REVIEW ARTICLE

Psychedelic-assisted psychotherapy: clarifying the role of the "psychotherapy"

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Summary

Psychedelic-assisted psychotherapy (PAP) is emerging as a novel intervention for major psychiatric disorders, most notably major depressive disorder (MDD) and post-traumatic stress disorder (PTSD). While psychotherapy is widely regarded as a core element of PAP its precise role remains poorly defined. This narrative review traces the development of PAP within contemporary Western psychiatry, outlines the therapeutic framework of preparation, dosing, and integration, and synthesizes findings from recent high-impact randomized controlled trials with psilocybin and MDMA. The primary purpose of this review is to clarify the role of psychotherapy in PAP. Despite methodological rigor, studies differ substantially in their therapeutic orientation, degree of manualization, and therapist involvement, yet all report significant clinical benefit. Some evidence points to the fact that treatment outcomes may not depend on the number of psychotherapy hours, raising questions about whether psychotherapy functions as an active ingredient, a facilitative context, or a safeguard. In light of these inconsistencies, we discuss novel phenomenological accounts of change in PAP, which propose that psychedelics exert therapeutic effects by altering "existential feelings," with psychotherapy primarily serving to stabilize and integrate these shifts. Current evidence highlights both the promise of PAP and the unresolved uncertainty regarding its psychotherapeutic components. Clarifying these issues will require trials that explicitly address psychotherapeutic variables, as well as the establishment of standardized protocols, ethical safeguards, and licensure pathways for practitioners.

Keywords: psychedelic-assisted psychotherapy, psilocybin, 3,4-methylenedioxymethamphetamine (MDMA), depression, post-traumatic stress disorder

INTRODUCTION

Defining psychedelics and psychedelic-assisted psychotherapy

Psychedelics are traditionally defined as psychoactive agents that induce perceptual changes and altered states of consciousness (1). They are potent psychoactive substances and include both synthetic compounds and naturally occurring alkaloids (2). Common examples studied in a therapeutic context include psilocybin, lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (MDMA), ketamine, and ibogaine (2,3).

Given the challenges of treating severe conditions such as chronic or treatment-resistant depression, novel interventions have been explored, including psychedelic compounds or related agents like ketamine (4–6), as well as modifications of existing psychotherapeutic approaches (7). Within this context, psychedelics administered in conjunction with psychotherapy (PAP) represent a logical candidate among new treatment strategies.

Psychedelic-assisted psychotherapy (PAP) is an emerging and experimental treatment modality that involves the administration of psychedelic substances in conjunction with psychotherapy (3,8). Current PAP models emphasize psychotherapeutic support provided before, during, and after the ingestion of a psychedelic to maximize both safety and clinical benefit (3,8). Although psychotherapy is routinely invoked as a central element of psychedelic-assisted psychotherapy, the field lacks a clear and operationalized definition of what this term entails in the context of PAP.

However, American Psychological Association (APA) defines psychotherapy as any "psychological service provided by a trained professional that primarily uses forms of communication and interaction to assess, diagnose, and treat dysfunctional emotional reactions, ways of thinking, and behavior patterns" (9). By this definition, much of the "psychological support" offered in PAP trials is considered psychotherapy (3). Lack of defining characteristics of what specifically makes up the "psychotherapy" in PAP may be one of the reasons for the uneven quality of evidence for the efficacy of this approach, which is explored in depth in the remainder of this paper.

HISTORY AND PRESENT STATE

We acknowledge that psychedelic plants have been used for millennia in Indigenous, shamanic, and other traditions; analysis of these approaches lies outside of our scope. In the present review, we focus on the contemporary Western biomedical research and practice.

Early research into the therapeutic potential of psychedelics, including their use in psychotherapy, was actively pursued between the 1950s and 1970s for a range of conditions, including neuroses, alcohol use disorder, end-of-life anxiety, and chronic pain (10). However, this initial wave of clinical and experimental work was largely ended by the early 1970s, driven by political backlash and increasing concerns over recreational misuse (2).

