



Current Perspective on the Therapeutic Preset for Substance-Assisted Psychotherapy

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Specialty section:

This article was submitted to
Psychology for Clinical Settings,
a section of the journal
Frontiers in Psychology

Received: 14 October 2020

Accepted: 31 May 2021

Published: 13 July 2021

Citation:

Thal SB, Bright SJ, Sharbanee JM,
Wenge T and Skeffington PM (2021)
Current Perspective on the Therapeutic
Preset for Substance-Assisted
Psychotherapy.
Front. Psychol. 12:617224.
doi: 10.3389/fpsyg.2021.617224

The present narrative review is the first in a series of reviews about the appropriate conduct in substance-assisted psychotherapy (SAPT). It outlines a current perspective on preconditions and theoretical knowledge that have been identified as valuable in the literature for appropriate therapeutic conduct in SAPT. In this context, considerations regarding ethics and the spiritual emphasis of the therapeutic approaches are discussed. Further, current methods, models, and concepts of psychological mechanism of action and therapeutic effects of SAPT are summarized, and similarities between models, approaches, and potential mediators for therapeutic effects are outlined. It is argued that a critical assessment of the literature might indicate that the therapeutic effect of SAPT may be mediated by intra- and interpersonal variables within the therapeutic context rather than specific therapeutic models *per se*. The review provides a basis for the development and adaptation of future investigations, therapeutic models, training programs for therapists, and those interested in the therapeutic potential of SAPT. Limitations and future directions for research are discussed.

Keywords: substance-assisted psychotherapy, psychotherapy, psychedelics, therapeutic rationale, therapeutic conduct

INTRODUCTION

Research on psychotherapy utilizing psychoactive substances, subsequently referred to as substance-assisted psychotherapy (SAPT), has been re-established in the 21st century. This renewed interest has been referred to as the “psychedelic renaissance” (Sessa, 2012). It has followed a period in which these substances were stigmatized, not due to their international prohibition in 1971 since the early evidence collected on SAPT suggested psychedelics could be effective in treating a variety of mental health conditions; but rather, due to the circumstances in which they were prohibited (Grinspoon and Bakalar, 1979). With public and professional interest in SAPT rapidly growing, this narrative review presents the perspective on the necessary preset (i.e., valuable preconditions and knowledge) for practicing SAPT that has been identified in the current literature on the topic.

The recent growth in research has included clinical trials demonstrating the safety and efficacy of this approach for treatment refractory post-traumatic stress disorder (PTSD;

Mithoefer et al., 2019), alcohol dependence (Bogenschutz et al., 2015), as well as anxiety and depression associated with end stage cancer (Agin-Liebes et al., 2020). Open label trials have also indicated that psychedelic-assisted psychotherapy could be effective in treating obsessive-compulsive disorder (Moreno et al., 2006), treatment-resistant depression (TRD; Carhart-Harris et al., 2016), and nicotine dependence (Johnson et al., 2017). Although there is recent progress in recording the safety and effectiveness of these approaches paving the way for their potential implementation and application in clinical practice (e.g., Kargbo, 2020; Nichols, 2020), the mechanisms responsible for therapeutic change across different psychotherapeutic approaches are still not fully understood.

Classic psychedelics (e.g., LSD, psilocybin, DMT and mescaline) are regarded as non-addictive and do not appear to present an independent risk factor for mental health problems (Krebs and Johansen, 2013; Johansen and Krebs, 2015; Hendricks et al., 2015). Meanwhile, other psychoactive substances with subjective effects that are similar to psychedelics, such as ketamine (Krupitsky and Grinenko, 1997; Serafini et al., 2014), MDMA (Thal and Lommen, 2018) and ibogaine (Alper, 2001), are being investigated as for their potential use in SAPT.

Classic psychedelics and MDMA have been found to produce acute and persistent positive personality changes (Bouso et al., 2018) and improved well-being in healthy individuals (Else, 2017; Jungaberle et al., 2018). These substances have been linked to heightened mindfulness (Soler et al., 2016, 2018), a sense of connection to nature (Forstmann and Sagioglou, 2017), creativity (Kuypers et al., 2016; Uthaug et al., 2018; Mason et al., 2019), and openness (Liechti et al., 2017). Many researchers have called for more extensive research into the potential of the clinical applications of these substances, particularly in respect to the current mental health crisis (see Belouin and Henningfield, 2018; Schenberg, 2018) and the limited awareness of their potential amongst health care professionals (Barnett et al., 2018).

It is becoming increasingly apparent that the potential effects of SAPTs are dependent on several contextual factors, including psychological preparation prior to the experience (Johnson et al., 2008), extra-pharmacological manipulations in the form of specific music playlists (Kaelen et al., 2018), and psychological integration subsequent to the experience (Hartogsohn, 2017; Richards, 2017; Carhart-Harris et al., 2018; Garcia-Romeu and Richards, 2018). Key components that mediate the therapeutic alliance (e.g., unconditional acceptance and therapeutic presence) and have been shown to be strong predictors of outcome in traditional psychotherapy (Frank and Frank, 1991; Geller and Greenberg, 2012; Norcross and Lambert, 2018), are also likely play a vital role in SAPT (Greer and Tolbert, 1998; Garcia-Romeu and Richards, 2018).

In this narrative review, we will summarize valuable considerations, methods, models, and current (theoretical) concepts regarding the psychological mechanism of action and therapeutic effects of SAPT that are identified in the literature. Thereby, we highlight similarities between models and approaches to outline potential mediators for therapeutic effects. Further, we critically discuss literature indicating that various schools

of psychotherapy may translate and incorporate their approaches to SAPT. This article is intended to provide the preface (or preset) to a series of systematic and narrative reviews examining each stage of the SAPT treatment process, by outlining the valuable prerequisite knowledge for psychotherapists interested in practicing SAPT. In doing so, we have not considered the additional medical training and knowledge required to provide SAPT (e.g., physiological conditions and concomitant medications that would contraindicate SAPT) in this article since it is not within our scope of clinical practice.

ETHICAL CONSIDERATIONS

There are strict conditions and frameworks required by ethical committees of universities and research institutes currently investigating SAPT, extensive bureaucratic and jurisdictional exchange with government institutions, and cautious storage, documentation, and safety procedures are necessary to conduct research in this field (Strassman, 2001; Johnson et al., 2008; Bogenschutz, 2013; Nutt et al., 2013). While standard ethical guidelines apply to SAPT, additional considerations are vital. The Council on Spiritual Practices offers a code of ethics for spiritual guides that provides a framework for guiding people through exceptional states of consciousness that can be transferred to therapeutic sessions with psychoactive substances (Jesse, 2001). Therein, it is firmly highlighted that it is crucial for therapists to be well-intended and empathetic towards their clients due to augmented transference, counter-transference, and suggestibility (Leary, 1961; Fadiman, 2011; Carhart-Harris et al., 2015). As such, risks (both physical and psychological) should be discussed, preventive measures should be taken, and the client should be educated on the comparatively rapid transformative potential of the therapy (see Griffiths et al., 2006).

