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COMMENTARY

Considering the nocebo effect in the psychedelic discourse

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ABSTRACT

This commentary addresses the potential for a nocebo effect arising from the public discourse on psychedelics, especially considering the increasing interest and engagement with these substances. The resurgence of psychedelics in the public and scientific arenas has led to a proliferation of discussions, both positive and cautionary, about their use. However, an imbalance in this discourse, particularly a focus on potential harms without adequate contextualisation, might inadvertently create a nocebo effect. This effect could manifest in naturalistic settings, influencing individuals' experiences with psychedelics, possibly leading to adverse outcomes. The paper discusses the importance of a balanced narrative that equally acknowledges the benefits and risks associated with psychedelic use. It advocates for comprehensive and transparent information dissemination to enable informed decision-making by users.

KEYWORDS

psychedelics, nocebo, public discourse

In the past decade, psychedelics have increasingly garnered attention from not just the research community and private sector but also the public. This growing fascination is reflected in the upward trend of psychedelic use amongst the general population, a phenomenon documented and expected to persist (Johnson, Hendricks, Barrett, & Griffiths, 2019; Monte et al., 2023); and presents its own set of challenges. As more individuals engage with psychedelics, a comprehensive understanding and responsible approaches to their use become imperative, balancing scientific insights with public health considerations.

For decades leading up to the present, since the 1970 Controlled Substances Act, and owing to concerns about their potential harms, psychedelics use has been prohibited (Marks, 2023). But there is a growing consensus that stringent drug laws may not effectively mitigate harm or protect users and the broader society (Wodak, 2014). In fact, the argument has been advanced that prohibiting access to consciousness-altering substances – and thereby overriding an adult's decision-making autonomy – could infringe upon human rights (Bone, 2019). As an alternative to outright prohibition, there is a growing advocacy for harm reduction measures as a more effective strategy to decrease drug-related harm (Klein, 2020). These proposals suggest a shift from a punitive approach to one that focuses on safety and informed use.

Given the upward trend in psychedelic use, it is somewhat surprising that developing systematic and empirical harm reduction measures has not been as prominent in public discussions compared to other areas of psychedelics research. Only recently have research papers begun to focus on tailoring psychedelic experiences to enhance safety and psychological benefits. Studies are now exploring ways to measure preparedness for a psychedelic experience (McAlpine, Blackburne, & Kamboj, 2023) and investigating potential difficulties that arise during experiences that might extend way beyond the drug effects (Evans et al., 2023). This is crucial in the process of establishing empirically-driven harm reduction practices. This shift is timely, especially as some jurisdictions are on the cusp of broadening access to psychedelics through decriminalisation, legalisation, and use in non-medical (Siegel, Daily, Perry, & Nicol, 2023) and medical settings (Dixon Ritchie, Donley, & Dixon Ritchie, 2023).

It is pertinent to consider how the general discourse on psychedelics, their effects, and potential dangers, might influence the outcomes of psychedelic experiences. With its inherent

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unpredictability, the psychedelic experience can be likened to an elevator journey where the individual inside has no absolute control over whether they ascend to heights of bliss or descend into the depths of a challenging experience – often referred to as a 'bad trip'. This metaphor captures the essence of the psychedelic journey; whilst one can prepare and set intentions, the exact nature and direction of the experience remain uncertain. The pre-existing state of an individual, a constituent of the 'set and setting' (Hartogsohn, 2017), plays a critical role in shaping the psychedelic experience. Recent years have witnessed psychedelics research propelled by a wave of enthusiasm, spotlighting the benefits these substances might hold. However, this commentary seeks to shift the lens toward the potential for a nocebo effect that might emerge from overemphasising the risks associated with psychedelics, or from not providing a thorough overview of what is known about the psychedelic experience to prospective users. Grasping the influence of negative expectations and partial information on personal experiences is pivotal, as these can skew outcomes unfavourably. By tackling this, we can safeguard the use of psychedelics, balancing the enthusiasm surrounding their potential with a grounded and comprehensive understanding of their effects.

