Status: scheduled for: 05-23-2021

MailChimp link: https://mailchi.mp/attiamedical/05232021

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Email subject/social copy: Psilocybin for depression?

MailChimp Preview/ Site Excerpt: The psychedelic drug goes head-to-head with Lexapro in a recent trial

Site Primary Category: Weekly Emails

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Greetings —

It wasn't so long ago that I wrote an email about the promise and yet-to-be answered questions of psychedelic-related therapies for treating psychiatric illnesses. Decades-long efforts have worked towards decriminalizing or approving some of these compounds for therapeutic use. It feels like this effort has recently coalesced in a psychedelic news flurry of developmental milestones, from psychedelic psychopharmaceutical companies going public to clinical trial publications that evaluate the therapeutic efficacy of these compounds in rigorous trial design.

A recent milestone trial at the Centre for Psychedelic Research at Imperial College London compared a new psychedelic treatment to the current gold standard for treating a type of clinical depression (called Major Depression Disorder). The 6-week trial was the first double-blinded, randomization controlled trial (RCT) of its kind. The trial did not show a difference between the two treatments, to mean that psilocybin was just as good as the current gold standard at treating depression. While the study found that the experimental psilocybin therapy was an equally effective treatment, I think it could prove to be an even better one, warranting larger and longer trials. But there are a lot of caveats for this trial and in my interpretation of it, so buckle up.

The two-armed study compared a synthetic form of the natural mushroom psychedelic compound, psilocybin, and escitalopram (a selective serotonin reuptake inhibitor (SSRI) otherwise known as Lexapro, as it will be referred to here). A total of 59 participants were randomly assigned to 2 treatment groups. About half the participants received 2 psilocybin therapy sessions of 25 mg each. They took one dose at the start of the study and a second dose 3 weeks later, taking a placebo pill on the other days. The remaining participants received a 6-week course of Lexapro as the primary treatment. To set equivalent expectations among the study participants, the trial researchers told all participants they would receive an undisclosed amount of psilocybin: when the psilocybin treatment group received its 25 mg dose of the drug, the Lexapro treatment group received a 1 mg dose of psilocybin (considered to be sub-therapeutic, that is, placebo). Both treatment groups also received an equivalent mix of in-person and over-the-phone psychotherapy in an effort to remove any form of what is known as performance bias, where one group does better because of more attention or knowledge.

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A quick word on exactly what 25 mg of psilocybin means. For those of you reading this who have journeyed with psilocybin, you're probably used to doses in *grams*, not

milligrams, and when you realize that most psychedelic journey doses are closer to 5 g, or 5,000 mg, the trial's 25 mg (0.025 g) dose seems incredibly small. However, this is where the difference between the mushroom and pure synthetic psilocybin comes in. Depending on the exact species of mushroom, the content of pure psilocybin in mushrooms, as a percent of dry weight, varies from 0.2% to 1.8%, which means 5 g of mushrooms could deliver anywhere from 10 to 90 mg of pure psilocybin. If you consider the median in the reference table here (0.765% of dry weight), 5 g of mushrooms equates to 38.3 mg of psilocybin. In other words, the 25 mg dose received by participants in this study was within the ballpark of a hallucinogenic dose. This study of subjects ingesting between 3 and 30 mg of psilocybin corroborates that 25 mg of psilocybin is a psychoactive dose. What this implies is that there was (at least some) unblinding of the subjects during the study, because they likely had a hallucinogenic experience and realized which treatment they received.

The study evaluated depression severity using a survey called a 16-item Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR-16; you can get a sense for the questions here[1]). QIDS scores are grouped in ranges that correspond with depression severity and the study investigators enrolled participants with scores that fell in the moderate to severe depression score range. Both treatment groups saw a score reduction by the end of the trial. The psilocybin treatment group mean depression score decreased by 8 points, from 14.5 points before treatment to 6.5 points post treatment. The Lexapro group mean score decreased by 6 points, from 16.4 points before treatment to 10.4 points post treatment. So the psilocybin treatment group had a depression score reduction that was 2 points more, on average, than the Lexapro treatment group. However, the study didn't detect a statistically significant difference between the depression treatments. The question is whether there is a significant effect that got overlooked and, if so, how might that happen? The answer is twofold and has both to do with the study design and the way the study is interpreted.