As for the present state of use of PAP for medicinal purposes, patchwork pathways to PAP implementation have already emerged internationally, already evident in Oregon, Colorado, and Australia (3). For example, in October 2022, Alberta became the first jurisdiction in Canada to create a formal regulatory framework for psychedelic therapy, including psilocybin and MDMA. Since January 2023, clinics in Alberta can provide psychedelic therapy if they meet licensing and practice requirements (11). This illustrates how patchwork legalization creates uneven clinical standards.

Literature on PAP is increasing and, frequently, while answering one question, opens more questions than answers. The field itself remains marked by unresolved issues and at times contradictory findings, particularly regarding the role and weight of psychotherapy. Thus, the goal of our paper is to provide a short overview of the PAP concept, to show key RCT trials in a narrative form of PAP in common psychiatric disorders – MDD and PTSD – and to discuss possible mechanisms of the clinical improvement.

METHOD

Studies were identified through targeted searches of PubMed/MEDLINE and Web of Science (January 2019 – December 2025) using keywords including "psychedelic-assisted psychotherapy," "psilocybin," "MDMA," "major depressive disorder," "depression," "PTSD," and "randomized controlled trial." Eligible studies were then selected based on methodological clarity, clinical relevance, and impact, with emphasis on the most highly cited RCTs in MDD and PTSD published in the past five years.

FORMALIZED PSYCHOTHERAPY FOR PAP: A NECESSARY COMPONENT?

As previously mentioned, despite the widespread consensus that psychotherapy is a central component of PAP, there has been surprisingly limited empirical examination of the psychotherapeutic process itself within PAP protocols (3,12).

There may be several reasons for this. The FDA's 2023 draft guidance for PAP trials recognizes the limited evidence on psychotherapeutic mechanisms and directs investigators to specify how psychotherapy influences outcomes (13). It further recommends assigning different therapists (i.e., preparation/integration versus dosing sessions), despite no data showing that this improves safety or efficacy or reduces expectancy bias (3).

However, Aday et al. (3) note that, beyond the drug session itself, PAP protocols frequently embed established psychotherapies in the preparation and integration phases, for example, CBT-oriented work (14), Motivational Enhancement Therapy (15,16), and integrative blends drawing on existential, psychodynamic, and CBT traditions (17). They further catalogue a rapidly expanding roster of candidate adjuncts: ACT (18), Internal Family Systems (19), EMDR (20), existential approaches (21), mindfulness-based methods (22), psychoanalytic frameworks (23), group formats (24), virtualreality augmentation (25), and PAPspecific therapeutic models (26,27). Since established psychotherapies often show comparable outcomes in a variety of psychiatric issues – likely reflecting shared "common factors" such as therapeutic alliance, expectancy, and a supportive relational frame (28) – current PAP trials (with heterogeneous and incompletely specified psychotherapeutic components) are not well suited to detect modality-specific differences between therapeutic orientations.

Moreover, comparisons between approaches seem debatable (3), given that evidence from the broader psychotherapy literature cautions that standard RCT designs are often insensitive to outcome differences across different psychotherapies. Because many common factors (e.g., alliance, expectancy, hope, reassurance) are shared across modalities, headtohead trials frequently yield minimal separation, a pattern long labeled the "Dodo Bird Verdict" (29,30).

Contemporary approaches to psychotherapy within PAP are largely derived from trial-and-error practices established by early psychedelic researchers and shaped by the experiential knowledge of modern community and "underground" practitioners, rather than grounded in systematic empirical study (2). This underscores a pressing need for rigorous research specifically targeting the psychotherapeutic components of PAP (if not the specific modalities), including their mechanisms, optimal structure, and contribution to clinical outcomes. This involves a shift from historically prominent first-person experience accounts to more rigorous third-person data obtained through controlled experimental models.

THERAPEUTIC FRAMEWORK

Even when no "formalized" psychotherapy is being used (i.e., CBT, ACT, etc.), clinical trials of PAP generally follow a three-stage intervention sequence: preparation, dosing, and integration (31).

Preparation sessions focus on establishing safety, clarifying intentions, and fostering a therapeutic alliance, while providing psychoeducation about the psychedelic experience and setting expectations regarding possible emotional and perceptual effects (3,32). These sessions aim to cultivate an attitude of openness and trust, often summarized by the guidance to "trust, let go, and be open," which is thought to reduce avoidance and anxiety during the acute experience (33).