Therapists should be aware of the possibility of substance-occasioned uncomfortable material (sexual, or traumatic), and be prepared to respond to this using methods and techniques for which they are qualified through education, training, and experience (Grof, 2000; Phelps, 2017). In these situations, therapists need to simultaneously help clients process this material and prevent colluding with clients in acting out inappropriately (see Grof, 2000). Therapists and clients should agree upon limits on behaviors prior to the session. Such limitations could include outlining the parameters for appropriate touch, prohibiting self-harm, violence against facilitators and others, destruction of property, and sexual acting out (Mithoefer, 2017).

Increased vulnerability to suggestions and manipulations due to the heightened suggestibility in psychedelic states was identified in healthy volunteers after the administration of LSD (Carhart-Harris et al., 2015). This vulnerability, combined with increased attribution of certain ideas holding personal meaning or perceiving the ideas and contents experienced under the influence of psychedelics to hold greater noetic truth value in both healthy and clinical samples (Timmermann et al., 2020), may lead to reduced agency and judgment when compared to regular psychotherapy sessions. Even simple misunderstandings

might be more likely to occur and the validation and mediation of the content and knowledge experienced in these states raises important ethical considerations: the increased risk of iatrogenic complications (e.g., false memory syndrome; Pope, 1996) through induced noetic feelings of revelation. Timmermann et al. (2020) propose a pragmatic framework founded on an ethical approach embedding these experiences within larger cultural- and historical contexts while considering their intersubjective character. They stress the importance of validation based on empathy by an experienced therapist to facilitate appropriate processing and integration of these experiences while considering aforementioned challenges. There is also an increased importance for therapists to be aware of the limitations on scope of practice required by most psychotherapy regulatory bodies, including preventing clients from being exploited, and therapists having an awareness of their own limitations, values, needs, and beliefs. Most importantly, therapists should be open for regular peer-review and seek council and feedback from other practitioners as required by most professional bodies. This is of utmost importance in SAPT because of the strict legal framework that must be considered and the aforementioned elevated potential for misperception and misjudgment.

The need for therapists' self-experience with altered states of consciousness and substances that are administered in SAPT is controversial. For example, Forstmann and Sagioglou (2021) found that the perception of a researcher's integrity and quality of their research by psychedelic naïve participants was reduced if the researcher self-admitted substance use (Forstmann and Sagioglou, 2021). While there will likely be a continuum amongst therapists engaged in SAPT clinical trials, ranging from those without any personal experiences to those with a vast amount of experience across substances and settings, open discussion of these experiences can be constrained for fear of personal, professional, and sometimes legal consequences (Nielson and Guss, 2018; Ross et al., 2020). Some practitioners in the field regard personal experiences with these substances as essential in order to emphasize with the client's experiences (Metzner, 1998; Bogenschutz, 2013; Bogenschutz and Forcehimes, 2017) and in certain countries, such as Switzerland, personal experience is required for therapists to work with clients in SAPT settings (Grof, 2000; Strassman, 2001). However, personal experiences may lead some therapists to become less curious about the client if they believe that their clients' experience will be similar to their own (Bogenschutz, 2013; Bogenschutz and Forcehimes, 2017). Thus, personal experience is a double edged sword that may be a potential confound to research and SAPT, though has not yet been empirically investigated (Nielson and Guss, 2018). Also, in line with standard ethical guidelines, we believe that therapists should not take any mind-altering substances before or during therapy sessions, regardless of whether they are providing SAPT or regular psychotherapy.

SPIRITUAL EMPHASIS OF THE THERAPY

Substance-occasioned spiritual or mystical experiences have been described as ineffable, noetic, and sacred, involving time

dilation and ego dissolution (Griffiths et al., 2006, 2008; MacLean et al., 2011). They may be compared to non-substance-induced personal encounters with God, a divine entity, or Ultimate Reality (Griffiths et al., 2019). Such research using psychometric outcome measures was first conducted at Harvard over 50 years using a 43-item tool developed by Pahnke (1969). More recent research has typically used a 30 item iteration of this tool (the revised Mystical Experience Questionnaire; MacLean et al., 2012), which appears to have more robust psychometric properties (Barrett et al., 2015).

Since this therapeutic experience may be regarded as one of the most meaningful experiences of the clients' lives (Griffiths et al., 2006, 2008; MacLean et al., 2011; Preller et al., 2017; Schmid and Liechti, 2018), Garcia-Romeu and Richards (2018) have proposed that therapists consider treating it accordingly throughout the entire therapeutic process. Adamson and Metzner (1988) have claimed that even though therapists may not be religious themselves and exclude these aspects from their usual work, spiritual perspectives on the experience that may arise in the clients engaged in SAPT should be respected and supported. While an emphasis on specific religious systems has been discouraged by Grof (2000), he has proclaimed it as useful to focus on the awareness of the aesthetic aspects of the world, basic philosophical questions of life, and the recognition of spiritual dimensions of existence in a non-specific way. Meanwhile, Stolaroff (2004) has proposed that unless clients are using the word "spiritual," it might be advisable to avoid labels, due to the danger of enhanced suggestibility. Importantly, avoiding the psychological blockages and focusing on the repetition of spiritual experiences (i.e., spiritual bypassing), may constitute a pitfall for therapeutic progress, with Frecska et al. (2016) cautioning that it may result in avoidance of the real psychological issues and an unhealthy relationship with spiritual aspects of substance-induced experiences.

As outlined below, therapeutic approaches that integrate contemplative spiritual practices like third wave behavior therapies (TWBTs) have been identified as valuable frameworks for SAPT in the literature (Walsh and Thiessen, 2018). Recent research investigating the interaction between meditation and psilocybin found potential synergistic effects of meditation practices and mystical experiences or ego dissolution occasioned by psilocybin (Griffiths et al., 2018; Smigielski et al., 2019). This finding may suggest that the development of mindfulness- or other spiritual or meditative practices through the preparatory and integration stages of therapy could potentiate the treatment effects (Walsh and Thiessen, 2018).

