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A Plea for Nuance: Should People with a Family History of Bipolar Disorder Be Excluded from Clinical Trials of Psilocybin Therapy?

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Abstract

Background: As the field of psychedelic therapy grows, it is vital to consider who can safely engage with psilocybin therapy. In most modern clinical trials of psilocybin therapy, individuals with a family history of bipolar disorder (BD) have been excluded from participation because of their genetic predisposition for developing BD.

Review: Case studies and survey data shed light on the risks of psilocybin therapy among those with a family history of BD in the absence of data from modern clinical trials. We review existing evidence that could inform risk stratification for these individuals, including genetic proximity to the affected relative, BD type, age at onset in the relative, and participant age. Hypothesizing that the risk of developing BD may predict the risk of developing serious adverse events when engaging with psilocybin therapy, we propose a risk stratification tool to be utilized when determining the relative risks of psilocybin therapy to those with a family history of BD in the context of clinical trials.

Conclusion: Balancing the need for effective treatments against the potential for serious adverse events in those undergoing psilocybin therapy with a family history of BD, we argue for caution in psychedelic clinical trials but not outright exclusion of these individuals. Our risk stratification tool allows for more nuanced inclusion and exclusion criteria.

Keywords: bipolar disorder, psilocybin, mania, psychosis

Introduction

Growing evidence suggests that psilocybin, the active ingredient in hallucinogenic mushrooms, combined with psychotherapy, can rapidly and durably improve symptoms of unipolar depression.[1–5] Psilocybin received breakthrough status designation by the United States Food and Drug Administration (FDA) in 2018,[6,7] opening a potential pathway toward widespread legalization for mental health treatment. As the field of psychedelic therapy grows, it is vital to consider who can safely pursue psilocybin therapy. In most modern clinical trials of psilocybin therapy, individuals with a family history of bipolar disorder (BD) have been excluded from participation.[8,9]

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First-degree relatives of individuals with BD have an approximate 10-fold increased risk of developing BD themselves compared with the relatives of unaffected individuals.[10] The implied concern is that psilocybin therapy may increase the risk of serious adverse events, such as unmasking or precipitating BD or prolonged psychosis, in those with a genetic predisposition for developing BD.[8,9] This common exclusion underscores the dearth of safety data for psychedelic use in those with a family history of BD and does not account for varying degrees of individual risk based on clinical phenotype and heritability data.[11]

The problem with uniform exclusion of those with a family history of BD is twofold. First, we may be excluding a significant number of people who could benefit from psilocybin therapy. BD is common: population-based studies estimate the lifetime prevalence of BD between 1% and 3%,[12] and up to 6.1% if adults with subthreshold, although still debilitating, symptomatology are included.[13] Consequently, a significant proportion of the population will have a first-degree relative impacted by BD.

In addition to the risk of developing BD, offspring of a parent with BD have higher rates of unipolar depression, anxiety, attention-deficit/hyperactivity disorder, substance use disorders, and other serious mental illness compared with offspring of parents with no psychiatric disorder.[14–16] Second, continued exclusion from research studies means that if and when psilocybin obtains regulatory approval, we will lack critical safety, tolerability, and efficacy data to guide treatment of this population. Quantifying the risks and benefits of psilocybin therapy among people with a family history of BD is an important step in developing evidence-based psychedelic treatment.

Owing to the lack of clear rationale and relevant data, extant clinical trials of psilocybin therapy have used varying criteria for exclusion based on a family history of BD (Table 1). For example, two trials excluded individuals if a ''family member'' had a history of BD,[17,18] perhaps allowing for clinical discretion in determining exclusion of these participants. Three trials ($N = 233$, 16, and 12) did not obviously exclude those with a family history of BD or psychosis, representing a combined 261 participants.[19–21] These trials did not report any serious or lasting adverse events although rates of family history of BD were not reported.

Thus, it is difficult to know how reassuring the data are.[19–21] Two studies allowed for a family history of BD but not psychosis.[3,5] Again, rates of relevant family histories were not reported so the lack of serious adverse events does not necessarily clarify the safety of dosing people with a family history of BD. These data need to be cross-referenced with the presence of a family history to better establish the safety of psilocybin therapy in those with a family history of BD. Clear reporting of the clinical trial exclusion criteria and their rationale, as well as documenting detailed family histories, are essential steps for investigators to take in future clinical trials.

In this study, we examine the risk of precipitating mania and other treatment-emergent adverse events to participants with a family history of BD by examining what relevant data do exist. We then propose a risk stratification tool for such individuals by merging risk considerations found in the BD literature. This risk stratification tool stands in contrast to the broad uniform exclusion of people with familial history of BD currently used in many clinical trials of psilocybin therapy.

