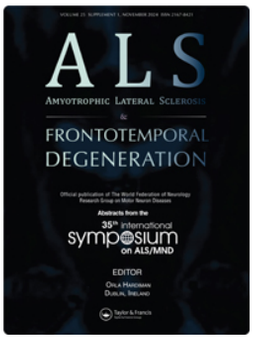

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Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iafd20

ALSUntangled #77: Psilocybin

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To cite this article: Bhavya Bakshi, Sandeep Yerraguntla, Carmel Armon, Paul Barkhaus, Tulio Bertorini, Robert Bowser, Sarah Breevoort, Mark Bromberg, Andrew Brown, Gregory T. Carter, Vincent Chang, Jesse Crayle, Timothy Fullam, Maxwell Greene, Terry Heiman-Patterson, Carlayne Jackson, Sartaj Jhooty, Elise Mallon, Javier Mascias Cadavid, Christopher J. Mcdermott, Gary Pattee, Kaitlyn Pierce, Dylan Ratner, Yuyao Sun, Olivia Wang, Paul Wicks, Martina Wiedau & Richard Bedlack (22 Dec 2024): ALSUntangled #77: Psilocybin, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: 10.1080/21678421.2024.2441274

To link to this article: https://doi.org/10.1080/21678421.2024.2441274

Published online: 22 Dec 2024.

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2024; 0: 1–4

BRIEF REPORT

ALSUntangled #77: Psilocybin

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Abstract

ALSUntangled reviews alternate and off-label treatments prompted by patient interest. Here, we review psilocybin, a chemical derived from mushrooms and belonging in the category of drugs known as psychedelics. Psilocybin has plausible mechanisms for slowing ALS progression because of its ability to cross the blood brain barrier and effect neurogenesis and inflammation. Currently, there are no pre-clinical ALS models, case reports, or trials for psilocybin and ALS in the context of disease modifying therapy. Depending on dosing, there can be a high risk of psychological side effects including hallucinations and physical harm. Based on the above information, we do not currently support the use of psilocybin as a means to slow ALS progression.

Keywords: *Psilocybin, neurogenesis, psychedelics, inflammation*

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(Received 13 November 2024; revised 1 December 2024; accepted 8 December 2024)

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2024.2441274

Introduction

ALSUntangled reviews alternate and off-label treatments prompted by patient interest. Here, we review psilocybin, a topic for which we have had 44 requests on our website (1).

Psilocybin is a chemical derived from certain species of mushrooms. It belongs to a category of drugs known as psychedelics, that are known for their hallucinogenic effects. Psilocybin is not currently FDA approved for any medical indication. It is considered "schedule 1" (high abuse potential), and its recreational use is illegal in several places (2). It is under study for ameliorating severe psychiatric symptoms in a variety of populations including people living with ALS (PALS, (3–7)). ALSUntangled does not review symptomatic treatments, but there are theoretical reasons that psilocybin could potentially affect ALS progression. Thus, we herein review the potential of psilocybin as a disease modifying therapy for PALS.

Mechanisms

Neurogenesis and neuroplasticity

Neurogenesis is the process of forming new neurons from progenitor and neural stem cells. In the past, neurogenesis was primarily associated with embryonic and perinatal neural development; however, accumulating evidence since the 1960s demonstrates that neurogenesis occurs throughout adulthood in restricted parts of the brain (8). Neurogenesis is one way to achieve neuroplasticity, defined as structural and functional changes to the brain. We and others have previously written about synaptic dysfunction in ALS and the potential for treatments that enhance neuroplasticity to improve disease progression (9,10). Some studies suggest that psilocybin and other psychedelics can affect neurogenesis and neuroplasticity (3,5,6,11,12).

Neuroinflammation

Neuroinflammation is believed to play an important role in ALS pathophysiology (13). Psilocybin can reduce various aspects of neuroinflammation. In a human macrophage cell line, for example, psilocybin extracts inhibited LPS-induced pro-inflammatory mediators consisting of TNF-α, IL-1β, IL-6, and COX-2 (14). In mice injected with LPS, psilocybin pretreatment treatment reduced brain levels of COX-2 and TNF-α compared to placebo pretreatment (15). Finally, in a trial of healthy humans under stress, a single dose of psilocybin transiently reduced serum TNF-α, and persistently reduced serum IL-6 and CRP, compared to placebo (16).

