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Exploring the case for research on incorporating psychedelics within interventions for borderline personality disorder☆

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ABSTRACT

Borderline Personality Disorder (BPD) is a severe psychiatric disorder characterized by behavioral dysregulation, emotion dysregulation, disturbances in self-identity, and social functioning. Despite the existence of evidence-based psychotherapeutic interventions for BPD, these interventions have important limitations (e.g., limited treatment efficacy). Furthermore, little evidence exists for the efficaciousness of pharmacological interventions for BPD. Thus, a strong need for improving current interventions for BPD exists. Although research incorporating psychedelics within interventions for a wide range of psychiatric disorders has shown promise, research has not yet explored the utility of incorporating psychedelics within interventions for BPD. Therefore, this paper reviews the impact of psychedelics on treatment targets in interventions for BPD (i.e., behavioral dysregulation, emotion dysregulation, disturbances in self-identity, and social functioning), as well as purported overlapping mechanisms of change between interventions for BPD and psychedelics (i.e., emotion dysregulation, mindfulness, and self-compassion). Finally, safety concerns, clinical recommendations, and proposed next research steps related to the administration of psychedelics to individuals with BPD are discussed. This paper aims to explore the case for conducting research on, and the potential clinical utility surrounding, incorporating psychedelics within interventions for BPD.

Borderline personality disorder (BPD) is a severe psychiatric disorder characterized by behavioral dysregulation, emotion dysregulation, disturbances in self-identity, and difficulties with social functioning (American Psychiatric Association [APA], 2013). BPD has a prevalence rate of approximately 1.5% in the general population and is especially prevalent within clinical populations (9.3%–46.3%; Torgersen, 2012). Moreover, BPD is associated with high rates of suicide (Temes, Frankenburg, Fitzmaurice, & Zanarini, 2019), intensive use of healthcare resources (Cailhol, Thalamas, Garrido, Birmes, & Lapeyre-Mestre, 2015; Zanarini, Frankenburg, Hennen, & Silk, 2004), and, due to healthcare utilization and reduced involvement in the workforce, creates significant economic burden on society (Van Asselt, Dirksen, Arntz, & Severens, 2007). Therefore, efficacious interventions for BPD are of great importance.

1. The current state of interventions for borderline personality disorder

1.1. Psychotherapeutic interventions for borderline personality disorder

Psychotherapeutic interventions are currently considered the first-line treatment for BPD (Paris, 2009). A number of psychotherapeutic interventions have been developed specifically for BPD, including dialectical behavior therapy (DBT; Linehan, 1993), transference-focused psychotherapy (TFP; Clarkin, Yeomans, & Kernberg, 1999), and mentalization-based therapy (MBT; Bateman & Fonagy, 2006). Randomized controlled trials (RCT; e.g., Bateman & Fonagy, 2009; Doering et al., 2010; Linehan et al., 2006) have shown that each of these interventions lead to significant reductions in BPD symptoms (e.g., suicidal behaviours and self-harm), compared with treatment as usual (for a review, see Stoffers et al., 2012).

Nonetheless, current psychotherapeutic interventions for BPD have important limitations, including limited treatment efficacy. For instance, compared with control interventions, a recent meta-analysis

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(Cristea et al., 2017; $N = 2256$) found only small to moderate effect sizes for DBT (Hedges' $g = 0.34$) and psychodynamic approaches (i.e., TFP and MBT; Hedges' $g = 0.41$) on BPD outcomes (i.e., BPD symptoms, self-harm, and suicidal behaviors). Similarly, a recent longitudinal study showed that 10 years after treatment 45% of individuals continued to meet criteria for BPD and few showed improvement in social and occupational functioning (Alvarez-Tomás et al., 2017). Therefore, a need for improving the efficacy of psychotherapeutic interventions for BPD exists.

1.2. Pharmacological interventions for BPD

Compared with psychotherapeutic interventions, there has been less success developing efficacious pharmacological interventions for BPD. Currently, medical guidelines related to pharmacotherapy for BPD take two approaches: recommending against pharmacotherapy for BPD (e.g., National Institute of Health and Clinical Excellence, 2009) and recommending pharmacotherapy for specific BPD symptoms (e.g., APA, 2001). A small number of studies have explored adding pharmacological interventions to psychotherapeutic ones, with limited improvement in outcomes compared with psychotherapy alone (for a review, see Marin, Kapil-Pair, Harris, & Goodman, 2018). Furthermore, meta-analyses and comprehensive reviews suggest that little evidence exists for the efficacy of current pharmacological interventions for BPD (Francois, Roth, & Klingman, 2015; Hancock-Johnson, Griffiths, & Picchioni, 2017; Lieb, Völlm, Rücker, Timmer, & Stoffers, 2010; Stoffers & Lieb, 2015), and no pharmacological interventions have health agency indication or approval for treatment of BPD (Starcevic & Janca, 2018).

Despite the limited evidence for pharmacological interventions for BPD, pharmacotherapy is frequently prescribed in the absence of a comorbid disorder (e.g., 82%; Paton, Crawford, Bhatti, Patel, & Barnes, 2015), suggesting that service providers are desperate to offer some form of treatment. Concerns with these practices include ethical issues, negative side effects, and high rates of medication abuse (Sansone & Wiederman, 2009). Given the limitations surrounding current interventions, a pressing need exists for exploring novel pharmacological interventions for BPD (Chanen, 2015).