This tool allows clinical trials to conceptually rank the probability of a trial participant developing mania or psychosis in the course of psilocybin therapy, using their genetic risk factors for BD as a proxy for the risk of developing serious adverse events. Indeed, the patient pool for clinical trials of psilocybin therapy will be widened by the addition of more nuanced exclusion criteria for individuals with a family history of BD.

Risks of psilocybin use in those with a family history of BD

A positive family history of BD is the strongest predictive factor for an individual developing BD.[14] A longitudinal study followed offspring of a parent with BD and age- and demographically matched offspring of parents without BD for a mean duration of 6.8 years to identify risk factors of mania/hypomania.[14] The offspring with parental BD had significantly higher rates of mania/hypomania (9.2% vs. 0.8%) and significantly higher rates of major depressive episodes (32.0% vs. 14.9%), in addition to other mental health disorders, during the study period.[14]

Of offspring who went on to develop BD, approximately two-thirds had a major depressive episode preceding the onset of a first episode of mania or hypomania.[14] For those suffering from major depression with a family history of BD, the risk of treatment-emergent conversion to mania or hypomania is a looming possibility and presents a conundrum for clinical trials of psilocybin therapy. Although not explicitly stated, clinical trials of psilocybin therapy assume that the genetic and neurobiological underpinnings that increase risk for developing BD, as in a family history of BD, portend increased risk of experiencing adverse events.

We review cases and survey data to gain insights into the risks of psilocybin therapy among those with a family history of BD, despite their inherent limitations. We also consider reports of psychedelic use among people with schizophrenia and with BD, each of which may be relevant for evaluating the risks faced by those with a family history of BD. These data represent psychedelic experiences largely unaccompanied by the rigorous preparation and integration that controlled trials employ to increase participant psychological safety and efficacy.

Table 1. Family History-Based Exclusion Criteria in Modern Clinical Trials of Psilocybin Therapy

Author (year), title	*Disorder*	*Psilocybin dosage*	*Sample size* (n)	*Study type*	*Exclusion criteria quote from methods*	*Exclusion criteria: Fam Hx of BD*	*Exclusion criteria: Fam Hx of psychosis*
Aaronson et al. (2023)[30], ''Single-dose synthetic psilocybin with psychotherapy for treatment-resistant bipolar type II major depressive episodes: a nonrandomized controlled trial''	BD	25 mg	15	Open-label		No	No
Raison et al (2023)[105], ''Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial''	MDD	25 mg	104	RCT	''… first-degree family history of psychosis or mania …''	Yes	Yes
von Rotz et al. (2023)[106], ''Single-dose psilocybin-assisted therapy in major depressive disorder: a placebo-controlled, double-blind, randomized clinical trial''	MDD	15.05 mg/70 kg	52	RCT	''Psychosis spectrum disorders and/or mania symptoms in … first-degree relatives''	Yes	Yes
Goodwin et al. (2022)[19], ''Single-dose psilocybin for a treatment-resistant episode of major depression''	TRD	25, 10 or 1 mg	233	RCT	No mention of exclusion based on Fam Hx of psychotic or bipolar disorder	No	No
Carhart-Harris et al. (2021)[3], ''Trial of psilocybin versus escitalopram for depression''	MDD	25 or 1 mg	59	RCT	''Immediate family member with a diagnosed psychotic disorder.''	No	Yes
Davis et al. (2021)[2], ''Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial''	MDD	20–30 mg/70 kg	24	RCT	''Have a first or second-degree relative [meeting DSM-5 criteria for] schizophrenia spectrum or other psychotic disorders (except substance/medication-induced or due to another medical condition), or Bipolar I or II Disorder''	Yes	Yes
Carhart-Harris et al. (2016)[5], ''Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study''	TRD	25 and 10 mg	12	Open-label	''… immediate family member with a diagnosed psychotic disorder.''	No	Yes

(*continued*)

Table 1. (Continued)