Embodying the profound influence of the brain on the body, the placebo and nocebo effects manifest in diametrically opposite ways and yet originate from the same psychological basis. These phenomena underscore the impact of beliefs and expectations on physical and psychological responses to treatments. The placebo effect occurs when an individual experiences a positive response, such as pain relief or symptom improvement, from a treatment lacking therapeutic action. Intriguingly, this effect is associated with reduced activity in the amygdala and stress-response circuits, indicating a tangible modulation of neurocircuitry (Ashar, Chang, & Wager, 2017). It is the person's belief in the efficacy of the treatment that triggers this response. In contrast, the nocebo effect materialises when negative expectations result in harmful outcomes. For example, anticipating adverse side effects from a non-harmful substance or procedure can lead to the actual manifestation of those side effects. The ethical implications of using interventions that might trigger placebo or nocebo effects are therefore significant, especially regarding the ethics of deception. The use of treatments that lack biological efficacy in research or therapy poses ethical dilemmas related to informed consent and the ethics of misleading patients. This issue calls attention to the need for balance between advancing scientific understanding and upholding ethical standards in patient care and research (Dodd, Forbes, & Berk, 2023).

There is growing discussion in psychedelic research around the placebo and nocebo effects, particularly in clinical trials. This interest is partly spurred by the consideration that the substantial positive media attention psychedelics have received recently could amplify expectations of what these substances could deliver. The conversation surrounding psychedelics in clinical trials has been largely centred on managing placebo effects driven by these heightened expectations. The nocebo effect has been given less emphasis, particularly in its broader implications. Aday et al. (2022) underscore the profound influence of participants' expectations in psychedelic clinical trials, emphasising how positive media portrayals can shape expectations of treatment benefits. They argue that participant awareness of their treatment assignment can significantly influence both placebo and nocebo effects in psychedelic therapy. In a similar vein, Flameling, Aday, and Van Elk (2023) point out the potential for both placebo and nocebo effects in MDMA trials. It is described that the nocebo effect becomes relevant when participants, upon realising they are not receiving the expected psychedelic or MDMA treatment, have negative expectations that lead to worsened outcomes. In turn, it is suggested that this could impact the perceived efficacy gap between intervention and control groups. Consequently, past research has highlighted the importance of rigorously measuring expectancy (Muthukumaraswamy, Forsyth, & Lumley, 2021) and maintaining blinding integrity. Failing to do so complicates the task of differentiating between the actual efficacy of the drug and the effects influenced by participant expectations. This understanding is crucial for not only accurately evaluating the therapeutic potential of psychedelics but also maintaining the integrity and validity of clinical trial results – ensuring that conclusions drawn are reflective of the substances' true effects rather than psychological biases.

Burke and Blumberger (2021) point out the complexities in placebo-controlled trials involving psychedelics, ketamine, and MDMA. These substances have distinctive and easily identifiable effects, posing challenges to the traditional practice of blinding in trials. Blinding becomes problematic with such conspicuous treatments, calling into question whether we should stick to this traditional method or prioritise assessing overall patient improvement, irrespective of its origin. There is a good argument to be made, as Butler, Jelen, & Rucker, 2022 put it, that 'although double-blinded RCTs indisputably produce the highest form of evidence when conducted appropriately, they may not be a perfect fit for interventions where expectancy can never be fully controlled'. Maintaining the integrity of blinding in randomised control trials (RCTs) presents significant challenges. To mitigate potential nocebo responses in the placebo arm two strategies could be employed: using an active placebo or a low dose of the psychedelic. The choice of active placebo is difficult though, as it should induce an altered state that sufficiently mimics the effects of a psychedelic without being one. Alternatively, lower doses of the actual psychedelic, acting on the same mechanism but with reduced intensity, may be more advantageous. They are less likely to induce the psychological shift that has been argued to be required for treatment efficacy (Roseman, Nutt, & Carhart-Harris, 2018) whilst also avoiding being perceived as ineffectual at all by the participants. This approach might be particularly effective with drug-naïve individuals, who are less likely to discern a low dose, unlike experienced users who may recognise it. If drug-naïve individuals are involved, it is essential for researchers to maintain balanced discourse during preparation sessions, avoiding suggestions of overly

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positive or overly negative impacts, or sharing their personal opinions. They should also advise participants against engaging with media or personal stories of others about such experiences until after their own experience. Finally, adhering to clinical trial methodology for establishing drug efficacy aside, there is a consideration that positive priming might enhance treatment benefits in practice. This debate underscores the urgency to re-evaluate conventional trial approaches in relation to psychedelics and leads to further complex questions, should it be the case that psychedelic treatments become licensed: should expectancy be dissociated from the psychedelic experience in future practical applications, or harnessed?