MECHANISM OF ACTION AND THERAPEUTIC EFFECTS OF SUBSTANCE-ASSISTED PSYCHOTHERAPY

It is predominantly believed that the therapeutic effects of substance-assisted treatments are a combination of the psychopharmacological effects of the substance (e.g., see Carhart-Harris et al., 2014;

Carhart-Harris and Friston, 2019; Preller et al., 2019), which influence the client's intrapsychic experience, but also the shared interpersonal experience between client and therapist (Adamson and Metzner, 1988), the mindset of the client and the therapist, and successful psychotherapeutic integration of the experience (Mithoefer, 2017; Bogenschutz et al., 2018; Malone et al., 2018). Thereby, the quality, intensity, and duration of challenging parts of the acute psychedelic experience may be key mediators for the therapeutic outcome (Carbonaro et al., 2016; Roseman et al., 2018). However, the acute and long-term or persistent effects (more relevant for treatment effects) differ substantially (Carhart-Harris et al., 2016), so the specific psychological mechanisms that account for their therapeutic efficacy are still not comprehensively understood. Various acute and persistent effects of psychedelics and entactogens were outlined by Jungaberle et al. (2018) and include, amongst others, positive effects on well-being, mood, empathy, cognitive flexibility, self-transcendence, and openness. However, individual experiences might be extremely variable and generalizations based on single sessions and small sample sizes are problematic (Grof, 2000; Bogenschutz et al., 2018) due to different personality structures of the client (Sandison and Whitelaw, 1957; Cohen, 1960; Gucker, 1963) amongst other individual differences. Consequently, attempts to depict and generalize the psychological mechanisms of action rendering SAPT an effective treatment option for certain disorders draw on similar terminologies to frame distinct theoretical concepts. These concepts may not be mutually exclusive (i.e., they tend to partially intersect). Thus, significant differences seem to be more evident in the theoretical foundations the concepts stem from rather than their conclusions. In this section, we have attempted to merge these concepts as derived from diverse models into meaningful clusters. We have also not attempted to distinguish the moderating factor of which psychedelics could differentially contribute to each mechanism, as the literature at present does not seem advanced enough for such an analysis.

Personal Significance, Insights, and Meaningfulness

Early psychedelic research assumed that a heightened sense of significance and meaningfulness (also described as prolonged "eureka" experience) under the influence of certain substances contributed to the therapeutic effects (Ludwig and Levine, 1965b). Material encountered during substance-assisted sessions is usually personal and uniquely meaningful (Griffiths et al., 2006, 2008; MacLean et al., 2011; Preller et al., 2017; Schmid and Liechti, 2018) and relevant to the facilitation of personal growth in each client (Cutner, 1959; Shanon, 2003; Bogenschutz et al., 2018).

The importance of personal meaning has been highlighted in various empirical studies. In a randomized, double-blind, active placebo-controlled study, 29 participants experiencing cancer-related anxiety and depression received a single-dose of psilocybin in conjunction with psychotherapy (Ross et al., 2016). Through synthesizing prior qualitative analyses of interviews with these participants (Belser et al., 2017; Swift et al., 2017), with a qualitative analysis of their written narratives

and their therapists' notes, Malone et al. (2018) found that psilocybin may support clients in gaining insight regarding the root cause of their issues or disorders due to the personalized nature of the subjective experiences that seems to be tailored to individual psychological needs.

This hypothesis is supported from the results of a pilot study of 13 participants ($N = 9$ with diagnoses of substance abuse and/or dependence) in which self-report measures of the Purpose of Life Test significantly increased at three and nine-month follow ups after treatment with Ayahuasca (Fernández et al., 2013). In another study, 36 participants without prior experience with psychedelics received psilocybin or placebo in a double-blind counterbalanced design (Griffiths et al., 2006). In a 14-month follow-up, 58% of the participants assessed the experience as one of the five most personally meaningful experiences of their lives with 64% indicating persistent increases in life-satisfaction or well-being (Griffiths et al., 2008). Similarly, 13 of 15 (i.e., 86%) participants in a one-year follow-up of a psilocybin-facilitated smoking cessation trial rated the experience amongst the five most meaningful experiences of their lives (Johnson et al., 2017) and 10 of 14 (i.e., 71%) healthy volunteers in an LSD study rated the experience as one of the ten most meaningful experiences of their lives at one-year follow-up (Schmid and Liechti, 2018). Personally meaningful and emotional experiences with mystical qualities or ego dissolution are now thought to have causal links to persisting positive effects (Bogenschutz and Ross, 2016).

Awe and Peak-Experiences

Awe can be defined as an emotion that is associated with profound pleasure bordering on fear while appreciating vastness (perceiving various stimuli as larger than the self) and accommodation (the need to revise mental structures to integrate novel experiences and perspectives; Keltner and Haidt, 2003). It is hypothesized that the profound awe that characterizes peak experiences occasioned by psychedelics may require habituated mental structures to accommodate to integrate and account for these novel perceptions and experiences. This process of cognitive re-accommodation may result in disorientation, fear, ego dissolution, and subsequent feelings of ultimate knowledge and enlightenment – once new information can be assimilated through the adaptation of mental structures (Hendricks, 2018). As a result, the profound feeling of awe may encourage one to superordinate the social collective to one's individual needs, i.e., decrease egocentrism (Bai et al., 2017), and thus facilitate cooperation (Gowdy and Krall, 2015), shift attention to the presence while expanding experience of time (Rudd et al., 2012), and decrease tolerance for uncertainty which in turn elevates the inclination to acknowledge the influence of supernatural agents in experiences (Valdesolo and Graham, 2014). Thus, the sense of heightened connectedness or oneness with others and the universe (Carhart-Harris et al., 2018), and the shift of attention towards the collective and away from the self are theorized to constitute the positive treatment effects of psychedelics across a range of disorders (see Hendricks, 2018).

Reconditioning

One potential mechanism of change in SAPT is the breaking of previously rigid maladaptive emotional and cognitive patterns, prior to them being reformed and reintegrated in a new structure (Freckska, 2011). This has been referred to as “restructuring,” “retraining” or “reconditioning” treatment (Spencer, 1964). The process can be seen as a “secure form of regression” (Freckska, 2011), in which old associations are broken down and unlearned. Thus, previously frightening stimuli could lose their association with threat, and become *deconditioned*, before being reintegrated in a less problematic way. This has also been described as “de-patterning” (Gasser et al., 2015). Neuroscientific evidence suggests that hyperexcitation in layer V pyramidal neurons mediated by the 5-HT_{2A} agonism of psychedelics may disrupt fixated and conditioned cognitions, psychological habits, and constraints on internal generative models (Swanson, 2018). Disinhibition of these neurons may reduce the rigidity of higher-level beliefs (in a hierarchical predictive processing model) making them more receptive for bottom-up prediction errors (Carhart-Harris and Friston, 2019). Thereby, prior fixed beliefs may be more easily challenged and restructured by novel information. This might be reflected by lasting changes in attitudes (i.e., increased openness and extraversion and decreased neuroticism; Erritzoe et al., 2018) and beliefs in individuals who used psychedelics (Nour et al., 2017; Jungaberle et al., 2018).