2. Psychedelic-assisted psychotherapy

Given the need for novel pharmacological interventions for BPD, this review considers the potential of incorporating psychedelics within interventions for BPD. Broadly defined, psychedelics are pharmacological agents that cause changes in affect, cognition, and perception, as well as induce non-ordinary states of consciousness (dos Santos, Osorio, Crippa, & Hallak, 2016). Although there is some overlap between the phenomenological properties of psychedelics, many of them have different primary mechanisms of action. Serotonergic psychedelics (also referred to as "classic psychedelics"), such as psilocybin, dimethyltryptamine (DMT; which is contained in the ayahuasca brew), and lysergic acid diethylamide (LSD), share a common primary mechanism of action via agonism of serotonin 5-HT_{2A} receptors (Nichols, 2016). 3,4-Methylenedioxy-methamphetamine (MDMA) is often defined as an entactogen (due to its modulation of feelings of interpersonal closeness and empathy; Bershad et al., 2019) and its mechanisms of action include increased levels of serotonin, dopamine, and norepinephrine (Sessa, Higbed, & Nutt, 2019). Ketamine is generally defined as a dissociative anaesthetic that acts as a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist (Molero et al., 2018). Despite these important differences, given that this is the first review on psychedelics and BPD, we will explore the potential surrounding incorporating a broad class of psychedelics within interventions for BPD.

Preliminary research on the clinical utility of psychedelics has yielded promising results for treatment of a wide range of difficult to treat psychiatric disorders, a number of which are highly comorbid with BPD (Zanarini, Frankenburg, Hennen, Reich, & Silk, 2004), including treatment-resistant major depressive disorder, posttraumatic stress disorder, substance use disorders, psychological distress associated with a life-threatening illness, and obsessive-compulsive disorder (for reviews, see Johnson, Hendricks, Barrett, & Griffiths, 2019; Sessa et al., 2019). A number of trials have also found that administration of psychedelics lead to long-lasting changes in personality (e.g., openness to experience; MacLean, Johnson, & Griffiths, 2011; Wagner et al., 2017), which may account for positive therapeutic outcomes (for a review, see Bouso, dos Santos, Alcázar-Córcoles, & Hallak, 2018). Furthermore, incorporating psychedelics within interventions for healthy individuals lead to long-lasting improvements in well-being (e.g., Griffiths et al., 2018; Nicholas et al., 2018). Despite important limitations surrounding research to date, including a limited number of trials, small sample sizes, and issues with maintaining blindness in placebo-controlled trials (due to the pronounced psychological effects of psychedelics; Barnby & Mehta, 2018), the preliminary results are promising and suggest that additional research on the clinical utility of psychedelics is warranted.

Given the wide range of psychiatric disorders for which psychedelics have shown promising results, Carhart-Harris, Erritzoe, Haijen, Kaelen, and Watts (2018) argue that psychedelics may target transdiagnostic mental health issues, which suggests that psychedelics may show promise for treatment of not yet researched psychiatric disorders. However, research to date has not yet explored the potential of incorporating psychedelics within interventions for BPD (and some research has actively excluded individuals with BPD; e.g., Danforth et al., 2018). Therefore, we review treatment targets in interventions for BPD, including (a) behavioral dysregulation, (b) emotion dysregulation, (c) disturbances in self-identity, and (d) social functioning, as well as the impact of psychedelics on these treatment targets. Furthermore, we describe research on purported overlapping mechanisms of change (i.e., *how* and *why* interventions lead to improvement; Kazdin, 2009) between interventions for BPD and psychedelics.

2.1. Behavioral dysregulation

2.1.1. Borderline personality disorder and behavioral dysregulation

BPD is characterized by a range of dysregulated behaviors including impulsivity, aggression, substance abuse, and suicidal behaviors (APA, 2013). Compared with healthy controls, individuals with BPD show higher levels of self-reported impulsivity (Sebastian, Jacob, Lieb, & Tüscher, 2013) and, among individuals with BPD, higher levels of impulsivity are associated with more frequent engagement in dysregulated behaviours (Terzi et al., 2017). Furthermore, among psychiatric inpatients, individuals with BPD are more likely to engage in serious violent and aggressive acts (Newhill, Eack, & Mulvey, 2009). BPD is also associated with high rates of comorbid lifetime alcohol (i.e., 48.1%) and drug (i.e., 45.9%) use disorders (Trull et al., 2016), as well as extremely high rates of non-suicidal self-injury (i.e., 65–80%; Clarkin, Widiger, Frances, Hurt, & Gilmore, 1983; Soloff, Lis, Kelly, Cornelius, & Ulrich, 1994), attempted suicide (e.g., 70.6%–83.6%; Soloff, Lynch, & Kelly, 2002; Wilson, Fertuck, Kwitel, Stanley, & Stanley, 2006), and completed suicide (i.e., 5.9%; Temes et al., 2019). Thus, behavioral dysregulation is an important target in interventions for BPD.

Although evidence-based interventions for BPD lead to significant decreases in behavioral dysregulation, important limitations with treatment outcomes remain. For instance, comparing DBT with waitlist control and treatment as usual, a recent meta-analysis found only small to moderate effect sizes for decreases in self-harm and suicidal behaviors (*Cohen's* $d = -0.324$; DeCou, Comtois, & Landes, 2019) and non-significant decreases in suicidal ideation ($d = -0.229$). Moreover, following treatment of BPD, the majority of individuals (e.g., 58%; Heath, Laporte, Paris, Hamdullahpur, & Gill, 2018) show minimal improvement in substance abuse. Given these limitations, a need for developing interventions for BPD that better target behavioral

dysregulation exists.

2.1.2. Psychedelics and behavioral dysregulation

Research suggests that psychedelics may show potential for reducing behavioral dysregulation. Interviewed patients report increased behavioral control after psilocybin-assisted psychotherapy (Bogenschutz et al., 2018). Similarly, among healthy subjects, a single dose of LSD led to increases in self-reported positive behavioral changes 1 and 12 months later (Schmid & Liechti, 2018). Additionally, an observational study found significant decreases in self-reported impulsivity after 3–9 months of biweekly ritual ayahuasca use (Fernández et al., 2014). Psychedelics are also associated with decreases in aggression in both humans (for a review, see Tomlinson, Brown, & Hoaken, 2016) and non-human animals (e.g., Kostowski, Rewerski, & Piechocki, 1972). For instance, lifetime psychedelic use is associated with less likelihood of perpetrating a violent crime (Hendricks et al., 2017) and intimate partner violence (Thiessen, Walsh, Bird, & Lafrance, 2018; Walsh et al., 2016).

