here patients with 'paranoid personality' six patients showed no improvement and in Chandler and Hartman's paper 3 patients showed an average of 'slight improvement'. One author also listed 'paranoid personality' as a contraindication for use of LSD. Schizoid patients fared better with 10 patients in Chandler and Hartman's paper averaging some improvement while in Savage, Whitaker and Cohen and Eisner's 2 worsened, 4 were unimproved and 3 improved. 'Schizotypal personality' might also seem unsuitable given its mild psychotic elements and the recommendation based on historical literature that psychosis is a contraindication for investigation with psychedelics [30].

Of Cluster B, although one author noted 'narcissistic personality' is well suited to psychedelic therapy, the difficulty in treating and the limited data available here makes this a less appealing candidate for further investigation. Of those with 'hysterical personality' (now histrionic) of 26; 20 improved, 3 did not, and 3 evaded. Of those with 'antisocial personality' there were 3 patients in Chandler and Hartman's paper who had an average of 'some improvement'; while in the other papers mentioned 15 patients; 12 improved and 3 evaded (including those subclassified as 'psychopathic personality'). Of those with 'emotionally unstable personality' there across all the papers where raw data was available 11 patients were reported with 8 improved and 2 unimproved, and one unimproved "depressive reaction in an emotionally unstable person".

Of those with 'compulsive personality', analogous to obsessive-compulsive PD, there were 8 patients in Chandler and Hartman's paper who had an average of 'some improvement'; while in Savage, Whitaker and Cohen and Eisner's papers of 29 patients, 27 had improvement and 2 were unimproved.

Discussion

How might psychedelics benefit personality disorder patients?

Treatments of PDs should have a "robust effect on core features for an extended period of time." The first thing to note is that psychedelics do seem to create enduring changes to psychopathology, like addictions and depression, but also to personality. For example, a double-blind study in psychiatrically well humans showed psilocybin increases the personality domain of openness with effects lasting for one year [63].

Interpersonal relationships specifically, which are a core dysfunction in PDs, appear to be one of the areas that psychedelics effect in an enduring way. Another double-blind study, also in psychiatrically well patients, showed when combined with spiritual practice higher doses of psilocybin increased

Table 2: Integration of compatible historical studies.

Outcomes for PD fitting modern classification (from 54, 56, 64)							
	Cluster A		Cluster B			Cluster C	
Outcome:	schizoid	paranoid	borderline	antisocial*	hysterical	compulsive	Total:
Improved	3	0	7	12	20	27	69
Unimproved	4	6	2	0	3	2	17
Worsened	2	0	0	0	0	0	2
Evaded	0	0	0	3	3	0	6
Total:	9	6	9	15	26	29	94

*Including psychopathic

prosocial behaviors and interpersonal closeness at six months. This effect was seen alongside amelioration of other positive psychological functions including life meaning, purpose, forgiveness, and coping [33].

More generally psychedelics may benefit comorbid conditions like depression, anxiety, substance abuse and appear to mitigate suicidality - which is a particular concern in borderline PD [41, 64, 65].

Which personality disorder is most suitable for investigation?

Based on the highly limited data available this section contains practical reasoning to refine which PD is most suitable for investigation. Specifically, we look at histrionic PD, antisocial PD, borderline or emotionally unstable PD, and obsessive-compulsive PD.

Histrionic PD is in the 21st century a dubious diagnostic category, with uncertainty preceding its inclusion in the DSM-V and a major drop off in research on the topic since the new millennia [66]. The clinical burden of those with histrionic PD is also relatively low with a prevalence of as low as 0.3% using conservative diagnostic rules [67]. Difficulties in recruitment for studies might be compounded by the frequency of histrionic personality types who don't feel treatment is suitable.

Those with antisocial PD and in grave need for new treatments, in large part due to the high disease burden, including the very high cost of illness to society [11, 68] and high prevalence of the condition - 3.8% by conservative diagnostic rules [66]. There is a strong need for new treatments for antisocial PD. Particularly there is very limited evidence that pharmacological treatments to date are beneficial, such that NICE guidance states that drug treatment for this condition or its associated behaviors are not recommended [69]. Practical difficulties may arise, however, in recruitment for studies treating this condition with classical psychedelics, and in getting these patients to engage with the treatment [3].

Borderline PD in many ways appears a good candidate for application of psychedelic therapy. This condition produces a high clinical burden due to its high prevalence (2.6% by conservative estimates) and high cost to society [70]. The cost to the individual is also marked, most ostensibly by the high suicide attempt rate and high lethality, with 10% of patients successfully taking their own life [71]. There is also an absence of effective pharmacotherapies, such that NICE guidelines state that drug treatment should not be used to treat borderline PD or its behaviors [69]. The major concern with use of classical psychedelics in borderline PD is that 20 - 50% of these patients report psychotic symptoms [72]. Based on historical data new studies using psychedelics are recommended to screen out those with personal or family histories of psychosis [30]. Rigorous screening may be sufficient to circumvent this concern. A second concern is the comorbidity of those with borderline PD for addiction [73]. The twin level pharmacology of LSD - stimulating 5HT2AR at low doses, and 5HT receptors and dopamine receptors at higher doses may be significant here. LSD and classical psychedelics appear to have a low abuse liability [74, 75]. However repeated, higher dose abuse has a theoretical dependence liability given the role of striatal dopamine and D_2 receptors in addiction [76].

It may be possible to maintain therapeutic efficacy with less dopaminergic compounds like psilocybin, and at lower doses, the so-called 'psycholytic' model of therapy with psychedelics [77]. Thereby reducing the tangible risk of triggering or exacerbating psychosis, or the more theoretical risk of addiction, seen at higher doses.

Modern day trials with psychedelics suggests they may be safe in and may better address the symptomatology of obsessive-compulsive PD [32-36], particularly states of high neuroticism and low openness [77]. Obsessive-compulsive PD has a relatively high prevalence of 2.4% [78] however it is generally a less impairing disorder than other PDs, including borderline PD [17]. This relative functionality seen in many patients may make it a less urgent initial candidate for investigation.

Drug-assisted psychotherapy for personality disorder: A recommendation and pilot study design

Due to the high clinical, societal, and individual burden as well as the absence of current effective pharmacotherapies we suggest borderline PD as an initial candidate for a small pilot study to investigate safety and later efficacy in this group of patients. Antisocial PD and obsessive-compulsive PD are also good candidates. We propose an open label phase I pilot study on 20 patients with borderline PD that has proven refractory to one or more existing psychotherapies. Rigorous screening for any present or historical psychotic symptoms should be enacted during recruitment. Psilocybin at a moderate dose could be administered as drug assisted psychotherapy in conjunction with preparatory and 'integration' psychotherapy sessions with one or two drug sessions (within one week). Follow-up using standardized questionnaires could be asked at 1 week before drug administration and 1 week, 12 weeks, and 6 months after.

Conclusion

Personality disorders are highly varied but share common features, not least difficulties with interpersonal relationships and a grave need for new treatments to tackle these debilitating conditions. In this paper we have presented the small and highly limited historical literature available that suggests a modern day investigation of the use of psychedelics, such as psilocybin, for these conditions. Despite theoretical risks and difficulties, we argue that this is warranted, and that borderline PD is the most suitable condition to investigate initially.

Acknowledgment

We are grateful to all the researchers mentioned in this paper.

Conflict of Interest

Authors declare no conflict of interest.

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