

Psilocybin as an Alternative Treatment for Chronic Pain

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INTRODUCTION: Chronic pain is described as pain lasting 12 weeks or more and can be a consequence of an acute injury where the pain persists beyond the time needed to heal or from progressive diseases like cancer and arthritis. It is traditionally treated using opioids, non-steroidal anti-inflammatories, or neuropathic medications. However, these treatments are associated with various health risks including tolerance, misuse, overdose, and gastrointestinal and renal damage. Classic psychedelics such as psilocybin have been proposed as an alternative treatment for chronic pain as they affect many of the same pain-signaling pathways without the risks associated with current therapy. Although the exact mechanism is unclear, evidence suggests that psilocybin and other psychedelics are effective for pain relief because they act on the 5-HT_{2A} receptor, a serotonin receptor that has been linked to the development of chronic pain. This study performed a systematic review and meta-analysis of the existing data on psilocybin as an alternative treatment for chronic pain compared to any other control. The research question was as follows: Does psilocybin result in pain relief for individuals suffering from chronic pain when compared to any other treatment?

METHODS: The PRISMA and STROBE statements, as well as the Cochrane Handbook were used to guide the planning, implementation, and reporting of the review. A literature search of five databases yielded ten studies meeting the inclusion criteria. Efficacy was assessed by overall pain relief on various ordinal scales, headache prevention, and headache abortion. Four inverse variance meta-analyses based on outcome measures were conducted using Excel. The Risk of Bias In Non-randomized Studies – of Intervention (ROBINS-I) tool and the Risk-of-Bias for randomized trials version 2 (RoB 2) tool were used to assess the level of bias in relevant studies. Certainty of evidence was assessed by creating a GRADE Evidence profile.

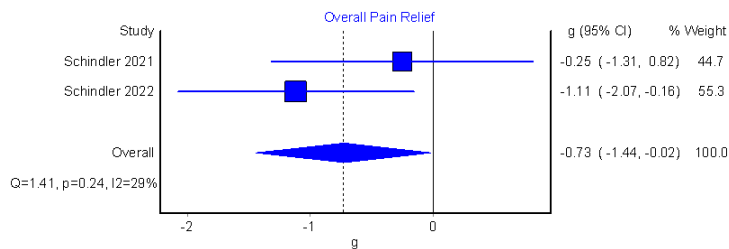
RESULTS SECTION: We include a total of ten papers – one randomized control trial, two quasi-randomized control trials, three surveys, one case series, and three case reports were identified as meeting all inclusion criteria for the review. A total of 498 participants were recorded across all three outcomes in all studies. Analysis yielded that psilocybin improved overall pain relief by 0.73 units (95% CI [-1.44,-0.22], P=0.035). Furthermore, psilocybin use resulted in 0.92 fewer headache attacks per week (95% CI [-1.65,-0.20], P=0.003) and 75% of participants rated psilocybin as more effective at preventing headache attacks compared to any other treatment (95% CI [64%,87%], P<0.001). Lastly, participants rated psilocybin 67 % more effective at headache attack termination relative to other therapies (95% CI [56%,81%], P<0.001).

DISCUSSION: The review of the current literature suggests that psilocybin is more effective than current treatments at relieving pain, as well as preventing and ameliorating headache attacks. However, drawing inferences from the results is precipitous, as psilocybin research is in an immature state. Large, randomized control trials and meta-analyses have not yet taken place. Accordingly, study populations are small and statistical power is limited rendering them insufficient to detect a true effect. Nevertheless, findings from the current evidence base suggest that psilocybin is a promising alternative treatment for both pain relief as well as headache prevention and abortion.

SIGNIFICANCE/CLINICAL RELEVANCE: From the results of this study, clinicians may be able to infer that psilocybin could be an effective future treatment for pain relief and headache prevention. It highlights a gap in the research base for robust, large scale randomized trials, which are needed to evaluate the efficacy and safety of psilocybin as an alternative and superior treatment to standard therapies.

IMAGES AND TABLES:

Meta-Analysis Results: Overall Pain Relief (Fixed-Effects Model using Inverse Variance Method; Effect Size Hedge's g)



No of studies	Study design	Certainty assessment					Other considerations	No. of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	psilocybin		any other treatment	Relative (95% CI)	Absolute (95% CI)			
Overall Pain Relief (follow-up: 2-3 weeks)													
2	randomised trials	not serious	not serious	not serious	serious ^a	none	18	16	-	SMD 0.73 SD lower (1.44 lower to 0.02 lower)	⊕⊕⊕○ Moderate	CRITICAL	
Headache Prevention (as measured by reduction in attack frequency) (follow-up: 2-3 weeks)													
2	randomised trials	not serious	not serious	not serious	serious ^a	none	18	16	-	SMD 0.92 SD lower (1.65 lower to 0.2 lower)	⊕⊕⊕○ Moderate	CRITICAL	
Headache Prevention													
3	observational studies	serious ^b	not serious	not serious	serious ^a	none	Study participants rated psilocybin as "effective" or "ineffective" at preventing headache attacks. All participants had history of a chronic headache condition, using various treatments. Pooling the results of all studies, the proportion of participants who reported psilocybin as "effective" was 0.75 (95% CI [0.64,0.87]).			⊕○○○ Very low	CRITICAL		
Headache Abortion													
2	observational studies	serious ^b	not serious	not serious	serious ^a	none	Study participants rated psilocybin as "effective" or "ineffective" at stopping headache attacks. All participants had history of a chronic headache condition, using various treatments. Pooling the results of both studies, the proportion of participants who reported psilocybin as "effective" was 0.67 (95% CI [0.56,0.81]).			⊕○○○ Very low	CRITICAL		

CI: confidence interval; SMD: standardised mean difference

Explanations

- a. Downgrade one level for small sample sizes
- b. Downgrade one level since survey data is subject to recall bias and expectation bias