Dosing sessions involve the administration of the psychedelic substance in a carefully controlled, supportive environment, typically lasting several hours depending on the compound. Therapeutic input during this phase is generally non-directive, emphasizing emotional containment, reassurance, and safety rather than active psychotherapeutic techniques, allowing patients to engage with internally generated experiences as they unfold (10,34).

Integration sessions are intended to help participants reflect on and contextualize the psychedelic experience, identify personally meaningful insights, and explore how these may be incorporated into everyday life. Clinically, integration is often described as a phase in which the experiential material elicited during dosing is stabilized and linked to ongoing psychological change, thereby supporting durability of treatment effects and mitigating potential distress or confusion following the acute experience (10,35).

While structured psychotherapeutic methods are typically employed during the preparation and integration phases of psychedelic-assisted psychotherapy, dosing sessions often rely on a "semi-structured, non-directive approach" (3,10). This non-directive stance emphasizes patient-led exploration within a supportive therapeutic presence. However, the approach remains a subject of debate, as some therapeutic models advocate for more active interventions by the therapist during the acute psychedelic experience (10).

The therapeutic effects of psychedelic-assisted psychotherapy are widely understood to emerge from the dynamic interaction between the pharmacological action of the drug and several contextual factors, namely, the patient's mindset ("set"), the external environment ("setting"), and the presence and role of the therapist (34).

CURRENT EVIDENCE FOR EFFICACY: DOES PSYCHOTHERAPY MATTER?

There are several studies that provided high-quality evidence on the efficacy of different psychedelics for MDD and PTSD. However, due to the extensive differences between psychotherapy protocols (among others), it is impossible to ascertain the significance of psychotherapy in this context. The current evidence base for psychedelic-assisted psychotherapy rests primarily on a small number of high-impact randomized controlled trials, notably the psilocybin studies for major depressive disorder (36,37) and the MDMA-assisted psychotherapy trials for PTSD (38,39). These four studies are widely regarded as some of the most methodologically rigorous and have set the standard for evaluating both efficacy and the role of psychotherapy in PAP.

Carhart-Harris et al. (36) conducted a phase 2, double-blind RCT comparing psilocybin with an active comparator, escitalopram, in patients with long-standing moderate-to-severe MDD. At six weeks, no significant difference was found in the primary outcome (QIDS-SR-16), but secondary measures, including remission rates (57% vs. 28%), generally favored psilocybin. Both treatments were well tolerated, with no serious adverse events.

A distinctive element of this trial was its carefully structured program of psychological support. As described in the supplementary materials, all participants received the same psychotherapy treatment, regardless of the randomization arm: (a) allocation of two "guides", typically trained clinicians, providing continuous support; (b) three-hour preparation sessions emphasizing emotional openness and the ACE model (33); (c) in-session non-directive support, with music serving as a "hidden therapist"; and (d) multiple integration sessions, both in person and via follow-up calls. The guiding stance emphasized trust, containment, and non-directive presence rather than active intervention. Thus, while the trial seemingly tested pharmacological efficacy, its design underscores that even when psilocybin is compared to a conventional antidepressant, outcomes are embedded in a framework of psychotherapeutic support, at least according to

Raison et al. (37) published a large, multicenter phase 2 RCT across 11 US sites, testing a single 25 mg dose of psilocybin against 100 mg niacin (active placebo) in 104 adults with MDD. Psilocybin significantly outperformed niacin on the primary outcome of MADRS reduction at day 43, as well as on several secondary measures, including early response (day 8) and functional impairment. Sustained response was observed in 42% of participants in the psilocybin group compared to 11% in the placebo group. The treatment was generally well tolerated, with adverse events limited to transient dosing-day effects, including headache, nausea, and perceptual changes.

As in the previously described study, these outcomes were embedded within a structured psychological support program. Both groups received a standardized package: approximately 6–8 hours of preparatory meetings with two trained facilitators, a monitored dosing session lasting 7–10 hours in a comfortable setting (including eyeshades and a curated music playlist), and around 4 hours of post-dose integration work. Lead facilitators were doctoral-level psychologists or physicians, supported by co-facilitators with at least a bachelor's degree in a mental health field. The manual was based on the set and setting protocol (40). Notably, the authors acknowledged that treatment fidelity was not assessed, leaving open the question of how much facilitator variability may have influenced outcomes.