Author (year), title	*Disorder*	*Psilocybin dosage*	*Sample size (n)*	*Study type*	*Exclusion criteria quote from methods*	*Exclusion criteria: Fam Hx of BD*	*Exclusion criteria: Fam Hx of psychosis*
O'Donnell et al. (2022)[107], ''Psilocybin for alcohol use disorder: Rationale and design considerations for a randomized controlled trial''	AUD	25 mg/70 kg	96	RCT	''A family history of schizophrenia or schizoaffective disorder (first or second degree relatives), or bipolar disorder type 1 (first degree relatives)''	Yes	Yes
Bogenschutz et al. (2022)[108], ''Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder''	AUD	25 mg/70 kg and 25–40 mg/ 70 kg	93	RCT	''Exclusionary psychiatric conditions … A family history of schizophrenia or schizoaffective disorder (first or second degree relatives), or bipolar disorder type 1 (first degree relatives)''	Yes	Yes
Bogenschutz et al. (2015)[109], ''Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study''	AUD	0.3 and 0.3 or 0.4 mg/kg	10	Open-label	''… exclusionary … psychiatric conditions*; family history of schizophrenia, bipolar disorder, or suicide''	Yes	Yes
Johnson et al. (2014)[18], ''Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction''	Cigarette dependence (smoking cessation) Tobacco addiction	20 mg/70 kg and 30 mg/70 kg	15	Open-label	''… family history of psychotic or bipolar disorders''	Yes	Yes
Griffiths et al. (2016)[110], ''Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial''	Depression and anxiety in patients with cancer	1 or 3 mg/70 kg and 22 or 30 mg/70 kg	51	RCT with crossover	''Current or past history of meeting DSM-IV criteria for Schizophrenia, Psychotic Disorder (unless substance-induced or due to a medical condition), or Bipolar I or II Disorder. Have a first or second degree relative with schizophrenia, psychotic disorder (unless substance induced or due to a medical condition), or bipolar I or II disorder.''	Yes	Yes
Ross et al. (2016)[111], ''Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial''	Cancer-related depression and anxiety	21 mg/70 kg	29	RCT with crossover	''… personal or immediate family history of schizophrenia, bipolar disorder, delusional disorder, paranoid disorder, and schizoaffective disorder.''	Yes	Yes

(*continued*)

Table 1. (Continued)

Author (year), title	*Disorder*	*Psilocybin dosage*	*Sample size* (n)	*Study type*	*Exclusion criteria quote from methods*	*Exclusion criteria: Fam Hx of BD*	*Exclusion criteria: Fam Hx of psychosis*
Grob et al. (2011)[21], ''Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer''	Cancer-related anxiety	14 mg/70 kg	12	RCT with crossover	''… lifetime history of schizophrenia, bipolar disease, other psychotic illness''	No	No
Moreno et al. (2006)[17], ''Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder''	OCD	1.75 mg/70 kg, 7 mg/70 kg, 14 mg/70 kg and 21 mg/70 kg	9	Open-label, dose-escalation	No description of exclusion criteria, but mentions in methods that ''none of the subjects had a personal or family history of psychosis''	N/A	N/A
Anderson et al. (2020)[112], ''Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label safety and feasibility pilot study''	HIV/AIDS related demoralization	21–25.2 mg/70 kg	18	Open-label	''Current or past history of meeting DSM-IV criteria for Schizophrenia, Psychotic Disorder (unless substance-induced or due to a medical condition), or Bipolar I or II Disorder. Have a first or second degree relative with schizophrenia, psychotic disorder (unless substance induced or due to a medical condition), or bipolar I or II disorder.''	Yes	Yes
Schindler et al. (2022)[20], ''Exploratory investigation of a patient-informed low-dose psilocybin pulse regimen in the suppression of cluster headache: Results from a randomized, double-blind, placebo-controlled trial''	Cluster headache	10.01 mg/70 kg	16	RCT	No mention of exclusions based on Fam Hx	No	No
Schindler et al. (2021)[113], ''Exploratory controlled study of the migraine-suppressing effects of psilocybin''	Migraine	10.01 mg/70 kg	10	RCT with cross-over	''Psychotic or manic disorders in … a first-degree relative were also exclusionary''	Yes	Yes

*Not specified.

AUD, alcohol use disorder; BD, bipolar disorder; Fam Hx, family history; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; MDD, major depressive disorder; N/A, not applicable; OCD, obsessive-compulsive disorder; RCT, randomized control trial; TRD, treatment-resistant depression.

Methodological shortcomings aside, in the absence of robust clinical trial data, these data are examined to uncover trends in risk to those with a family history of BD.

Case studies. Two exemplary case studies highlight possible risks to those with a family history of BD. First, a 32-year-old female with a history of mild depression and anxiety well-controlled on venlafaxine recreationally consumed an unknown quantity of psilocybin mushrooms and subsequently developed mania and paranoid delusions.[22] Second, a 21-year-old female with a history of anxiety and active depression and posttraumatic stress disorder reported ingesting a ''substantial'' amount of psilocybin-containing mushrooms in a recreational setting, with subsequent mania requiring psychiatric hospitalization.[23]

In all, these two individuals were of young age, had a first-degree relative with BD, ingested psilocybin once in an unregulated setting, and developed symptoms consistent with BD. It is unclear whether psilocybin *caused* mania in these individuals versus ''unmasked'' symptoms of underlying preexisting BD.

We completed a systematic review of published case studies describing psychedelic ingestion with apparent manic or psychotic symptoms persisting beyond immediate drug events.[11] Of the 17 cases identified, only 5 involved psilocybin consumption. Of the five cases reporting psilocybin consumption, four reported using high doses of psilocybin, typically over multiple sessions. The remaining case was the only to report a family history significant for BD (this is the second case study described earlier, the 21-year-old female; the aforementioned first case study was not published at the time of our systematic review).