Research also suggests that psychedelics may decrease substance abuse. A meta-analysis found that treatment with LSD led to significant improvement among individuals with alcohol dependence (Krebs & Johansen, 2012). Small open-label studies have also found promising effects for treatment of tobacco (Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014) and alcohol dependence (Bogenschutz et al., 2015) with psilocybin-assisted psychotherapy. Additionally, lifetime use of psychedelics is associated with reduced risk of past-year opioid abuse (27%) and opioid dependence (40%; Pisano et al., 2017).

Psychedelics may lead to decreases in suicidal behaviors. A wide range of research has shown support for the rapid-acting anti-suicidal effects of ketamine (for a review, see Molero et al., 2018). Importantly, two of these studies included individuals with BPD (Grunebaum et al., 2017; Murrough et al., 2015) and BPD was not found to impact treatment outcomes (Grunebaum et al., 2017). Furthermore, among individuals with treatment-resistant depression, two doses of psilocybin with psychological support led to reductions in self-reported suicidal ideation 1 and 2 weeks after the intervention (Carhart-Harris, Bolstridge et al., 2018). Similarly, clinical trials have found that psilocybin-assisted psychotherapy and administration of ayahuasca lead to reductions in predictors of suicidal behaviors (for a review, see Johnson et al., 2019), such as depressive symptoms and hopelessness. Finally, lifetime use of psychedelics is associated with a reduced risk of becoming suicidal (Argento, Braschel, Walsh, Socias, & Shannon, 2018; Argento et al., 2017) and lower levels of past-year suicide ideation, planning, and attempts (Hendricks, Thorne, Clark, Coombs, & Johnson, 2015). However, these results may also be due to factors associated with psychedelic use (e.g., openness to experience), rather than use of psychedelics themselves. Overall, this research suggests that administration of psychedelics leads to decreases in a wide range of dysregulated behaviors associated with BPD.

3. Emotion dysregulation

3.1. Borderline personality disorder and emotion dysregulation

The core dysfunction of BPD is often identified as emotion dysregulation (Carpenter & Trull, 2013; Linehan, 1993). Emotion dysregulation is a multidimensional construct that consists of heightened negative affect, emotional sensitivity, and deficits in using emotion regulation strategies (Carpenter & Trull, 2013). Current neurobiological research suggests that emotion dysregulation among individuals with BPD stems from increased activity in limbic regions of the brain (e.g., amygdala, insula), which are associated with emotion detection and generation, coupled with decreased activity in prefrontal regions (e.g., prefrontal cortex), which are associated with emotion regulation (Schulze, Schmahl, & Niedtfeld, 2016). Therefore, emotion dysregulation is thought to occur due to deficits in “top-down” modulation of emotional responses.

Given its centrality to BPD, emotion dysregulation is a primary target and purported mechanism of change in interventions for BPD (Rizvi & Thomas, 2017; Rudge, Feigenbaum, & Fonagy, 2017). Changes in self-reported emotion dysregulation, and related processes, mediate BPD treatment outcomes (Axelrod, Perepletchikova, Holtzman, & Sinha, 2011; Gratz, Bardeen, Levy, Dixon-Gordon, & Tull, 2015, 2012; McMain et al., 2013). Research also suggests that psychotherapeutic interventions for BPD alter the function, structure, and connectivity of regions of the brain essential to emotion dysregulation (for a review, see Herpertz, Schneider, Schmahl, & Bertsch, 2018). Overall, these findings suggest that emotion dysregulation is likely a key mechanism of change in interventions for BPD.

3.2. Psychedelics and Emotion Dysregulation

Empirical and theoretical research suggests that psychedelics impact emotional processes and emotion dysregulation (Vollenweider & Kometer, 2010). First, in a recent observational study with a community sample (Domínguez-Clavé et al., 2019), administration of ayahuasca led to significant decreases in components of emotion dysregulation (i.e., emotional non-acceptance, emotional interference, and lack of control) 24 h after administration. Within a subgroup of this sample, individuals high in BPD traits also showed decreases in components of emotion dysregulation (i.e. emotional interference and lack of control). Second, within community samples, lifetime psychedelic use is associated with lower levels of emotion dysregulation (Thiessen et al., 2018) and self-reported psychological distress (Hendricks et al., 2015). Third, research on psychedelic-assisted psychotherapy has shown long-lasting (e.g., 6–6.5 months) decreases in affective symptoms (for a review, see Johnson et al., 2019), as well as decreases in neuroticism (Erritzoe et al., 2018). Among individuals with a broad range of affective disorders, those that received high and low dose LSD showed greater improvement in affective symptoms than those who received conventional treatment alone (e.g., psychotropic medication, electroshock therapy, individual psychotherapy or group psychotherapy; McCabe, Savage, Kurland, & Unger, 1972). Furthermore, among five individuals with BPD and comorbid treatment-resistant depression who received ayahuasca, all five individuals showed decreases (i.e., 30–84% decrease from baseline) in clinician-assessed symptoms of depression 7 days later (Palhano-Fontes et al., 2019).

Administration of ketamine has also been shown to lead to rapid reductions in affective symptoms (for a review, see Molero et al., 2018). Interestingly, compared with individuals with low symptom burden at baseline (e.g., lower levels of suicidality), ketamine-assisted psychotherapy leads to greater decreases in affective symptoms among individuals higher in symptom burden (e.g., higher levels of suicidality; Dore et al., 2019). Finally, individuals with BPD and alcohol use disorder who received ketamine-assisted psychotherapy, showed improvements in characteristics related to emotion dysregulation, including measures related depressive symptoms and neuroticism (Krupitsky & Grinenko, 1996).