Perspective-Shifts and Cognitive Flexibility

Another proposed mechanism of action is perspective-shifts or cognitive flexibility. Seemingly, this mechanism can be interpreted as a combination of a restructuring or shifting of pre-existing concepts through experiences that carry emotional and/or intellectual value (see Section “Awe and Peak-Experiences”). New perspectives and insights might be gained and more rapidly accepted because of a novel sense of emotional and intellectual appreciation occasioned by the substance (Ludwig and Levine, 1965a). Some authors suggest that processing of significant emotional or intellectual content, combined with loosened ego functions in an altered emotional state, may allow for a reduction of ruminations and egocentricity (Northoff, 2007; Pizzagalli, 2011) wherein novel perspectives may be gained (Leuner, 1967; Carhart-Harris et al., 2014) and problems may be appreciated for their true significance (Hofmann and Ott, 1980). The potential for a client to experience an alternative view of themselves has been referred to as “stripping away layers of onions” by some therapists (Cattell, 1957, p. 227). Gasser et al.’s (2015) mixed methods data from 10 participants who received LSD-assisted psychotherapy suggest that amongst other variables, the cognitive experience (i.e., altered cognitive associations allowing for novel perspectives on intra- and interpersonal problems and relationships) mediates positive outcomes.

In a phenomenological discussion of the Ayahuasca experience, Shanon (2003), reported shifts in the locus of consciousness, self-consciousness, and personal identity (i.e., positive self; see Griffiths et al., 2008) that may result in heightened cognitive flexibility and support the adaptation

to different contexts (Franquesa et al., 2018). Subjective feelings of increased connection with oneself were linked to positive treatment effects of Ayahuasca for substance use in an observational study of 12 participants in a retreat combining 4 days of group counseling and two Ayahuasca sessions (Thomas et al., 2013).

Ayahuasca and psilocybin were both shown to have acute and prolonged effects on cognitive-thinking style (Kuyppers et al., 2016; Uthaug et al., 2018; Mason et al., 2019) and positive treatment effects of psilocybin may result from shifts in self-representation (Smigielski et al., 2019). Neurocognitively, these shifts may be linked to enhanced cognitive flexibility (Gallimore, 2015) and altered neural connectivity (Tagliazucchi et al., 2016; Carhart-Harris et al., 2017; Preller et al., 2019). This may also be reflected in changes in personality measures like decreased neuroticism and increased conscientiousness and extraversion (i.e., openness) that have been observed in an open-label trial of 20 participants with moderate to severe TRD (Erritzoe et al., 2018).

Qualitative data (Watts et al., 2017) from aforementioned open-label study investigating psilocybin for TRD (Carhart-Harris et al., 2016) suggests that psychedelics combined with psychotherapy may increase psychological flexibility more than psychotherapy itself (Watts and Luoma, 2020). It is suggested that increased psychological flexibility may mediate therapeutic effects (Hayes et al., 2012) in Acceptance and Commitment Therapy (ACT). This has led some authors (e.g., Sloshower et al., 2020; Wolff et al., 2020) to suggest that ACT might exhibit synergistic therapeutic mechanisms with SAPT. However, these speculations have yet to be verified.

Mindfulness and Acceptance

Mindfulness and acceptance are important aspects of TWBT that share conceptual links and presumptions with the mechanisms outlined above. Namely, Wolff et al. (2020) proposed that shifts from experiential avoidance to acceptance (which is closely related to mindfulness-practices and a mediator of therapeutic effects in TWBTs) may be facilitated by the relaxation or disinhibition of higher level avoidance-related beliefs (see Sections “Reconditioning” and “Perspective-Shifts and Cognitive Flexibility”), elicitation and intensification of private events (see Section “Personal Significance, Insights, and Meaningfulness”), and operant conditioning of acceptance. During substance-assisted experiences, avoiding aversive aspects of the experience may increase adverse responses, while acceptance of the experiences may result in more rewarding responses (this was termed “avoidance sensitivity”). This results in the operant conditioning of acceptance instead of avoidance. The conditioned openness and acceptance may allow for exposure and consideration of private events that would otherwise be avoided. As a result, previously held beliefs may be revised during the relaxation of avoidance-related beliefs since this state allows for strong experiential contradictions to negative expectancies, i.e., the experience of oceanic boundlessness, blissful ego dissolution, and long-term increases in well-being (Wolff et al., 2020).

Substance-induced dissociation from one’s learned roles and habits coupled with a conflict-free state of being may foster

acceptance of oneself. This hypothesis is supported by an independent group ($N = 20$ participants) self-report study comparing four consecutive Ayahuasca sessions with an eight-week mindfulness-stress reduction (MBSR) course (Soler et al., 2018). Results indicated that Ayahuasca and MBSR led to comparable increases in acceptance on the Non-Judging Subscale of the Five Facet Mindfulness Questionnaire. Meanwhile, a thematic analysis of semi-structured interviews of 20 participants' accounts of an open-label trial of psilocybin for TRD at 6 months follow-up found change processes from disconnection (from the self, fellow human beings, and the world) to connection and from emotional avoidance to acceptance (Watts et al., 2017).

The potential for more open exploration of psychodynamic connections has been noted in early psychedelic research (Hausner and Dolezal, 1963). Further, decentering – observing one's feelings and thoughts in a detached manner (Kerr et al., 2011) – was positively associated with Ayahuasca use in a self-report study of 41 participants without prior experience with the substance and 81 experienced participants (Franquesa et al., 2018). In a randomized, double-blind, placebo-controlled study of 38 participants in a mindfulness retreat, a single psilocybin experience was linked to alterations in mood, social behavior, spirituality, and attitudes about life (Smigielski et al., 2019). Long-term increases in mindfulness following a single dose of psilocybin in ten psilocybin-naïve participants persisted for at least 3 months, even without explicit mindfulness training. This increase in mindfulness may represent a key mechanism of psilocybin therapy (Madsen et al., 2020). Perceptual and qualitative changes regarding intra- and interpersonal consciousness and perceived mindfulness capacities have also been reported by clients who have received SAPT. Bogenschutz et al. (2018) have proposed that these changes mediate positive treatment effects.