Survey of those with self-reported BD. To further explore risks of psilocybin use to those with BD, we conducted an international web-based survey ($N=541$) to understand the experiences of individuals with a self-reported diagnosis of BD who had consumed psilocybin and experienced a ''full psychedelic trip.''[24] Nearly one-third of respondents in this survey noted negative experiences from psilocybin use, notably new or increasing manic symptoms, sleep difficulty, and anxiety.

In a large randomized clinical trial of psilocybin therapy in individuals with treatment-resistant depression receiving 25 mg of psilocybin ($n=79$), only 5% of participants reported both anxiety and insomnia within the 3 weeks after dosing.[19] Precipitating sleep difficulties in patients with personal or familial history of BD is a particularly risky venture given the association between poor sleep and increased vulnerability to mood episodes.[25–29] These findings must be interpreted against many respondents' reports of perceived positive benefit, even among those who reported negative experiences.

Open-label controlled trial of psilocybin therapy in individuals with BD2. The first study of psilocybin therapy in people with depression and BD2, an open-label nonrandomized clinical trial of a single dose of 25 mg of psilocybin combined with psychotherapy, aimed to assess safety and preliminary efficacy of the intervention.[30] In all 15 participants, no symptoms indicative of mania or psychosis were observed up to 12 weeks post-dosing.[30]

Three weeks after psilocybin administration, investigators observed a large effect on depressive symptoms, with 12 participants meeting the response criterion and 11 participants meeting the remission criterion, with mild adverse events comparable with those found in clinical trials of psilocybin therapy in other populations. The authors highlight the additional safeguards and highly supportive environment employed to maximize participant safety in this population, including a mandatory support person, intensive preparatory and integration sessions, and select psychotropic medication tapers.[30]

Population data. Population-level data find reduced odds of psychological distress in people with lifetime psychedelic usage compared with those who have not used psychedelics, and do not suggest that psychedelics cause serious and lasting adverse events.[31–34] Furthermore, among nearly 20,000 psychedelic users in the United States, psychedelic use was not predictive of subsequent mania or other serious psychological distress.[34] In another survey of nearly 2000 individuals with a self-reported history of psychologically difficult experience during psychedelic usage (i.e., a ''bad trip''), only three cases reported enduring psychotic symptoms.[33]

Among this same sample, 39% of respondents rated psilocybin ingestion as among the top five most challenging experiences of their lifetime, although 84% also endorsed significant benefit from the experience.[33] Given the high base rate of BD, we would expect many individuals with a family history of BD to be included in these large studies. Although not specifically delineating risks to those with a family history of BD, we do not see trends between psychedelic usage and lasting adverse events, including mania or psychosis.[31] Regardless, more data specifically examining safety and efficacy of psilocybin therapy in those with a family history of BD are needed.

Chronic psychosis. Owing to a shared genetic etiology, the risks of psychedelic ingestion in those with a family history of schizophrenia or other psychotic disorder may be relevant to those with a family history of BD. Schizophrenia and BD share extensive genetic makeup, one study finding 114 shared genome-wide loci between the two disorders.[35] Schizophrenia and BD are more genetically correlated than BD and major depressive disorder, which also share a genetic etiology.[35,36]

In addition to similar genetic underpinnings and high heritability, both BD and schizophrenia share considerable symptom overlap, including mood and psychotic symptoms. Some hypothesize these disorders are more appropriately contextualized as residing on a unifying schizoaffective disorders spectrum.[37]

A small number of studies have examined the effects of psychedelic ingestion among those with a family history of schizophrenia. In 1962, 44 siblings of individuals with schizophrenia were administered 1–1.5 μg/kg of lysergic acid diethylamide (LSD).[38] Nineteen of these 44 participants were described as having a ''pathological reaction.'' The authors describe one such reaction: ''Paranoid features e.g., that the dimness of consciousness was the result of external influence, they had fallen into a trap prepared by the doctor, professional rivals, personal enemies etc. as well as misinterpretation of events in the environment, all of which seemed to have some meaning for the intoxicated person.''[38]

Notably, the article describes that the ''acute phase of the intoxication led to a period lasting from a few days to six weeks …'' and was commonly accompanied by persistent insomnia, although further details of this prolonged state are not described.[38] In 1983, clinical characteristics of 52 patients who developed psychosis for at least 2 weeks after ingestion of LSD were compared with 29 patients with a first episode of psychosis attributable to schizophrenia between 1967 and 1972.[39] No differences in parental pathology were found between the cohorts save for higher rates of paternal alcoholism in the LSD group.