The impact of psychedelics on emotion dysregulation may be accounted for by the agonist action of psychedelics on 5-HT_{2A} receptors in the pre-frontal cortex, which lead to enhanced “top-down” control of circuits related to emotion dysregulation (for a review, see Vollenweider & Kometer, 2010). In line with this hypothesis, experimental research with humans indicates that psychedelics alter neural activity in regions associated with emotion processing and emotion dysregulation (e.g., Bedi, Phan, Angstadt, & De Wit, 2009; Kraehenmann et al., 2016; Sanches et al., 2016). Furthermore, administration of psychedelics has been shown to promote structural and functional plasticity, and related effects (i.e., increased gene transcription), in the pre-frontal cortex of rats (Ly et al., 2018; Nichols & Sanders-Bush, 2002). Therefore, preliminary research suggests that psychedelics may target emotion dysregulation.

4. Mindfulness

4.1. Borderline personality disorder and mindfulness

One important emotion regulation strategy relevant to BPD is mindfulness, and related capacities, including decentering (i.e., the ability to observe one's thoughts, emotions, and sensation from a detached perspective; Kerr, Josyula, & Littenberg, 2011) and acceptance (i.e., tolerating and approaching, rather than avoiding, one's experiences; Orzech, Shapiro, Brown, & McKay, 2009). Compared with individuals with other personality disorders (Zanarini, Temes, Frankenburg, Reich, & Fitzmaurice, 2019), as well as community (e.g., Tortella-Feliu et al., 2018) and college (Baer, Smith, & Allen, 2004) comparison groups, individuals with BPD show lower levels of mindfulness and acceptance. Moreover, among individuals with BPD, mindfulness is positively associated with emotional well-being and negatively associated with healthcare utilization (O'Toole, Diddy, & Kent, 2012). Furthermore, within a psychiatric sample, deficits in mindfulness account for the relationship between BPD features and behavioral dysregulation (Wupperman, Fickling, Klemanski, Berking, & Whitman, 2013). Thus, deficits in mindfulness play an important role in BPD.

Mindfulness is purported to be a key target and mechanism of change in interventions for BPD (Bliss & McCardle, 2014; Linehan, 1993; Rudge et al., 2017). Time spent engaging in mindfulness practice (Feliu-Soler et al., 2014; Soler et al., 2012), use of mindfulness skills (Stepp, Epler, Jahng, & Trull, 2008), as well as increases in mindfulness (Mitchell, Roberts, Bartsch, & Sullivan, 2019; Zeifman, Boritz, Barnhart, Labrish, & McMain, 2019), acceptance (Krantz, McMain, & Kuo, 2018; Perroud, Nicastro, Jermann, & Huguelet, 2012; Zanarini et al., 2019), and decentering (Elices et al., 2016) are associated with positive BPD treatment outcomes. Finally, increases in mindfulness throughout interventions for BPD are associated with less likelihood of treatment drop out (Stratton, Alvarez, Labrish, Barnhart, & McMain, 2018). These results suggest that mindfulness may be an especially important mechanism of change in interventions for BPD. Therefore, pharmacological interventions that increase mindfulness may strengthen BPD treatment outcomes.

4.2. Psychedelics and Mindfulness

Mindfulness has been proposed as a mechanism of change in psychedelic-assisted psychotherapy. Qualitative research has highlighted mindfulness (Bogenschutz et al., 2018) and acceptance (Wagner, Mithoefer, Mithoefer, & Monson, 2019; Watts, Day, Krzanowski, Nutt, & Carhart-Harris, 2017) as important processes of change associated with psilocybin and MDMA-assisted psychotherapy. Furthermore, experimental studies show that administration of ayahuasca leads to increases in mindfulness-related capacities, including acceptance and decentering (Domínguez-Clavé et al., 2019; Sampedro et al., 2017; Soler et al., 2018, 2016; Thomas, Lucas, Capler, Tupper, & Martin, 2013). In one ayahuasca study, participants continued to show significant improvement in acceptance at 2-month follow-up (Sampedro et al., 2017). Similarly, Soler et al. (2018) found that four sessions of ayahuasca result in increases in acceptance that are comparable with 8-weeks of mindfulness-based stress reduction (Kabat-Zinn, 1990). Finally, lifetime use of ayahuasca is associated with higher levels of decentering (Franquesa et al., 2018). Overall, these results suggest that administration of psychedelics may lead to increases in mindfulness.

5. Self-identity

5.1. Borderline personality disorder and self-identity

Individuals with BPD experience disturbances in their self-identity (APA, 2013), which have been conceptualized in two primary ways (Gad et al., 2019): (a) as an inconsistent and non-integrated sense of self (Kernberg, 1975) and (b) as a generally elevated negative view toward the self with only brief periods of positive views (Zanarini et al., 2007). Research has provided support for both of these models. For instance, compared with healthy controls, individuals with BPD show less consistency when listing their personality traits (Beeney, Hallquist, Ellison, & Levy, 2016), as well as less coherent and more disoriented life narratives (Jørgensen et al., 2012). Furthermore, compared with healthy controls and clinical populations, individuals with BPD show heightened negative self-evaluation and self-criticism, as well as less self-compassion (e.g., Costa, Marôco, Pinto-Gouveia, Ferreira, & Castilho, 2016; Gad et al., 2019; Kopala-Sibley, Zuroff, Russell, Moskowitz, & Paris, 2012; Winter, Bohus, & Lis, 2017). Moreover, self-criticism and self-compassion are associated with maladaptive behaviors associated with BPD, including self-injury and suicidal behaviors (Gregory, Glazer, & Berenson, 2017; Hasking, Boyes, Finlay-Jones, McEvoy, & Rees, 2019).