Re-assessment of Memories

Re-experiencing and re-assessing memories under the influence of certain substances may be another mechanism of action underlying SAPT that evidences conceptual links to personal meaning and perspective-shifts. This overlap of mechanisms may be most evident in the current rationale of the treatment effects of MDMA-assisted psychotherapy. MDMA increases cortisol, prolactin, oxytocin, dopamine, norepinephrine, and serotonin which in turn increases empathy and self-confidence and reduced feelings of anxiety and depression. This allows clients to revisit memories and experiences while staying emotionally engaged without being overwhelmed by negative emotions which may facilitate memory reconsolidation (Mithoefer, 2017; Thal and Lommen, 2018).

Based on clinical experiences with clients who have undergone SAPT with serotonergic psychedelics, Sandison (1959) has suggested that early memories could be re-experienced in vivid detail. While these memories are likely a mixture of facts and fantasies that contain archetypical experiences, these experiences (Spencer, 1964) may allow for acceptance of more important emotional connotations (see Sections "Personal Significance, Insights, and Meaningfulness" and "Mindfulness and Acceptance")

and thus result in personal growth regardless of their factual truth. Similarly, positive effects of abreaction itself under the influence of certain substances may not be dependent on the factual truth of the traumatic incident, but rather linked to the release and re-assessment of trauma-related emotions (see also Mithoefer, 2017). Curiously, describing specific episodic content of the psychedelic experience is usually more difficult than illustrating its cognitive and emotional impact (Bogenschutz et al., 2018). However, the ineffability of the experience does not seem to impact its treatment effects or its perceived meaningfulness (Malone et al., 2018).

In contrast, a placebo-controlled crossover study with 20 healthy participants by Speth et al. (2016) found that the intensity of the LSD experience was positively correlated with reduced mental time travel to past events. The authors argue that mind-wandering to past events may be more specific but less frequent under LSD. Since ruminating about past events is linked to reduced happiness (Killingsworth and Gilbert, 2010), psychedelics may display similarities to mindfulness-based therapies and thus foster mental focus on the presence (Shapiro et al., 2006; Soler et al., 2016, 2018). Gasser et al. (2015) found that, besides the cognitive experience, the psychodynamic experience (i.e., emergence of unconscious material into consciousness and/or reliving of past experiences) and the associated abreactions and catharsis plus the peak-experiences (i.e., ego dissolution, transcendence of time and space, and the sense of having meaningful novel insights), mediated positive outcomes in LSD-assisted psychotherapy. Intense emotional experiences with a state of well-being, pure presence (i.e., existing in the here and now), and freedom from past concerns, guilt, anxiety, and depression combined with the absence of former tensions had the most significant effect on clients. Similar experiences of psychodynamic material, catharsis, connection, love, and self-compassion have been reported in clinical investigations with psilocybin (Bogenschutz et al., 2018).

Neuroscientific research suggests that reactivation of past memories, reconsolidation through incorporations of new emotional responses related to these memories, and reintegration through altered behavior in everyday situations may result in therapeutic change in non-substance assisted therapy (Lane et al., 2015). It is possible that this similar mechanism contributes to the change in SAPT as well.

Dreamlike Qualities

Some psychoactive substances have been associated with experiences with dreamlike qualities (Jacobs, 1978; Fischman, 1983; Wilkins et al., 2011; Carhart-Harris and Nutt, 2014; Morris and Wallach, 2014; Kraehenmann, 2017; Kraehenmann et al., 2017; Rodger, 2018; Sanz and Tagliazucchi, 2018) and it has been suggested (e.g., Kraehenmann, 2017) that the positive effects of dreaming on well-being and social functioning may also be applicable for psychedelics. It is further hypothesized that altered self-awareness occasioned by some substances may result from perspective-shifts (from first-person to third-person

perspective) as is often reported in dreams (Thompson, 2014; Sanz and Tagliazucchi, 2018). Kraehenmann (2017) proposed that fear extinction and formation of novel extinction memories through associative learning in contexts that are not associated with fear (Nielsen and Levin, 2007; Levin and Nielsen, 2009) and memory reconsolidation (Schiller et al., 2010; Rolls et al., 2013) may be related to similar cognitive processes in psychedelics and dreams. These concepts overlap with deconditioning, and re-assessment of memories.

THE DEVELOPMENT OF MODELS FOR SUBSTANCE-ASSISTED PSYCHOTHERAPY

In the literature, models of SAPT have been distinguished primarily according to the dose of the active substance (Mangini, 1998). Low dose SAPTs, or *psycholytic therapy* (Pahnke et al., 1971), and high dose SAPTs or *psychedelic therapy*, sometimes referred to as *psychedelic peak-therapy* (Sherwood et al., 1968; Pahnke et al., 1971; Grof et al., 1973), each attempt to facilitate different processes. In *psycholytic therapy*, low to medium doses of psychoactive substances are used to foster the gradual and progressive unfolding of various levels of the unconscious activating and accelerating the process of psychodynamic or psychoanalytic psychotherapy (Leuner, 1967; Grof, 2000; Bogenschutz, 2013; Majić et al., 2015). Active verbal psychotherapy is conducted while the client experiences the effect of the substance that is used to facilitate revival and abreaction of past experiences and emotional releases, loosen defense mechanisms, and deepen introspection and insight. This is mediated by the therapist's interpretation of unconscious material (Eisner and Cohen, 1958; Sandison, 1959; Leuner, 1967; Bogenschutz, 2013). Repeated sessions of SAPT (sometimes up to 80) are embedded within a psychodynamic or psychoanalytic psychotherapy process (with significantly more substance-free than SAPT sessions) stretching over several months or years (Chandler and Hartman, 1960; Leuner, 1967). This extensive time-frame renders the comparison to other models and the isolation of the effects of SAPT-sessions extremely difficult. Psycholytic therapy was employed as preferred treatment model for patients with less severe disorders, such as psychosomatic-, mood-, neurotic-, or personality disorders and those with an intellectual interest in the therapeutic process (Grinspoon and Bakalar, 1979; Gasser, 1995; Grof, 2000). Conveniently, the gradual unfolding of various layers of the unconscious may allow for unique insights across a variety of domains. In doing so, clients might achieve an enhanced understanding of different mechanisms and areas of the mind through which alterations in behavior or cognition may be achieved (Grof, 2000). Disadvantages include that this can require a long duration of treatment, and lower doses may mean clients ignore or resist more challenging qualities of the experience. Over the course of therapy, the experience of transference may inevitably intensify, leading to a deterioration of symptoms and decompensation. Finally, the conventional psychodynamic framework of the approach may be challenging

to apply to more extraordinary experiences that transcend interpersonal and verbalizable realms (Grof, 2000). While psycholytic therapy has influenced current investigations into therapeutic applications of psychoactive substances, it has not been employed as the main model in recent clinical trials.