The authors found the LSD group similar to the patients with schizophrenia in ''genealogy, phenomenology, and course of illness,'' suggesting psychotic decompensation after LSD ingestion in those with genetic vulnerability, as in having a parent with history of psychosis.[39] These two studies point to a potential interaction between psychedelic ingestion and genetic vulnerability in predicting adverse events such as prolonged psychosis.

Treatment-emergent affective switch. Treatment-emergent mania or hypomania (affective switch) is a well-described sequela of antidepressant treatment in those with underlying BD.[40–42] Nearly every antidepressant medication is thought to confer some degree of risk for this phenomenon[43,44] and the risk of treatment-emergent mania or hypomania is higher with serotonergic medications.[45–47] Because those with a family history of BD are at higher risk of developing mania/hypomania, treatment-emergent mania or hypomania is a hypothetical risk in the context of clinical trials of psilocybin therapy.

As outlined by Gard et al., psilocybin may increase the risk of treatment-emergent mania or hypomania through several possible mechanisms.[11] First, all antidepressants appear to confer some degree of risk of affective switch and this phenomenon impacts 14.4% of individuals with BD treated with daily antidepressants.[43,44] Second, psilocin, the active metabolite of psilocybin, has a largely serotonergic mechanism of action.[48]

Psilocin is both a serotonin transporter inhibitor and a 5-HT2A receptor partial agonist with dual mechanisms at 5-HT2C, 5-HT1A, and 5-HT1B receptors: this combination of serotonergic effects could theoretically increase the risk of treatment-emergent affective switch.[45,49–51] In clinical trials thus far, psilocybin therapy has been typically delivered through a single high-dose administration. This produces subjective effects in the context of real-time psychotherapy during drug intoxication.[11] Antidepressant effects are rapid, and these improvements appear to be sustained for weeks to months without further treatment in some individuals.

In contrast, antidepressants (selective serotonin reuptake inhibitors, etc.) are typically dosed daily with little subjective change day to day; rather, the effects of these medications are gradual and may only become clinically significant over weeks to months.[52] It remains to be seen whether the dramatically different administration between these substances confers more or less risk for affective switch,[11] although emerging evidence suggests that ketamine, a rapid acting antidepressant, can precipitate manic symptoms in some individuals.[53–55] Given these outstanding questions, it is difficult to determine psilocybin's risk of precipitating affective switch in those with a family history of BD.

Considerations for risk stratification in participants with a family history of BD

In light of the potential for serious risks of psilocybin therapy to those with a family history of BD, utilizing a risk stratification tool may allow investigators to take a more nuanced approach to exclusion criteria. Assuming that one's risk for developing BD predicts the risk of developing serious adverse events with the use of psilocybin, examining an individual's genetic proximity to the affected relative, BD type (BD1 or BD 2, with or without psychotic features), age at onset in the relative, and participant age, researchers can systematically assess and quantify the potential risks to trial participants. These assessments will allow for informed decision-making when creating inclusion and exclusion criteria in clinical trials of psilocybin therapy.

Heritability: first versus second-degree relatives. As described previously, BD is among the most highly heritable mental health disorders.[56] In a large population-based cohort of nearly 55,000 people with BD, the relative risk of BD was as high as 7.9 for first-degree relatives, and heritability estimated at 58%.[57] This

heritability estimate is lower than that drawn from twin studies, which estimates heritability at 85%.[58]

Individuals with a first-degree relative with BD have a 10-fold excess risk of also developing BD, and this risk increases with a higher number of affected first-degree relatives, with up to 75% risk of developing BD in those with two affected first-degree relatives.[10,59,60] Heritability is also increased above background risk if a second-degree family member (but not first-degree family member) has BD, although not as significantly as with an affected first-degree relative.[61,62]

Studies have not yet quantified the heritability of BD for an individual with an affected second-degree relative but no affected first-degree relative. Together, having a first-degree relative with BD presents a higher risk of developing BD as compared with having a second-degree relative with BD, and that risk increases with more affected first-degree relatives. Thus, although data are lacking, the risk of psilocybin therapy likely tracks with the number of affected relatives and genetic proximity to relatives with BD.

Heritability: BD 1 versus 2. Heritability estimates for BD change with phenotypic presentation, with BD2 (depressive and hypomanic episodes) considered less heritable than BD1 (depressive and manic episodes).[60,63–65] One study estimates the heritability of BD2 at 46%, with an odds ratio of 13.6 if a first-degree relative has BD2 compared with the general population.[63] Despite lower heritability, BD2 is not less severe than BD1; rather, BD2 is associated with higher rates of depressive episodes[66–68] and significant functional impairment.[69]

Compared with the high heritability of BD1, an individual with a first-degree relative with BD2 likely has a lower risk of developing BD and thus a lower risk of developing affective switch, chronic psychosis, or other lasting adverse event from psilocybin therapy compared with having a first-degree relative with BD1.