Qualitative analysis of interviews conducted with BPD treatment providers and users identify self-compassion as an important theme in the process of recovery (Katsakou & Pistrang, 2017; Katsakou, Pistrang, Barnicot, White, & Priebe, 2017). Research has also suggested that incorporating self-compassion-based exercises improves outcomes in interventions for BPD (Feliu-Soler et al., 2017). Furthermore, compared with BPD non-responders, treatment responders show lower levels of baseline negative self-views and greater decreases in negative self-views (Gad et al., 2019), as well as steeper increases in self-acceptance (Zanarini et al., 2019). Finally, a cross-sectional study showed that, after treatment for BPD, personal recovery was negatively associated with self-criticism and positively associated with self-compassion (Donald, Lawrence, Broadbear, & Rao, 2019). Accordingly, disturbances in self-identify, including instability of views toward the self, as well as increasing positive views toward the self and increasing self-compassion are important, and especially challenging, treatment targets in interventions for BPD (Krawitz, 2012).

5.2. Psychedelics and self-identity

Research suggests that psychedelics have an acute, and potentially long-lasting, impact on an individual's sense of identity. Qualitative research indicates that self-compassion and self-acceptance are important themes that emerge from interviews with individuals that received psilocybin, LSD, and MDMA-assisted psychotherapy, or used ayahuasca for therapeutic purposes (Barone, Beck, Mitsunaga-Whitten, & Perl, 2019; Bogenschutz et al., 2018; Gasser, Kirchner, & Passie, 2015; Lafrance et al., 2017; Malone et al., 2018). Cross-sectional and experimental research similarly suggests that psychedelics lead to increased self-compassion and positive views of the self. Among healthy individuals, controlled studies with psilocybin (Griffiths, Richards, McCann, & Jesse, 2006, 2008, 2011, 2018), and an open-label study with LSD (Schmid & Liechti, 2018), have shown long-term increases in positive views toward the self. Relatedly, compared with individuals without a history of ayahuasca use, individuals with a history of ayahuasca use show more positive views of the self (Franquesa et al., 2018). An open-label study with healthy volunteers showed that a single dose of ayahuasca leads to significant increases in self-compassion (Sampedro et al., 2017). Similarly, among recreational MDMA users, use of MDMA is associated with subsequent increases in self-compassion and decreases in self-criticism (Kamboj et al., 2015, 2017). Among individuals with BPD and substance use, ketamine-assisted psychotherapy was found to lead improvement in personality characteristics associated with self-criticism (Krupitsky & Grinenko, 1996). These findings suggest that administration of psychedelics may lead to long-lasting changes in self-identity in general and increases in self-compassion in particular.

To date, research has not yet explored the impact of psychedelics on stability of views toward the self (i.e., BPD-related identity disturbance

as defined by Kernberg, 1975). However, given research suggesting that decreased emotion dysregulation (Gratz et al., 2015) and use of mindfulness skills (Stepp et al., 2008) lead to decreases in disturbance in self-identity within interventions for BPD, the impact of psychedelics on emotion dysregulation (see above, '**Psychedelics and Emotion Dysregulation')** and mindfulness (see above, '**Psychedelics and Mindfulness'**) may, in turn, lead to decreases in disturbances in self-identity. Additional research will be necessary to explore this possibility.

6. Social functioning

6.1. Borderline personality disorder and social functioning

BPD is characterized by deficits in social functioning, including unstable and intense interpersonal relationships, and frantic efforts to avoid abandonment (APA, 2013). Individuals with BPD are especially likely to experience heightened levels of social pain (i.e., emotional distress due to social exclusion, rejection, or loss; Renneberg et al., 2012; Staebler, Renneberg et al., 2011) and rejection sensitivity (Domsalla et al., 2014; Staebler, Helbing, Rosenbach, & Renneberg, 2011b). Furthermore, individuals with BPD may show additional deficits in aspects of social functioning, including trust, emotion recognition, and empathy (for a review, see Lazarus, Cheavens, Festa, & Rosenthal, 2014).

Deficits in social functioning are among the most difficult targets in BPD interventions, with little evidence for increases in social functioning following treatment (Alvarez-Tomás et al., 2017; Gunderson et al., 2011). One of the means through which deficits in social functioning can manifest itself in interventions for BPD is through interference with the therapeutic alliance (i.e., the relationship between the patient and therapist). Maintenance of therapeutic alliance can be especially difficult (Bender, 2005), and is an important predictor of drop-out and treatment outcomes in interventions for BPD (Barnicot et al., 2012; Barnicot, Katsakou, Marougka, & Priebe, 2011; Bedics, Atkins, Harned, & Linehan, 2015; Wnuk et al., 2013). Therefore, improving social functioning, as well as enhancement of the therapeutic alliance, are important targets in interventions for BPD.

6.2. Psychedelics and social functioning

Research suggests that psychedelics may have a positive impact on social functioning. Among individuals with BPD and substance use, ketamine-assisted psychotherapy led to improvements in social functioning and interpersonal sensitivity (Krupitsky & Grinenko, 1996). Furthermore, among individuals that received psilocybin with psychological support, thematic analysis identified connectedness to others as an important process of change (Watts et al., 2017). Similarly, after psilocybin and MDMA-assisted psychotherapy, individuals reported experiencing improvements in their relationships (Barone, Beck, Mitsunaga-Whitten, & Perl, 2019; Belser et al., 2017). Furthermore, in an RCT, healthy individuals receiving standard support for spiritual practice and two high doses of psilocybin (vs. two low doses) showed increases in closeness to others (Griffiths et al., 2018). Moreover, in healthy participants, a single dose of LSD leads to increases in positive social effects 1 and 12 months later (Schmid & Liechti, 2018). Finally, within a community sample, use of psychedelics leads to increased social connectedness 2 weeks later (Carhart-Harris, Erritzoe et al., 2018). In line with these findings, Carhart-Harris, Erritzoe et al. (2018) argue that connectedness may be a core transdiagnostic issue that is targeted by psychedelics.