Psychedelic therapy employs high doses of psychoactive substances that substantially exceed those administered under psycholytic frameworks (although there is a certain variability to "low" and "high" doses in reported studies and standardized "high" and "low" doses are not distinctly defined). It assumes that the therapeutic effect is produced by the facilitation of the experience of ego dissolution, also referred to as mystical- or peak experience (Griffiths et al., 2006), thereby transcending the psychodynamic levels (Grof, 2000). As such, substances are only used in one to three sessions (guided by the intended effect and the model of treatment being used), while preparation- and integration sessions without substances may or may not be incorporated (Grof, 2000; Johnson et al., 2008; Bogenschutz, 2013). While psychotherapy is used to maximize the probability of these experiences to occur (Sherwood et al., 1968; Pahnke et al., 1971; Grof, 2000; Bogenschutz, 2013), the approach is not based on classic psychological theories (Leuner, 1967; Majić et al., 2015). The therapist supports the client in surrendering to and accepting the experience, but is non-directive and does not guide the client towards or away from particular experiences (Pahnke et al., 1971; Rhead et al., 1977; Bogenschutz, 2013). While music is provided, and therapists observe the client quietly, verbal interventions are usually not applied during the peak-substance effects (Bogenschutz, 2013).

Recent research has used the psychedelic approach (Bogenschutz et al., 2018; Nielson and Guss, 2018) as treatment for conditions such as addiction disorders and depression (Johnson et al., 2014; Bogenschutz et al., 2015; Carhart-Harris et al., 2016; Griffiths et al., 2016). The advantage of the model is that, due to the high doses used, clients may be less likely to be able to resist the effect of the substances and may be more likely to completely surrender to the experience. This can allow for much more substantial effects in a single session compared to psycholytic therapy, which in turn makes psychological and environmental factors, i.e., set and setting (see Leary, 1961; Hartogsohn, 2016) more important for positive therapeutic effects. Due to its non-directive nature, there is no imperative for confrontation of psychodynamic conflicts. Instead, a greater depth, intensity, and spontaneity of the session has been described (Grof, 2000). Disadvantages may include the risk of greater emotional upheaval due to the more profound effects of the substances and greater physiological risks because of the higher doses (depending on the substance, of course). The non-directive approach may require the therapist to surrender to and support the process rather than focus on techniques and methodologies. It is mentioned that this requires a high level of expertise and trust in the process and that it is currently not clear whether improvements and transformations experienced in psychedelic therapies represent temporary shifts, or if deep structural psychodynamic changes may be attained. Although the general expectations may be higher in clients receiving this approach, it is impossible to guarantee profound experiences

in all clients, which may lead to disappointment. The mechanism of action of therapeutic change is still not well understood and the entire experience can be difficult to capture, quantify, and integrate (Grof, 2000).

There is considerable overlap between certain fundamental assumptions of psycholytic and psychedelic models, leading some authors to suggest the approaches might be blended in practice to form a hybrid model (Mechanek et al., 1968; Metzner, 1998). Non-directive approaches may be used during intense parts of the session, while discussion, interpretive work and meaning making may start before the effects of the substance have ceased completely (Masters and Houston, 1966; Grof, 2000; Bogenschutz and Forcehimes, 2017; Nielson and Guss, 2018). In this case, the adaptability of the therapist based on the client's process would be vital.

In current models of MDMA-assisted psychotherapy for PTSD, this mixed approach has been recommended by Mithoefer (2017). The substance-assisted sessions are predominantly client-led; clients are encouraged to lie back with eyeshades on, focus inwards, and be present with their traumatic memories. Therapists gently guide clients to consider particular aspects of their traumas, and if necessary a short general discussion of the content of the session follows once the effects of the substance begin to subside (Mithoefer, 2017; Sessa, 2017; Sessa et al., 2019). There are reported exceptions to this approach. In a study by Wagner et al. (2019) clients alternated between spending time focused inside and time focused outside without headphones and eyeshades spend in conversation with their partner or therapists. In theory, all models for SAPT may allow for an incorporation of a variety of different schools of psychotherapy.

SIMILARITY BETWEEN PRIMARY MECHANISMS OF CHANGE IN VARIOUS FORMS OF PSYCHOTHERAPY AND MECHANISMS OF CHANGE IN SAPT

Some of the mechanisms presented in the SAPT literature may also overlap with putative mechanisms of change posited in the non-SAPT psychotherapy literature. In this section we will relate the SAPT mechanisms to four key putative mechanisms, each highlighted as a central change mechanism by one of the major psychotherapy traditions: insight, cognitive restructuring, mindfulness, and experiencing.

Even though there has been a temporal shift from Freudian techniques to humanistic orientations (Grof, 2000), most of the therapies in the first wave of psychedelic research applied historically dominant psychoanalytic models (Roseman et al., 2018). Additionally, there have been case studies including use of exposure therapy (Costello, 1964), arguments for the application of learning theory for behavioral re-programming (Grieco and Bloom, 1981), and comparisons between approaches used in indigenous cultures using Ayahuasca and transpersonal, depth psychological, and parapsychological approaches and interpretations (Andritzky, 1989).

In recent studies, humanistic therapies such as logotherapy (Ross et al., 2016), as well as CBT models (Johnson et al., 2014; Wolff et al., 2020) and third wave CBT approaches like ACT (Hayes and Wilson, 1994; Carhart-Harris and Nutt, 2017; Watts et al., 2017; Sloshower et al., 2020), DBT which has been described as “behavioral translation of Zen”; Nuys, 2007) and mindfulness-based cognitive therapy (MBCT; Walsh and Thiessen, 2018) or motivational enhancement therapy (MET; Bogenschutz et al., 2015; Sessa et al., 2019) are used or being proposed as therapeutic frameworks. These therapies each attempt to target similar mechanisms to those identified as potential mechanisms in SAPTs.

Insight in Psychodynamic Therapies

Insight has been considered to be a central mechanism of change, emphasized primarily in the psychodynamic tradition. Originally, Freud postulated that symptoms developed from repressing unacceptable material. From this perspective, a central mechanism of change involved making the repressed unconscious material conscious, especially regarding the historical developmental origins (Freud, 1920). Since the relational turn, this focus has shifted slightly, to specifically highlight the importance of insight into internalized relational configurations or models of self and other that developed from early experiences with attachment figures (Greenberg and Mitchell, 1983).

This focus on change through insight into previously repressed material, and insight into the effect of early relationships in psychodynamic treatments closely links to the SAPT mechanisms we have identified as *re-experiencing of memories* and *personal significance, insights, and meaningfulness*. Psychodynamic treatments would primarily use genetic interpretations into the developmental origins of the difficulty, and transference interpretations into the replaying of the relational patterns, to both identify and make meaning out of this material. However, with SAPTs we could see the initial process of insight being facilitated by the evocative function of the substance. The traditional meaning-making process of psychodynamic treatment would be highly relevant integrating the evoked material during a subsequent integration stage.