Whilst clinical trials represent a significant focus in psychedelic research, it is crucial to recognise that psychedelics use in the world extends far beyond these controlled settings. Placebo and nocebo responses are equally relevant outside of clinical trials, namely in naturalistic or recreational use of psychedelics. In such scenarios, the user, rather than being assigned a treatment, makes an independent decision to use psychedelics. Whilst therapeutic intent for this use has been documented (Móró, Simon, Bárd, & Rácz, 2011; Søgaard Juul, Ebbesen Jensen, & Fink-Jensen, 2023), people have a range of different reasons for using psychedelics not limited to recreation, social bonding, personal growth, spiritual enhancement, or simply curiosity (Basedow & Kuitunen-Paul, 2022). Nonetheless, this does not diminish the potential for these experiences to contribute meaningfully to an individual's wellbeing, particularly if the experience is positive. A key concern in the naturalistic use of psychedelics relates to how the individual's prior knowledge and the prevailing narrative about psychedelic effects can shape their mindset before and during the experience. A person exposed to a discourse heavily emphasising the dangers of psychedelics could experience a nocebo-like response. Considering the heightened suggestibility during a psychedelic experience, these negative expectations could amplify and result in psychological distress. This distress could persist even after the effects of the drug have worn off.

The concern here is that in response to the current trend of highlighting the positive aspects of psychedelics, there might be a reactionary surge in discourse concentrated intensely on potential harms. This scenario could typify the classic movement-countermovement dynamic described by Meyer and Staggenborg (1996), where visible movements often catalyse a mobilisation of opposing viewpoints. In the context of psychedelics, such a counter-movement could lead to an era where narratives about the risks of psychedelics are as passionately disseminated as those touting their benefits. There is precedence in this regard. Despite the physiological risks of psychedelics being generally low, this has not prevented historical representations of these substances being extremely skewed towards the negative, with adverse effects being sensationalised after a period of intense optimism (Schlag, Aday, Salam, Neill, & Nutt, 2022).

Psychedelics are powerful substances, with substantial acute effects on brain function (Balaet, 2022). Whilst an overemphasis on the benefits of psychedelics may lead individuals to underestimate potential risks and venture into their use unprepared, unaware of how to manage potential challenges, inadvertently heightening the risks involved, it is not unreasonable to hypothesise the converse, in the light of heightened suggestibility of the brain under the influence of psychedelics, that expectations of negative outcomes may increase their occurrence. In the psychedelic state, predominant narratives and expectations can significantly shape the experience. As Hartogsohn (2022) notes 'A person's expectations regarding the psychedelic experience and their intentions going into one, are also crucially framed by the cultural discourse surrounding these agents'. Consequently, 'bad trips' have historically been interpreted as stemming more from the social and environmental contexts in which psychedelics are used, rather than from their pharmacological properties (Bunce, 1979). This perspective gains credence from early research experiments where participants, pre-conditioned with the belief that psychedelics would induce temporary insanity, exhibited adverse reactions characterised by tension and paranoia (Hartogsohn, 2022). Dyck and Elcock (2020) further elaborated that the essence of the negative psychedelic experiences is rooted in varying degrees of fear, manifesting distinctly depending on the individual's personal journey. Such fears might range from a loss of control to the re-emergence of traumatic memories, overwhelming sensory overload, or difficulties in social interactions. Whilst it is heartening to acknowledge that integrating even these challenging experiences could yield therapeutic benefits (Carbonaro et al., 2016; Gashi, Sandberg, & Pedersen, 2021), this process is not universally straightforward. Jivanescu (2022) highlights the difficulties faced by individuals returning to environments rife with negative discourse about psychedelics, where integration becomes notably more complex. On the other end of societal discourse influence, reducing social conflict surrounding psychedelics was linked to a decline in the occurrence of bad trips among new users (Bunce, 1979). Additionally, there is evidence suggesting that altered states of consciousness are more manageable in societies where they are culturally accepted (Grob & De Rios, 1992).