Psychedelics may also target deficits in social functioning that are associated with BPD, including social pain, rejection sensitivity, trust, empathy, and emotion recognition. For instance, among individuals with treatment-resistant depression, psilocybin with psychological support improved emotional face recognition two weeks after administration, such that they were no longer different from healthy controls (Stroud et al., 2018). Similarly, double-blind randomized controlled experiments with healthy controls have shown that administration of psilocybin, LSD, and MDMA acutely reduce feelings of social pain, social exclusion, and recognition of negative emotions, and increase emotional empathy, trust, and closeness to others (e.g., Dolder, Schmid, Müller, Borgwardt, & Liechti, 2016; Frye, Wardle, Norman, & de Wit, 2014; Gabay, Kempton, Gilleen, & Mehta, 2019; Hysek et al., 2013; Kometer et al., 2012; Pokorny, Preller, Kometer, Dziobek, & Vollenweider, 2017; Preller et al., 2015, 2016). Based on these results, it has been suggested that psychedelics may be used to target psychiatric disorders characterized by social deficits, as well as enhance therapeutic alliance, which are important targets within interventions for BPD.

7. Risk, safety, and clinical considerations

Research suggests that psychedelics are safe when administered within controlled environments after careful screening. Serotonergic psychedelics show low levels of physiological toxicity, are not associated with bodily harm, neuropsychological deficits, or mental health problems and show low abuse and dependence potential (Hamill, Hallak, Dursun, & Baker, 2019; Johnson, Griffiths, Hendricks, & Henningfield, 2018; Johnson, Richards, & Griffiths, 2008), which is important given high rates of substance abuse among individuals with BPD (Trull et al., 2016). Mental health concerns very rarely occur (i.e., $< 0.2\%$ in vulnerable populations) following administration of serotonergic psychedelics in controlled settings (Cohen & Ditman, 1963). Among over 2000 patients that have been administered psilocybin, LSD, and ayahuasca in controlled research settings, there have been no serious adverse events reported (dos Santos et al., 2016; Johnson et al., 2008). Although MDMA is associated with greater abuse liability than serotonergic psychedelics, MDMA has been identified as being less dangerous than other frequently prescribed pharmacological agents (e.g., benzodiazepines; Nutt, King, & Phillips, 2010) and use of MDMA in a non-medical setting is rare after its administration in clinical contexts (Mithoefer et al., 2013). MDMA has been administered more than 1600 times within controlled settings and only one serious adverse event (i.e., a brief increase in pre-existing ventricular ectopy) and no deaths have been reported (Multidisciplinary Association for Psychedelics Studies, 2017).

The safety profile of ketamine is less clear, with potential side effects including dependence, craving, cognitive, urological, and hepatic concerns (for a review, see Strong & Kabbaj, 2018). Nonetheless, within clinical contexts, administration of ketamine has not been associated with persistent medical or mental health issues (e.g., substance abuse; Dore et al., 2019) and has been approved for a range of clinical indications, including treatment-resistant depression. As with all pharmacological interventions, important considerations exist related to the potential for negative interactions between psychedelics and other medications (e.g., serotonin reuptake inhibitors), as well as physical health issues (e.g., high blood pressure; for guidelines, see, Johnson et al., 2008; Kim & Mierzwinski-Urban, 2017; Sessa et al., 2019).

The primary issues related to administration of psychedelics are the potential for acute physiological discomfort (e.g., dizziness, weakness, tremors, nausea, vomiting, paraesthesia, blurred vision, and increased tendon reflexes) and challenging psychological experiences (e.g., anxiety, fear, and confusion; Hamill et al., 2019; Nichols, 2004). These challenging psychological experiences are generally considered an important component of the psychotherapeutic process (e.g., Carbonaro et al., 2016) and can generally be managed within clinical settings through preparation, session monitoring, and integration of challenging experiences.

Limited data regarding the safety and tolerability of psychedelics for individuals with BPD exists. A search of the literature identified nine studies that administered a psychedelic to individuals with BPD,

including a 3–9 month study of biweekly ritual ayahuasca administration that included one individual with BPD (Fernández et al., 2014), a single dose of ayahuasca to five individuals with BPD (Palhano-Fontes et al., 2019), and one to six administrations of ketamine to 63 individuals with BPD (Aust et al., 2019; Cole et al., 2018; Feifel, Malcolm, Boggie, & Lee, 2017; Grunebaum et al., 2017; Krupitsky & Grinenko, 1996; Lauritsen, Mazuera, Lipton, & Ashina, 2016; Murrough et al., 2015). Importantly, no serious adverse events were reported related to administration of psychedelics in any of these studies. Interestingly, Peter Gasser who has been conducting therapy with psychedelics in Switzerland for several decades, notes that "From 1988 to 1993, a significant number of patients with narcissistic personality disorders sought therapy with psychedelic drugs. The borderline personality disorder was also diagnosed rather often, as were depressed mood disorders and adjustment disorders. We can presume that the treatment is well suited for these disorders (Gasser, 1994, p. 7)."

It is important to note that Carhart-Harris, Bolstridge et al. (2018) report that they plan to exclude individuals with BPD from future trials with psilocybin for treatment of depression (see clinicaltrials.gov; NCT 03429075). Similarly, past MDMA-assisted psychotherapy trials have excluded individuals with BPD (e.g., Danforth et al., 2018; Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2011). Furthermore, other trials have excluded "psychiatric conditions judged to be incompatible with establishment of rapport or safe exposure to psilocybin (e.g., Griffiths et al., 2016, Supplementary material)." Additionally, some trials have excluded individuals with current serious suicide risk (e.g., Palhano-Fontes et al., 2019) or substance abuse (e.g., Ross et al., 2016), which may have indirectly resulted in exclusion of certain individuals with BPD.