Cognitive Restructuring in Cognitive Therapies

The central putative mechanism associated with Cognitive Therapy is changing beliefs through reasoning, or *cognitive restructuring* (Ellis, 1962; Beck, 1976). This mechanism has primarily been targeted by disputation (Ellis, 1962) and Socratic dialogues (Beck, 1976), in which people are lead to examine their beliefs through open questioning and evaluating evidence. This mechanism overlaps with what we have identified here as *reconditioning* and *perspective-shifts and cognitive flexibility*. While clearly, the initial shifts in SAPT come from substance induced evocation, not through reasoning processes, but the overlap of the identified mechanisms suggests that they may shift a common mechanism. This also implies that standard cognitive techniques may be relevant to consolidate the *restructuring* and *perspective shifts* during the integration stage of SAPTs.

Mindfulness in Third Wave Behavioral Therapies

There are theoretical affinities between TWBTs (Hayes et al., 1999; Segal et al., 2002) and psychedelic therapy, such as their common root in contemplative spiritual practices, and the development of mindfulness as a putative mechanism of action (Soler et al., 2016, 2018; Smigielski et al., 2019). In TWBT, the psychological state of mindfulness is developed primarily through the practice of mindfulness techniques, such as imagining thoughts on a leaf in a stream, and meditation. While achieved through a different method, the resulting state of mindfulness may be similar to the state observed after the ingestion of psychedelics (Soler et al., 2016). This synergy suggests that mindfulness, acceptance, and meditation practices, like those included in TWBTs could be used to sustain the state of mindfulness during the integration stage of SAPTs (Walsh and Thiessen, 2018; Sloshower et al., 2020; Wolff et al., 2020).

Therapeutic Relationship Conditions and Experiencing in Humanistic-Experiential Therapies

Humanistic-experiential therapies, such as Client-centered (Rogers, 1966), Gestalt (Perls et al., 1951), and Emotion-Focused Therapy (Greenberg and Johnson, 1988; Greenberg et al., 1993) have emphasized two key change mechanisms – the therapeutic relationship conditions and client experiencing – as central to the psychotherapeutic change. Rogers (1959) posited that when someone perceives that others' positive regard for them is conditional, then they develop "conditions of worth" reflecting how they need to be in order to be accepted. Symptoms then manifest from needing to distort experience to be congruent with these conditions of worth. From this perspective, healing and growth can occur when therapeutic relationship conditions, including empathy, unconditional positive regard, and congruence (Rogers, 1957), mean that a client does not need to defensively distort their experience to be accepted. Thus, it is the therapist providing the relational conditions, as the soil for a seed, that would allow a client to change.

The second change mechanism is *client experiencing*, which is that healing comes from accessing, feeling and symbolizing the previously distorted or disavowed emotions. In recent versions of experiential theory, this has been described as "changing emotion with emotion," such that accessing previously disavowed emotions is what changes the problematic emotions. For example, shame could be changed by accessing assertive anger or compassion (Greenberg, 2015). This requires the safety provided by therapeutic conditions as a necessary prerequisite, but also then suggests that actively directing clients towards their emotional experience through internal focusing (Gendlin, 1996), or through the use of evocative imagery and enactment tasks, such as chairwork (Greenberg et al., 1993; Perls, 1996), further facilitates the change process.

These two mechanisms may also overlap with some of the identified SAPT mechanisms, as well as the technique suggestions for conducting SAPT. Firstly the perception and receptiveness

to the Rogerian relational conditions could be facilitated by some substances, such as MDMA (Thal and Lommen, 2018). The *experiencing* mechanism also seems closely tied to the SAPT mechanism we have identified as *personal significance, insights, and meaningfulness*, given that emotions inform about things that are personally significant and meaningful. The SAPT mechanism of *reassessment of memories*, could also be considered a subset of the experiencing construct, given the memories that are often referenced as being *reassessed* therapeutically in SAPT tend to be emotionally salient and development significant memories. These overlaps have lead for some to argue that substances such as MDMA which functions to enhance the sense of connection, meaningfulness and processing of emotions, make it a natural adjunct for experiential therapies such as emotion focused couples therapy (Almond and Allan, 2019). There, *awe and peak-experiences* potentially amplify emotional signals such as compassion to everything as well as fear.

Whilst the other therapeutic modalities seemed to be technically suited to the integration stage of SAPTs; the humanistic-experiential techniques most closely relate to those that have been described for the administration stage. For example, the current treatment-model for MDMA-assisted psychotherapy for PTSD (Mithoefer, 2017) and some trials for depression and anxiety (Carhart-Harris et al., 2016; Griffiths et al., 2016; Roseman et al., 2018; Palhano-Fontes et al., 2019) suggest a framework-free and predominantly non-directive and client-centered approach seems especially relevant for SAPTs, given the substances function to elicit relevant material. Therefore a process following stance, as is typical in humanistic-experiential therapies, seems the appropriate for this stage of therapy, and that content directive therapeutic techniques could interfere the substances eliciting function. The non-directive approach of MDMA-assisted psychotherapy can empower clients to understand and resolve problems in their lives on their own. This may be reflected in enhanced measures of personal strength and sense of possibility (Gorman et al., 2020) and qualitative reports suggesting that clients prefer non-directive approaches (Watts et al., 2017).

Synergistic Therapeutic Mechanisms

Nielson and Guss (2018) outline similarities between psychedelic therapy, mindfulness-based interventions, and psychoanalysis. First, they all evoke altered states of consciousness allowing inaccessible parts of the self to be retrieved. As mentioned above, increased cognitive flexibility (i.e., increased bottom-up prediction errors) induced by psychedelics may result in de-patterning and perspective-shifts, increased insights, and personal meaningful re-experiencing of memories. Second, the therapist gives shape and direction to the course of the therapy, but has limited control over the tools for healing which are inherited in the client's mind (Freud, 1912; Walsh and Grob, 2006; McCown et al., 2010). Third, the therapist's personal perception, presence, and experience during the therapeutic sessions is used to guide the client and the process (Rubin, 1985; Kabat-Zinn, 2003; Phelps, 2017). In turns, the creation of the ideal set and setting is supported by the therapist, to

facilitate an altered state of consciousness that supports the unfolding of the inner healing capacities of the client (Nielson and Guss, 2018).