The years following the polarising discourse that culminated in the classification of psychedelics as illegal substances under the Controlled Substances Act in 1970 indeed witnessed a decrease in the use of psychedelics, both in naturalistic settings and research contexts (Schlag et al., 2022). It seems plausible to suggest that a rise in negative discourse around psychedelics in the present day could be linked with a decrease or stagnation in their naturalistic use trends that have been on the rise in recent years. Certain individuals might perceive these substances as too dangerous and thus refrain from their use. However, it is important to acknowledge the potential for various scenarios where individuals might still engage in psychedelic experiences, despite the surrounding discourse, whether through personal choice or peer pressure. This latter factor is especially relevant among younger populations, where peer influence plays a crucial role in their decisions regarding drug use (Pruitt, Kingery, Mirzaee, Heuberger, & Hurley, 1991).

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Assessing the current incidence of adverse experiences with psychedelics in naturalistic settings poses significant challenges, primarily due to the obstacles in obtaining representative samples for research. To gain a deeper understanding, future studies will need to concentrate on exploring this issue. They should aim to discern how fluctuations in the discourse surrounding psychedelics, alongside major global events or cultural shifts, might impact the range of negative effects experienced by those who use psychedelics, as well as the long-term implications of these experiences (Balaet et al., 2023). With more information available, the challenge for the field then remains striking a balanced discourse that neither underestimates the risks nor overstates the benefits and provides a comprehensive and realistic understanding of psychedelic use. This aligns with the wishes stated by individuals previously exposed to negative narratives around psychedelics who have encountered difficulties in integrating their experiences (Jivanescu, 2022). Finally, on the pathway of achieving a balanced discourse, it is crucial that information conveyed to individuals interested in psychedelics is transparent and comprehensive, covering both the positive aspects and the risks involved. Whilst acknowledging and preparing for possible adverse effects is necessary, it should not lead to the overarching assumption that psychedelic experiences are inherently dangerous and unmanageable despite precautions – a stance that does not align with the evidence (Krebs & Johansen, 2013; Schlag et al., 2022). It is correspondingly important to avoid the overly protective narrative that diminishes individual agency, that is, disparaging the individuals who choose to use psychedelics. Whilst having support in the form of a sitter, therapist, or medical professional can be reassuring for some individuals and by consequence enhance safety, it should not be portrayed as the only legitimate or safe way to engage with psychedelics. People should be empowered with knowledge and options, allowing them to make informed decisions about their psychedelic experiences. This includes understanding the importance of set and setting, being aware of potential risks, and knowing how to access support if needed. A balanced approach respects individual autonomy without trivialising safety and informed choice.

A tangible parallel between the discourse on psychedelics and the medicalisation of pregnancy and childbirth sheds light on the importance of autonomy and informed choice. In the medical system, home or free births are often viewed as risky or unconventional, mirroring concerns about psychedelic use outside controlled settings. Just as some argue that the female body is naturally equipped to handle pregnancy and childbirth, with medical interventions necessary only in specific circumstances, there is a similar argument for psychedelics. Humanity has coexisted with psychedelics for millennia, with these substances (and more) having played integral roles in various cultures (George, Hanson, Wilkinson, & Garcia-Romeu, 2022). Furthermore, our neurochemical systems, though significantly influenced by psychedelics, do not typically suffer neurotoxic effects from these substances (Meyer & Maurer, 2011). In both scenarios – childbirth and psychedelic experiences – there is an emerging trend of shifting autonomy from the individual to a regulated 'system'. This commentary also advocates for rethinking this approach. Individuals should be equipped with comprehensive information, enabling them to make informed decisions about their experiences. This includes the freedom to choose the setting and support system that aligns with their personal needs and preferences. Just as some women may opt for home or free births, individuals should have the option to engage with psychedelics in a manner they deem fit, whether independently or under professional guidance.

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