When considered together, the trials by Carhart-Harris et al. (36) and Raison et al. (37) illustrate both the consistency and the variability in how psychotherapeutic support has been operationalized in PAP research. In the Carhart-Harris trial, psychological support included preparation sessions explicitly oriented around the ACE model ("accept, connect, embody") (33), in-session non-directive support supplemented by music as a "hidden therapist," and multiple integration sessions extending beyond the dosing day. The emphasis here was on cultivating emotional openness and facilitating post-session meaning-making. The Raison et al. trial appeared to use a more manualized, standardized support protocol designed for scalability across 11 US sites. However, fidelity to the support manual was not systematically monitored, while the therapeutic stance was deliberately kept non-directive, focusing on safety, containment, and patient-led exploration rather than formal psychotherapeutic techniques.

This highlights a broader issue in the field: while both studies provided structured psychological support, they seemed to differ in the theoretical orientation, manualization, and "therapists" who provided guidance. The fact that both trials nevertheless reported significant antidepressant effects underscores the current uncertainty regarding which psychotherapeutic elements are necessary, sufficient, or merely supportive within PAP protocols.

On the other hand, representative studies of MDMA-assisted therapy for PTSD include those performed by Mitchell et al (38,39).

In the phase 3 RCT multisite trial of Mitchel (39; MAPP1), 90 patients with chronic, severe PTSD were randomized to MDMA-assisted therapy vs. placebo with identical therapy. All participants received a manualized therapy protocol consisting of 3 preparatory sessions, 3 day-long MDMA or placebo dosing sessions, and 9 integrative therapy sessions. Results at two months post-treatment showed MDMA with therapy was far more effective: CAPS-5 PTSD symptom scores dropped by -24.4 points in the MDMA group vs. -13.9 in placebo. Functional impairment (SDS scores) also improved more with MDMA. Notably, both arms had the same therapeutic support, underscoring that MDMA enhanced the effects of supportive therapy, with 67% of MDMA-treated participants no longer meeting PTSD criteria (vs 32% on placebo) by study end.

In the follow-up trial (MAPP2), Mitchel et al. (38) assigned 104 participants with PTSD to MDMA-assisted therapy or placebo, with the same study design (blinded, 1:1). The CAPS-5 scores improved by -23.7 points with MDMA vs. -14.8 with placebo. Once again, functional impairment was reduced.

These trials of MDMA-assisted psychotherapy for PTSD employed a manualized protocol developed by Mithoefer et al (35). Each participant was paired with two therapists and received three preparatory sessions prior to dosing to establish trust and expectations. This was followed by three-day-long dosing sessions (6–8 hours)

spaced approximately one month apart, during which participants received either MDMA or a placebo in a comfortable, non-clinical setting, with music and eyeshades often used to facilitate inward focus. Therapists adopted a supportive but non-directive stance, encouraging participants to attend to their inner process and intervening only to ensure safety, grounding, or containment. After each dosing day, participants engaged in three integration sessions designed to help them process traumatic material, derive meaning from the experience, and consolidate insights into daily life. In total, the protocol involved approximately 42 hours of therapist contact across preparation, dosing, and integration (38,39,41).

Even with the efficacy data, a key question arises: should this be considered psychotherapy, or is it more accurately a hybrid support model unique to PAP? And further: If much of the work consists of non-directive presence during altered states, is it closer to therapeutic facilitation than psychotherapy proper?

IS PSYCHOTHERAPY EVEN NECESSARY FOR TREATMENT WITH PSYCHEDELICS?

A central unresolved question is whether therapeutic benefit in PAP stems from the psychedelic substance itself, its combination with psychotherapy, or from non-specific supportive elements (42). There is no consensus on the optimal type of psychotherapy, its duration, or the balance of preparation and integration sessions (40). Strikingly, a new meta-analysis by Hultgren et al. applied mixed-effects meta-regression, examining findings in MDD and psilocybin in the context of therapy hours, and found that the amount of psychotherapy provided was not associated with clinical outcomes, suggesting that the efficacy of PAP may hinge less on therapy hours than on other factors (40). Importantly, the absence of a relationship between the number of psychotherapy hours and outcome should not be interpreted as evidence that psychotherapy is unnecessary. Rather, all trials included in this meta-analysis provided a baseline level of structured psychological support, suggesting that additional therapy hours beyond this minimum may not linearly enhance outcomes.