Moving Towards an Incorporation of Various Frameworks

In general, psychotherapy usually produces similar outcomes across different orientations and it might be more effective to fit and adapt the intervention to the particular client's needs (APA, 2012). Likewise, the extensive review of the literature suggests that the effectiveness or reported benefits of SAPT might not be due to the theoretical orientation of the therapist *per se*, but rather derived from important similarities and overlap between different schools of psychotherapy and dependent on intra- and interpersonal variables (Frank and Frank, 1991; Asay and Lambert, 1999; Wampold, 2015). Altered states of consciousness often allow clients to employ state alteration (Jiang et al., 2017) to change their point of view on an issue (as in cognitive restructuring with hypnosis; Spiegel, 2013) or experience negative events and let feelings pass without struggling against them (as in mindfulness; Paulson et al., 2013). Further, memory reactivation, reconsolidation, and reintegration (Lane et al., 2015) during SAPT may aid therapeutic change. This can be aided by CBT, interpersonal psychotherapy, psychodynamic psychotherapy, emotion-focused-therapy, or hypnosis and mindfulness (Lane et al., 2015; Spiegel, 2016). Providing a framework in which the client's problems can be understood may be more important than a particular orientation (Ludwig and Levine, 1965a).

CONCLUSION

In this narrative review, we have outlined valuable prerequisites for therapists who are considering engaging in SAPT that comprise a preset of knowledge and considerations for investigations and interventions. In doing so, several approaches to SAPT have been outlined to illustrate how literature on various schools of psychotherapy can be linked to the literature we reviewed about SAPT. Thereby, similarities across models and therapeutic orientations were highlighted. From this review, it may be suggested that various schools of psychotherapy could be incorporated into the development of respective therapeutic models. We hope this provides a basis for the development and adaptation of future investigations, therapeutic models, training programs for therapists, and those interested in the therapeutic potential of SAPT.

There are limitations to the findings outlined above since the mechanisms of action and therapeutic models depicted in this article have yet to be validated and further investigation employing rigorous research is required. Moreover, comorbidity is a common issue with substance use, anxiety, mood disorders, and post-traumatic stress (Rytwinski et al., 2013; Lai et al., 2015) – the very conditions for which current clinical investigations of SAPT are being conducted. It may be argued that comorbidity between disorders could facilitate the therapeutic application of SAPT across disorders (Breeksema et al., 2020).

Palhano-Fontes et al. (2019), for instance, reported that five participants with TRD and comorbid borderline personality disorder who received Ayahuasca showed significant decreases in clinical symptoms of depression 7 days post treatment. However, treatment of comorbid disorders introduces unique challenges in terms of diagnoses and screening (e.g., Shivani et al., 2002; Wu and Fang, 2014), effective treatments (e.g., Roberts et al., 2015), and potential side-effects (e.g., with bipolar- and/or psychotic disorders). More research regarding the potential harms and benefits of SAPT for the treatment for comorbid disorders and potential transdiagnostic approaches (Dalglish et al., 2020) is needed. Another limitation pertains to TRD: many forms of TRD belong to the bipolar spectrum and some have argued that treatment-resistant unipolar depression may be considered a prodromal phase of bipolar disorder (Dudek et al., 2010). Non-diagnosed bipolarity was further identified as an independent risk factor for treatment resistance in TRD (Bennabi et al., 2015). The diagnostic distinction between unipolar depression and bipolar depression is of utmost importance because antidepressant medication, commonly used for the treatment of unipolar depression, may induce mania, hypomania, insomnia, and irritability in those with bipolar depression (Ghaemi et al., 2000; Pacchiarotti et al., 2013). Since some people with bipolar disorder may experience psychotic episodes after substance use (Starzer et al., 2018), it is listed as a contraindication for most clinical investigations applying SAPT. However, the safety and efficacy of psilocybin is currently investigated for those with bipolar disorder type 2.¹ For the treatment of TRD with SAPT, the identification of unipolar and bipolar depression (especially bipolar depression type 1) has to be closely monitored during the screening process and more research is needed to improve screening for and treatment of bipolar depression with SAPT.

We have outlined the mechanisms of change in SAPT that have been identified in the literature and their similarity to mechanisms of change described in traditional psychotherapy. Through this analysis it was highlighted that different traditional therapeutic approaches and techniques might be effectively combined with and related to certain stages of SAPT and different therapeutic outcomes. The purposeful application and investigation of different approaches and techniques and their relation to therapeutic outcomes should be assessed in the future.

Furthermore, current literature may suggest that like traditional psychotherapy, the therapeutic effect of SAPT may not only be mediated by specific substances, therapeutic orientations, or models *per se*; rather the therapeutic effect may depend on factors like the therapeutic- and interpersonal relationship, empathy, therapeutic presence, and unconditional acceptance (Asay and Lambert, 1999; Geller and Greenberg, 2012; Wampold, 2015). Despite the validation of current standardized models, future research should investigate these intersecting variables across models, as well. Careful attention to pre-screening, contextual factors (i.e., set and setting), substance and dosage, as well as preparation (intentions) and integration (meaning)

¹<https://clinicaltrials.gov/ct2/show/NCT04433845>

of the experience are commonalities across different models of SAPT (Bogenschutz and Ross, 2016) and thought to be key determinants of the therapeutic outcome (Bogenschutz and Forcehimes, 2017). Combining these key determinants with common factors that are important for producing positive treatment outcomes in psychotherapy such as therapeutic relationship, empathy, expectations, and therapist differences (Wampold, 2015), may be important to allow for the broader application of SAPT across different models of psychotherapy (that share these common factors). Consequently, future studies should, as a standard, include valid measures of the therapeutic relationship (Horvath and Greenberg, 1989), therapeutic presence (Geller et al., 2010), empathy (Dziobek et al., 2008), expectations, and personality factors of therapist and client (e.g., Benjamin et al., 2006) in order to assess their potential influence on the treatment outcome. Eventually, it is conceivable that certain substances (or their combination) will be more compatible

with certain therapeutic approaches and/or clinical targets, synergistically fostering particular mechanisms. Thus far, no controlled studies have been conducted in which different models of psychotherapy have been compared using the same compound, or in which different substances have been compared using the same models of psychotherapy. More research is needed to determine which substances and forms of therapy may be effectively combined.

AUTHOR CONTRIBUTIONS

ST and TW conceived the presented idea, and reviewed and analyzed the literature. The first draft of the manuscript was written by ST, SB, and JS. PS contributed substantial ideas and feedback. All authors discussed the results. All authors contributed to the article and approved the submitted version.

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- Conflict of Interest:** Stephen Bright is a Director of the Australian not-for-profit company Psychedelic Research in Science & Medicine Pty Ltd (PRISM). PRISM's mission is to initiate, fund and facilitate psychedelic science in Australia. Stephen Bright has received funding from PRISM to assist with his research, including this paper.
- The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
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