Heritability: psychosis as phenotype. The presence or absence of psychosis in a first-degree relative with BD may be prognostically valuable as exclusion criteria are determined for clinical trials of psilocybin therapy. Although schizophrenia and BD already share significant genetic overlap, the presence of psychosis in BD predicts an even stronger and more homogeneous genetic etiology.[36,57,70–73] Some studies observe similar neuroanatomical changes in those at-risk for either schizophrenia or BD with psychosis.[74] Furthermore, BD with psychotic features is considered a more strongly heritable phenotype of BD.[36]

These findings highlight the need for a more nuanced risk mitigation strategy: Those with a first-degree relative with BD without psychotic features are likely at lower risk of developing BD and thus carry less risk for treatment-emergent adverse events in the context of psilocybin therapy as compared with a participant with a first-degree relative with BD with psychotic features. Of note, those with a family history of other primary psychotic disorder represent an even higher risk population with unique risk considerations; although data are also lacking on the safety and efficacy of psilocybin therapy in this population, discussion of individuals with non-BD-related psychosis is beyond the scope of this review.

Age at onset—relative. Age at onset of BD is recognized as an important etiological and clinical indicator in BD and the age at which the family member developed BD may be a particularly salient metric by which risk is stratified for potential trial participants with a family history of BD. Age at onset of BD, or the age at which clinical symptoms emerged to meet diagnostic criteria for BD, likely aggregates into a bimodal or trimodal distribution,[75–80] with more recent data favoring a trimodal distribution.[81]

A recent systematic review shows the average age at onset of this trimodal distribution to be 17.3 years of age (early onset), 26.0 years of age (mid onset), and 41.9 years (late onset).[81] The majority of cases in this sample ($N = 22{,}981$) were early onset, and only 20% were considered late-onset BD.[81]

Earlier age at onset of parental BD is associated with a significantly higher statistical risk of affected offspring developing BD.[14,82–84] Indeed, those with early-onset BD show increased polygenic liability for BD as well as for other psychiatric disorders such as schizophrenia.[85] Early-onset BD is associated with a more severe disease course with greater impairment[85] and is typically less responsive to mood stabilizing medications.[86] These distinctive features of early-onset BD suggest it is a unique genetic subtype and more highly heritable as compared with mid- or late-onset BD.

Late-onset BD is considered less heritable than early-onset BD as it is associated with higher rates of medical comorbidity, namely cerebrovascular disease, in addition to higher rates of behavioral health comorbidities.[81,87–90] Thus, trial participants with a first-degree relative with early-onset BD may be at higher risk of developing BD themselves as well as likely being at higher risk for treatment-emergent adverse events compared with participants with a first-degree relative with mid- or late-onset BD. Whereas the aforementioned data describe parental transmission of BD, age at onset of an affected sibling likely confers similar risk.

Age at onset—participant. In addition to the age at onset of BD in the affected relative, the age of the potential trial participant contributes to risk stratification. As aforementioned, threshold symptoms for BD typically emerge in adolescence and early adulthood (45% of

cases in one epidemiological study).[81] Thus, even without any personal history of symptoms concerning for BD, participants in adolescence and early adulthood remain at elevated risk of BD emerging irrespective of enrollment in a clinical trial of psilocybin therapy.

For older participants (≥40), a history of familial BD is still a risk factor for late-onset conversion to BD, so risk cannot be entirely excluded with increasing age, although the risk is likely decreased.[91] In all, younger participants are at higher risk of developing affective switch (treatment emergent or otherwise) and older participants are less likely to develop new-onset BD.

Although participant age represents a continuum of risk based on additional genetic and environmental factors, we recommend a risk threshold at 40 years of age for risk stratification, as this captures the time frame for both early- and mid-onset BD to emerge according to the trimodal distribution for age at onset. The risks of increasing age are unlikely to be linear, for example, a younger participant still at risk for early-onset BD presents much greater risk than a participant at age 38, and similarly a participant at age 45 is likely at less risk than a participant at age 41. For ease of utilizing the risk stratification tool, we choose 40 years of age as a critical inflection point in risk.

Bipolar prodrome. Increased attention is being paid to prodromal symptoms of BD, whereby detection and intervention earlier in the course of illness may yield a more robust treatment response.[92,93] The bipolar prodrome is complicated by overlapping symptomatology with numerous other behavioral health disorders and low specificity. Affective symptoms, as well as nonaffective psychopathology, may predict BD several years before onset, with early anxiety symptoms (panic, separation anxiety, among others) emerging as more reliably predictive.[94–96]

Subsyndromal mania, hypomania, and chronic irritability are also predictive of future BD in youth at high genetic risk.[14,97] Clinical rating instruments are being developed to reliably identify prodromal symptoms, although questionable validity and burdensomeness have limited their application in clinical trials.[98,99] Prospective studies of validated instruments are needed to justify their use in clinical trials for those participants at risk for BD.