EXISTENTIAL FEELINGS AS A POSSIBLE MECHANISM OF CHANGE

Approaches to resolving this issue of whether psychotherapy is necessary must address the proposed mechanism of change. Multiple explanatory frameworks have been proposed, ranging from neurobiological accounts (e.g., receptor- and network-level changes) to psychological models (e.g., expectancy effects and common factors of psychotherapy).

Recent phenomenological work suggests that the therapeutic efficacy of psychedelic-assisted therapy may be understood primarily through its capacity to facilitate fundamental alterations in existential feelings (43–46). Existential feelings are pre-intentional background orientations that shape how individuals experience their relationship to the world, including possibilities for action, connection, and meaning. In psychopathology, these orientations are often altered (constricted). For example, depression is associated with a felt loss of future possibilities, estrangement, and existential loneliness, resulting in a world experienced as closed, threatening, or devoid of significance (46,47).

Psychedelics, as Tijhuis and colleagues argue, may be uniquely capable of producing acute "oceanic shifts" in existential feelings, marked by ego-dissolution, boundary loss, and experiences of profound unity or connectedness. Such experiences are consistently correlated with clinical improvements across trials (48–50). Importantly, when these episodic existential shifts consolidate into more lasting "oceanic orientations", patients report enduring changes such as increased openness, connectedness, and future-directed narratives.

An open question is whether such existential feelings can change without psychotherapy. We have hypothesized elsewhere that alterations in existential orientation may, in principle, be induced directly through pharmacological action, given that all kinds of psychotropic drugs affect the embodied mind rather than merely the "objective body" (Körper) (51). From this perspective, at least part of the therapeutic effect might arise independently of structured psychotherapeutic input.

However, as Tijhuis and colleagues (46) emphasize, for transient "oceanic shifts" to develop into more enduring "oceanic orientations," the experience must be processed as meaningful and positively integrated into a person's life-world. This makes it unlikely that therapeutic benefit can occur in the complete absence of psychological support, even in its most basic form. Such support, whether framed as preparation, containment, or integration, arguably falls within the APA's definition of psychotherapy, insofar as it relies on interaction, communication, and relational guidance to foster change (9).

This perspective also helps explain why the quantity or modality of psychotherapy has not consistently predicted outcomes (40): the therapeutic leverage may lie less in the formal content of psychotherapy and more in its capacity to hold open the experiential possibility space for existential change.

Still, findings that psilocybin's efficacy in depression does not depend on the number of psychotherapy hours (and strikingly, not even on psilocybin dose) call into question the very premise of how treatment components contribute to outcome (40). These results run counter to evidence from conventional depression care, where combining psychotherapy and antidepressants improves

efficacy (52). Yet, as Hultgren et al. (40) emphasize, all representative studies from the literature still provide at least a minimal level of therapy (no less than 4.5 hours on average; 53), suggesting that while extensive psychotherapy may not be essential, some degree of structured therapeutic support remains a likely prerequisite for safe and optimal outcomes.

LIMITATIONS AND FUTURE DIRECTIONS

A major limitation in the current literature is the "surprisingly little empirical investigation of the 'psychotherapy' in PAP," leaving fundamental questions about its necessary and sufficient components unresolved (3). Compounding this issue is the lack of consensus on terminology for those delivering psychotherapeutic support, with terms such as "guide," "sitter," "facilitator," and "psychedelic therapist" used inconsistently across studies (3). Furthermore, as Aday and colleagues note, descriptions of psychotherapeutic interventions in clinical trials are often minimized or insufficiently detailed, hindering both replication and the development of standardized training protocols.

Secondly, most studies have rarely systematically manipulated the non-pharmacological aspects (e.g., psychotherapy content) compared to drug components. Issues like inadequate double-blinding (difficult due to the intense psychedelic experience) and the common practice of combining multiple psychological interventions make it hard to isolate the unique effects of psychedelics on treatment gains (1,3).