Given the complexity surrounding BPD, the short-term nature of these trials, and that other psychiatric disorders were the primary interest, these decisions are understandable. Nonetheless, it is important to note that clinical trials with psychedelics have reported including individuals with current serious suicidal ideation and past suicidal behaviors (e.g., Ot'alora et al., 2018). Furthermore, current safety guidelines for conducting clinical research with serotonergic psychedelics do not specifically mention exclusion of individuals with BPD (although they do suggest excluding individuals with risk of psychotic disorders, as well as bipolar I or II disorder; Johnson et al., 2008).

The primary safety concerns related to administration of psychedelics are during their acute effects. Given the association between BPD and suicidal behaviors, it is especially important that any potential safety risks be minimized. Therefore, in line with common practice in psychiatric trials (e.g., Linehan, McDavid, Brown, Sayrs, & Gallop, 2008), we recommend that initial studies on the safety and tolerability of psychedelics for individuals with BPD exclude individuals with recent (i.e., in the past 8 weeks) serious self-harm or suicidal behaviors. Furthermore, in line with treatment guidelines for psychedelic-assisted psychotherapy (Johnson et al., 2008), it is recommended that administration of psychedelics occur (a) within controlled settings in which safety can be ensured, (b) in the presence of a treatment provider that can provide support, guidance and, although generally unnecessary, medication (e.g., benzodiazepines) if needed, (c) in a warm and comfortable environment, accompanied by the opportunity to listen to a selectively chosen music playlist (for the important role of music in psychedelic-assisted psychotherapy, see Kaelen et al., 2018), and (d) that preparation and integration sessions prior to and following administration of psychedelics be provided. Furthermore, during the preparation and integration sessions, we suggest that patients be encouraged to take time to integrate their experiences before making any major life decisions or changes (e.g., quitting their job, ending a marriage). Given the importance of the therapeutic alliance within psychedelic-assisted psychotherapy, as well as the potential difficulty surrounding establishing a strong therapeutic alliance with individuals with BPD (Bender, 2005), it is important psychedelic sessions occur only after patients report trusting their therapist. Additionally, with serotonergic psychedelics and ketamine, it may be helpful to begin with small doses and increase the dosage as the therapeutic alliance and commitment to change develop.

Given the complexity associated with BPD, we recommend that psychedelic-assisted psychotherapy be incorporated within an already established evidence-based intervention for BPD (e.g., DBT, TFP, or MBT). Relatedly, a recent study incorporating MDMA-assisted psychotherapy within an adapted version of DBT showed promising results for treatment of autistic adults with social anxiety disorder (Danforth et al., 2018). There is substantial overlap between BPD treatment targets and psychedelics. The principles of DBT and psychedelic-assisted psychotherapy show substantial overlap, including emphases on emotion dysregulation and enhancing mindfulness (for a discussion, see Walsh & Thiessen, 2018). There is also evidence that combining psychedelics with meditation, an essential component of DBT (Linehan, 1993), has positive and long-lasting synergistic effects (e.g., Smigielski, Scheidegger, Kometer, & Vollenweider, 2019). Furthermore, given the emphasis on behavioural change within DBT (Linehan, 1993) and suggestions that psychedelics induce a heightened state of plasticity (i.e., enhanced capacity to change; Carhart-Harris & Friston, 2019; Carhart-Harris & Nutt, 2017), integrating psychedelics and DBT may allow for optimal levels of behavioural change. Given the conceptual overlap between mentalization (i.e., making sense of one's social world by understanding one's own and others mental states) and mindfulness (Choi-Kain & Gunderson, 2008), integrating psychedelics with MBT may similarly help to optimize improved mentalization capacities. Finally, it has been suggested that psychedelics facilitate experiences of transference (Goldsmith, 2007) and enhance therapeutic alliance (e.g., Dolder et al., 2016; Mithoefer et al., 2011), which are essential components of MBT and TFP. Moreover, the altered sense of self (for a discussion, see Nour & Carhart-Harris, 2017) and relation to others (Bershad et al., 2019; Carhart-Harris, Erritzoe et al., 2018) induced by psychedelics and the emphasis on targeting the patient's representation of the self and others within TFP (Clarkin, Cain, & Lenzenweger, 2018), may benefit from one another. Accordingly, compared with either treatment alone, utilizing psychedelics alongside evidence-based interventions and their techniques, such as DBT (e.g., mindfulness, radical acceptance), MBT (e.g., 'validation of the transference,' 'mentalizing the transference'), and TFP (e.g., 'working with transference,' clarification, confrontation), may have positive synergistic effects for the treatment of BPD (see Fig. 1). Therefore, we argue that integrating evidence-based interventions for BPD with psychedelics will be essential for ensuring treatment safety and optimizing therapeutic outcomes.

8. Limitations and future research

The research described in this review has a number of important limitations. Much of the research described is cross-sectional, includes small sample sizes, fails to explore the long-term impact of psychedelics, and are based on open-label trials. Furthermore, maintaining blindness in placebo-controlled psychedelic research remains challenging (Barnby & Mehta, 2018). Most importantly, the research described in this review was not conducted with individuals with BPD. Therefore, in order to determine the safety, tolerability, and clinical utility of incorporating psychedelics within interventions for BPD, future research should aim to (a) establish the safety and tolerability of administering psychedelics to individuals with BPD, (b) explore the impact of psychedelics on behavioral dysregulation, emotion dysregulation, disturbances in self-identity, and social functioning among individuals with BPD, and (c) determine whether incorporating psychedelics within interventions for BPD improves treatment outcomes. Until such studies have been conducted, caution surrounding administration of psychedelics to individuals with BPD is strongly recommended.