Excitotoxicity

Glutamate-mediated excitotoxicity probably plays an important role in ALS progression (17). Indeed, riluzole, an approved disease modifying medication for PALS, is believed to work in part by reducing glutamate-mediated excitoxicity (18). In the trial of healthy humans under stress mentioned above, psilocybin treatment decreased glutamate concentrations in the hippocampus as measured by magnetic resonance spectroscopy (16).

Because psilocybin can act on ALS-relevant mechanisms (neuroplasticity, neuroinflammation and brain glutamate levels), but has not yet been shown to do so in pre-clinical ALS models or in PALS, we assign a TOE "Mechanisms" Grade of C.

Pre-clinical models

We found no studies of psilocybin in pre-clinical ALS models. Therefore, we assign a TOE "Pre-Clinical" Grade of U.

Cases

There is currently one published case report for an ALS patient using psilocybin along with psychotherapy for depression and emotional distress. While these symptoms improved, no details on ALS progression were provided (19). We found no other reports of PALS using psilocybin to treat any aspect of ALS.

Based on a lack of case reports evaluating the effects of psilocybin on ALS progression, ALSUntangled assigns a TOE "Cases" Grade of U.

Trials

We found no trials of psilocybin for patients with ALS. Therefore, we assign an ALSUntangled TOE "Trials" grade of U.

Risks, dosing, costs

Dosing and risks

The most beneficial dose of psilocybin for treating ALS (if any) is not known. Meta-analyses of psilocybin trials for depression concluded that the optimal dose for a person weighing 70 kg is between 25 and 40 mg of pure psilocybin delivered once or twice over a several-week period (20,21). In terms of LSD equivalents, 30mg of pure psilocybin produces similar effects to 150ug LSD (22). At these "high" doses, risks included hypertension, tachycardia, nausea, vomiting, headache, and prolonged psychosis (20). The frequency of all these side

effects increased with increasing doses (20). Prolonged psychosis was encountered in 12 patients out of 465 (2.5%) included in the trials in one meta-analysis (20). The immediate and long-term psychiatric side effects of high dosage psilocybin can be quite severe. In a survey of 1993 individuals who experienced a difficult or challenging experience after using psilocybin, 11% reported that their "bad trip" put themselves or others at risk of harm (23). An epidemiological study found significant association between consumption of hallucinogens like psilocybin throughout life and risk of substance use disorders, PTSD, personality disorders, and suicide attempts (24).

Some have suggested that "microdosing" psilocybin might be safer but still as effective, at least for treating depression. Microdosing involves using more frequent, smaller (0.1-0.5 g) of less pure psilocybin (ex. dried mushrooms, (25–27)). In terms of comparison to LSD, 0.1g of impure psilocybin from dried mushrooms is equivalent to 4.6ug of LSD (26). These impure preparations may contain other harmful ingredients (28). In our opinion, these have not been thoroughly studied in depression and not studied at all in people with ALS and so the possible risks are not known at this time.

Whether any dose of psilocybin might interact with medications used by PALS (such as riluzole) is not known. Some clinical trials exclude patients who are using illegal recreational drugs.

Based on this information, we assign a TOE "Risks" grade for high dose psilocybin of F and U for microdosing.

Costs

According to a recent media report, a single session of supervised psilocybin treatment for a psychiatric disorder is $2500 (29).

Conclusion

Psilocybin may be able to influence ALS-relevant mechanisms including neuroinflammation and brain glutamate levels, but this ability has not yet been demonstrated in ALS models or in PALS. There have been no studies of psilocybin in ALS relevant preclinical models, and no case reports documenting the effects of psilocybin on ALS progression. Given the potential for serious side effects, we do not currently support the use of psilocybin to slow ALS progression.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding

ALSUntangled is sponsored by ALS Association [Grant 23-SI-62].

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