As for understanding the proposed mechanisms of how psychedelic treatment might work, it is important to underline that even comprehensive phenomenological frameworks of psychedelic therapy, such as that proposed by Tijhuis et al. (46), are not currently intended as manuals for clinical intervention but rather as explanatory models of change, which highlights the gap between phenomenological insight and operationalized psychotherapeutic techniques.

It is also important to illustrate several ethical issues. Cheung et al. (11) emphasize that, unlike other areas of psychiatry, robust practice guidelines are lacking for PAP. The Institute of Medicine and APA frameworks recommend evidence-based systematic reviews followed by guideline panels, but in the case of psilocybin, such processes have not yet been undertaken due to the novelty of regulatory changes and the scarcity of large-scale trials (11). As a result, physicians often rely on heterogeneous, potentially biased sources (e.g., producer manuals and advocacy documents).

Other important issues include the possibility of profound changes in consciousness and long-term personality shifts, which participants need to be aware of (54). Because patients in psychedelic states are highly suggestible and vulnerable, clear ethical guidelines are needed to prevent exploitation or inappropriate therapist behavior. From this point of view, psychotherapy may be an additional safeguard: even if modality-specific techniques are less important, ethical safeguards, training, and boundaries in therapeutic conduct are essential (11).

The evidence base for PAP is still characterized by inconsistencies and open questions. Core assumptions – such as the extent to which psychotherapy contributes to outcomes, or how much its structure matters – remain unsettled. These contradictions underline the need for clearer definitions, greater methodological rigor, and standardized approaches to psychotherapy in PAP. Thus, we join in the almost universal call among researchers in this topic, that is, the imperative to establish clear licensure, training, and competency standards for psychedelic therapists (3,12,55). Future work should directly test the psychotherapeutic components of PAP. Priority questions include designing and performing dismantling studies comparing psychedelic treatment with minimal vs. structured preparation/integration; mechanistic studies examining how variables such as alliance, expectancy, and integration processes relate to outcomes; and development and empirical evaluation of standardized therapy manuals, including therapist training and fidelity monitoring.

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PSIHOTERAPIJA POTPOMOGNUTA PSIHODELICIMA: RAZJAŠNJAVANJE ULOGE „PSIHOTERAPIJE"

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Sažetak

Psihoterapija potpomognuta psihodelicima (PAP) sve se češće razmatra kao novi terapijski pristup u lečenju psihijatrijskih poremećaja, pre svega depresivnog poremećaja i posttraumatskog stresnog poremećaja. Ovaj narativni pregled razmatra razvoj PAP-a u savremenoj zapadnoj psihijatriji, opisuje osnovni terapijski okvir koji obuhvata faze pripreme, primene supstance i integracije, te sumira nalaze najznačajnijih randomizovanih kontrolisanih studija sa psilocibinom i MDMA-om. Cilj ovog preglednog rada jeste razumevanje uloge psihoterapije u PAP. Uprkos visokom kvalitetu dokaza, studije se znatno razlikuju u pogledu terapijske orijentacije, stepena manualizacije i uključenosti terapeuta. Istovremeno sve opisane studije beleže značajnu terapijsku efikasnost. Neki dokazi ukazuju da terapijski ishod nije u direktnoj vezi sa obimom psihoterapije postavljajući sledeće pitanje: da li psihoterapija u ovom kontekstu dejstvuje kao aktivni terapijski činilac, kao podržavajući okvir ili pre svega ima bezbednosnu svrhu? Polazeći od ovih pitanja, u radu se razmatraju savremeni fenomenološki pristupi koji sugerišu da psihodelici dejstvuju putem promena tzv. egzistencijalnih osećanja, dok psihoterapija ima ulogu u stabilizaciji i integraciji tih promena. Dosadašnji dokazi istovremeno ukazuju na značajan terapijski potencijal PAP-a, ali i na otvorena pitanja u vezi sa njegovim psihoterapijskim komponentama. Razjašnjavanje ovih pitanja zahteva buduće studije koje bi sistematski ispitale psihoterapijske činioce, kao i razvoj standardizovanih protokola, etičkih smernica i jasnih okvira za obrazovanje i licenciranje praktičara.

Ključne reči: psihoterapija potpomognuta psihodelicima, psilocibin, 3,4-methylenedioxymethamphet amine (MDMA), depresija, posttraumatski stresni poremećaj

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