Polygenic risk scores. Genome-wide association studies have shown how a multitude of genetic risk variants contribute to the development of complex psychiatric disorders, such as BD. The use of polygenic risk scores (PRS), a way to systematically predict an individual's genetic susceptibility to a disorder,[100,101] could plausibly help trials predict the risk of treatment-emergent affective switch or other serious adverse event in participants with a family history of BD. However, PRS in its current form is not sufficiently predictive to inform clinical decisions or pharmacological intervention.[102,103]

The nonrandom inheritance of population risk alleles and shared familial environmental factors renders PRS scores more useful for population-level analysis with less individual clinical significance.[104] Emerging research suggests that PRS may distinguish or predict BD subtypes among individuals with higher familial polygenic risk load,[104] although prospective longitudinal studies are needed to confirm whether PRS scores are sufficiently predictive. At present, PRS cannot be broadly recommended for individual risk determination for participants with family history of BD.

Discussion

The following risk stratification tool provides a framework to help determine the relative risks to participants related to their family history of BD. This risk stratification tool is not a quantitative model derived from available data but rather a conceptual approach after merging associations drawn from the aforementioned literature. Our assumption is that individuals at greater risk for developing BD are at higher risk of experiencing mania, psychosis, or other lasting adverse events during the course of psilocybin therapy.

Consolidating the risk considerations for individuals developing BD (genetic proximity to affected relative, BD subtype, psychosis phenotype, age at onset in the relative participant age) the higher/highest risk participants represent those with the most pronounced risk milieu. Conversely, the tool further categorizes those with comparatively diminished levels of risk when undergoing psilocybin therapy. We recommend the following risk stratification tool for patients with familial history of BD but no personal history of symptoms concerning for BD (see Fig. 1):

If additional trials of psilocybin therapy in those with a personal history of BD2 show safety and efficacy data as compelling as those found by Aaronson et al., similar safeguards could significantly mitigate risk for those without personal history but with family history of BD. There is one ongoing clinical trial of psilocybin therapy for depression in individuals with BD2 (NCT05065294).

This trial recognizes the increased potential for adverse events in this population, including affective switch and chronic psychosis, and has implemented modified protocols and safeguards to account for the risks specific to this population, including more conservative dose-escalation protocols and mandatory community supports.[24] If these safeguards significantly mitigate the risk of serious adverse events during this novel period of inquiry for patients with a *personal history* of BD, they are likely to mitigate risk in those with a family history of BD.