One important barrier to conducting research with psychedelics are federal regulations (Nutt, King, & Nichols, 2013), which currently classify psychedelics, such as psilocybin, LSD, DMT, and MDMA as

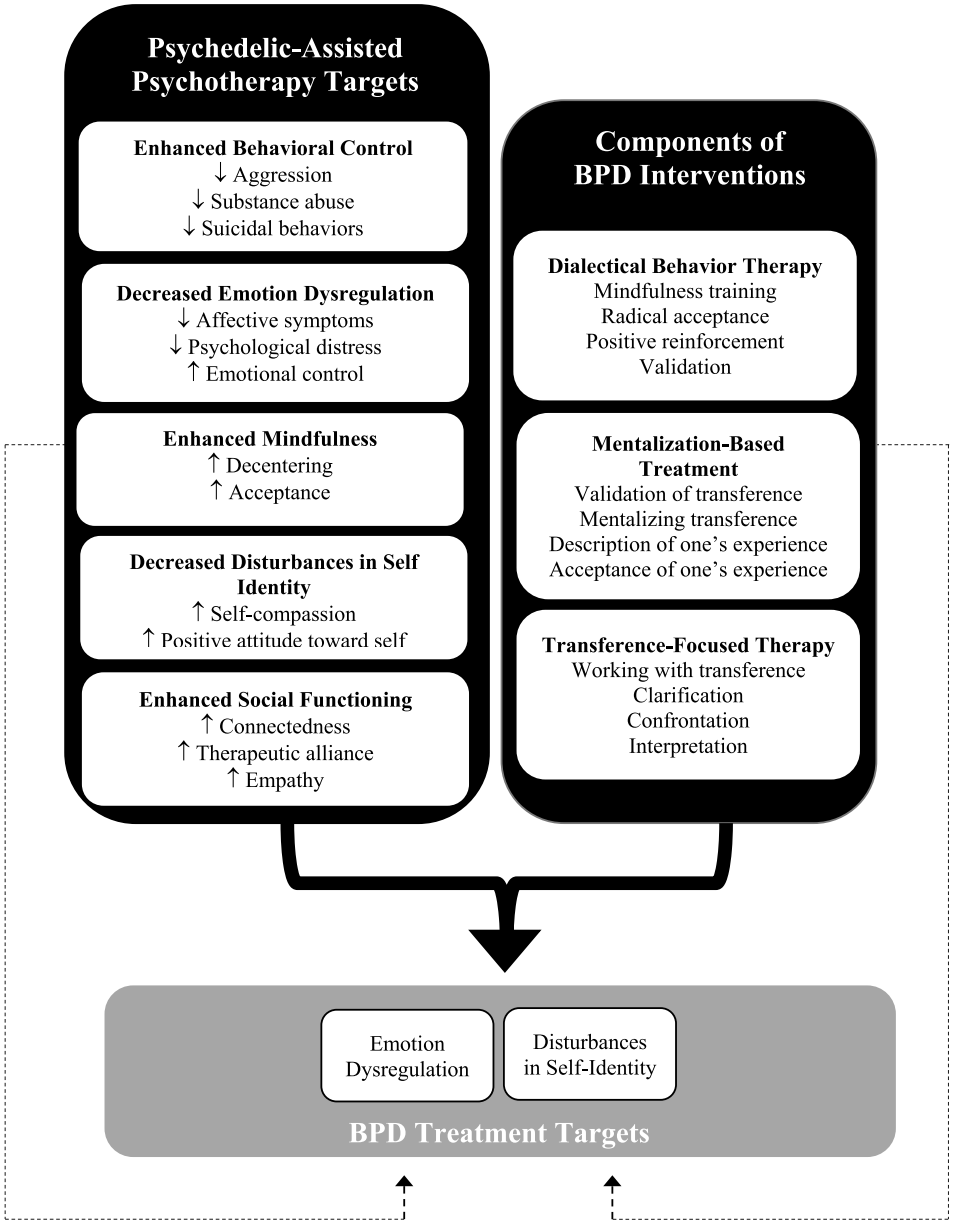

Fig. 1. Psychedelic-assisted psychotherapy targets, components of BPD interventions, and BPD treatment targets.

Schedule 1 drugs and ketamine as a Schedule 3 drug. Nonetheless, approval for conducting clinical research with psychedelics has been granted for a range of psychiatric disorders. Moreover, MDMA, psilocybin, and esketamine have received "Breakthrough Therapy Designation" by the US Food and Drug Administration (FDA) for posttraumatic stress disorder, treatment-resistant depression, and major depressive disorder with imminent risk of suicide, respectively. Furthermore, esketamine being approved by the FDA for treatment-resistant depression may allow for additional research on its impact on individuals with comorbid BPD. Interestingly, an ongoing phase 2 clinical trial is exploring ketamine (vs. Midazolam) as an intervention for BPD (single dose, with no indication of including concurrent psychotherapy; clinicaltrials.gov, NCT 03395314). Therefore, although challenging, conducting research with psychedelics appears possible and may ultimately contribute to improving interventions for BPD.

9. Conclusion

In summary, BPD is a severe psychiatric disorder characterized by behavioral dysregulation, emotion dysregulation, disturbances in self-identity, and deficits in social functioning. Despite the existence of evidence-based interventions for BPD, important limitations surrounding current interventions remain, including limited psychotherapeutic treatment efficacy (i.e., small-moderate effect sizes) and limited evidence for the efficacy of pharmacological interventions. Therefore, there exists a need for improving current interventions for BPD. Psychedelics, including psilocybin, ayahuasca, LSD, MDMA, and ketamine, show promise for treatment of a wide range of psychiatric disorders. Furthermore, research suggests that psychedelics may positively impact BPD treatment targets (i.e., behavioral dysregulation, emotion dysregulation, disturbances in self-identity, and social functioning) and target overlapping mechanisms of change in interventions for BPD (i.e., emotion dysregulation, mindfulness, and self-compassion). However, research has not yet directly explored the impact of psychedelics on BPD. Given safety considerations surrounding administration of psychedelics to individuals with BPD, we recommend strict guidelines, including administration of psychedelics within controlled and safe settings. Overall, this review suggests that conducting research on

incorporating psychedelics within therapeutic interventions for BPD (e.g., DBT) is warranted. Ultimately, research will be necessary to determine the clinical utility of incorporating psychedelics within interventions for BPD.

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