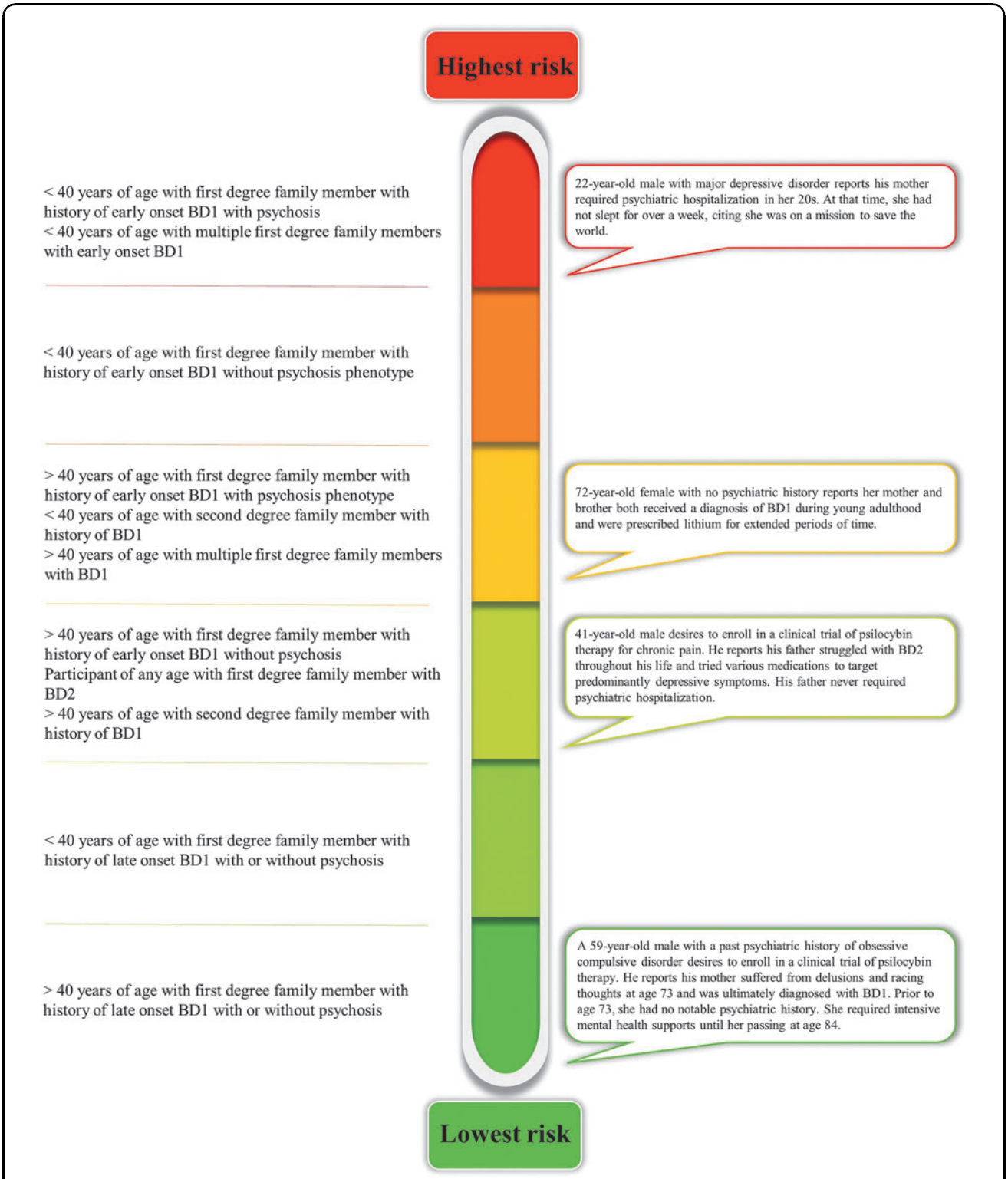

FIG. 1. Risk stratification tool for participants with a family history of BD in clinical trials of psilocybin therapy with case examples. "Early onset BD" denotes <40 years of age, which includes early- and mid-onset BD if using a trimodal distribution. Late-onset BD denotes ≥40 years of age. Although participant age represents a continuum of risk based on additional genetic and environmental factors, we recommend a risk threshold at 40 years of age to best capture those at higher risk (early- and mid-onset BD) versus lower risk (late-onset BD). BD, bipolar disorder.

Limitations of this risk stratification tool include the overarching assumption that the genetic risk for developing BD corresponds to the risks of developing serious and lasting adverse events during psilocybin therapy. Individual environmental and temperamental considerations, which interact with genetic predisposition to precipitate BD, are not accounted for in the risk stratification tool. Emerging evidence suggests some risk factors for developing BD may be more or less predictive depending on the sex of the individual.[91]

This evidence was also not incorporated into the risk stratification tool. Changes in diagnostic practices over time with respect to BD, as well as the challenges of uncovering accurate family history, are a limitation of this approach. If family history cannot be ascertained, we recommend weighing the participant's other risk factors against the level of risk presented by the clinical trial itself.

Important elements to consider include (1) study population—clinical populations at elevated risk of adverse events (substance use disorders) may be deemed higher risk than those with other mental health disorders; (2) drug dosage/administration—protocols with higher and more frequent doses may confer more risk; (3) level of support and monitoring offered by study—protocols with frequent participant contact, including preparatory and integration therapy, and the ability to add additional participant support if needed, may decrease risks to participants; and (4) availability of caregiver or other social supports to participant outside of trial, for additional monitoring and support.

Balancing the need for effective treatments against the potential for serious adverse events in those undergoing psilocybin therapy with a family history of BD, we argue for caution in psychedelic clinical trials but not outright exclusion of these participants. We find some evidence for an increased adverse effect burden after psychedelic ingestion in individuals with a family history of BD. However, the psychedelic renaissance appears to hold great promise for a range of mental health conditions and the potential efficacy of psilocybin therapy warrants investigation in those with a family history of BD, whereas remaining cognizant of serious risks.

The outright exclusion of these participants limits the generalizability of findings and presents a challenge if and when psilocybin therapy gains regulatory approval for therapeutic use: the widespread exclusion of individuals with a family history of BD will be untenable. We propose that investigators use a risk stratification approach rather than broad exclusion of these individuals from clinical trials of psilocybin therapy.

The risk stratification tool may have broader clinical implications for those with a family history of BD, as in decision-making for psychopharmacological interventions such as the use of selective serotonin reuptake inhibitors or ketamine. Comprehensive documentation of adverse events will be critical to continually refine risk stratification tools and optimize inclusion and exclusion criteria in this population.

Authors' Contributions

Conceptualization by J.W. and E.R.B.; methodology by J.W. and A.E.D.; writing—original draft by A.E.D., A.S.L., and J.W.; writing—reviewing and editing by A.E.D., E.R.B., A.O., A.S.L., A.D.K., and J.W.

Author Disclosure Statement

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