It is very possible that a significant psilocybin treatment effect was missed because the study sample size was too small. The trial size was predetermined based on a power analysis that assumed a far greater between-group effect size—almost 3 times larger, to be exact. (I wrote about how to determine and understand statistical power and significance in a previous post here. But briefly, statistical power is used to determine how many subjects are needed in a study based on the prediction of how great the difference in effect size will be between said groups.) The study researchers based

[1] As the name suggests, the survey has 16 questions; each question is scored on a scale of 0 to 3, and total scores range from 0 to 27. The higher the score corresponds to more severe depression; scores less than 5 denote no depression and scores greater than 21 denotes very severe depression.

sample size assumptions on a between group difference of *at least* 5.2 points and assumed a 4.7 point mean QIDS score reduction associated with Lexapro treatment. Translation: the study wasn't powered to detect the minimal important difference that a patient would identify as meaningful. To ascertain if the study missed a meaningful effect, I would consider the clinical importance of what the 2 points could represent; to me, that depends on the actual QIDS survey question. Imagine the participant scores decreased as a result of improved responses to the questions pertaining to sleep disturbance, such as the following QIDS survey question: "I sleep longer than 12 hours in a 24-hour period including naps" (3 points) to "I sleep no longer than 10 hours in a 24-hour period including naps" (1 point). Score decreases to the sleep disturbance questions alone do not necessarily convince me that the 2 point change is a difference that makes a clinical difference. However, consider a change in response to an alternative QIDS survey question: "during the past seven days I feel sad nearly all of the time" (3 points) to "during the past seven days I feel sad less than half the time" (1 point). I would venture to say that this difference makes a difference. The point is that the significance of the effect size is not so clear cut and depends on which questions participants changed their answers. This detail gets lost in looking at an aggregate group score change and depending on the individual answer changes, there could be clinical significance even if there is not a statistical one between groups (and vice versa).

Indeed, looking at the secondary outcomes from the study gives the impression that psilocybin has clinical efficacy that exceeds Lexapro. The study evaluated 10 secondary outcomes related to depression treatment efficacy such as suicidality, psychological well-being, flourishing and social functioning. They all favored psilocybin treatment over Lexapro. Notably, the psilocybin treatment group had more participants with what's called a QIDS score response, defined as a 50% reduction in depression scores, and it had almost twice the remission rate as the Lexapro treatment group by the end of the study[2]. The study has not (yet) corrected the confidence intervals for the secondary outcomes so conclusions can't be drawn from these data, but it is doubtful that all of the outcomes in favor of psilocybin are due to false positives alone.

While a significant effect could have been missed due to study design, one also could be overlooked based on how the study is framed. The study was published as a "negative trial" due to the lack of statistically significant difference on its primary depression severity outcome, but I propose that the psilocybin treatment in this trial did not necessarily have to accomplish a statistically significant treatment effect to be

[2] By the end of the study, 70% of the participants in the psilocybin group had depression scores reduced by half, compared to 48% of participants in the Lexapro treatment group that had the same score reduction. Participants in the psilocybin treatment group had almost twice the remission rate as the Lexapro treatment group (57% vs 29%).

considered successful, and here is why: this trial pitted psilocybin head-to-head with Lexapro, one of the best known treatments for depression[3]. Since it did not compare psilocybin treatment to a placebo, it is akin to a noninferiority trial, which demonstrated psilocybin treatment to be just as good as the tried and true antidepressant standard of care; it could stand-up to the antidepressant treatment. As such, I consider the trial's finding a success, warranting larger and longer trials.

There are a couple of reasons to question the external validity of the study results, being the trial's selection bias and its ability to maintain blinded study participants and investigators. It is very possible that there was a selection bias in favor of psilocybin treatment which would impact the generalizability of the QIDS depression score improvement that was seen across treatment groups: volunteers mostly self-referred for the trial and many expressed preference for the experimental psilocybin therapy. Since all study participants believed they were receiving some dose of psilocybin treatment (to honor participant expectations and an attempt to maintain a blinded trial) there may well have been an expectation bias that inflated depression score reductions across treatment groups[4]. Moreover, and as I alluded above, this study likely had a blinding problem because the subjective effects of 25 mg of psilocybin are strong enough to be identifiable. It is curious that the study investigators did not ask participants which conditions they thought they were allocated to, to evaluate if the study remained blinded.

One more thing I would point out: only 2 doses of psilocybin treatment effectively achieved what Lexapro treatment requires daily administration to do. (Granted, it is also possible that the short, 6-week treatment time was not long enough for the antidepressant treatment to take full effect.) From a clinical efficacy point of view, that is a win. Further, psilocybin treatment demonstrated equivalent safety and overall less adverse effects compared to Lexapro (for many people the sexual side-effects of Lexapro, for example, make it a non-starter despite its antidepressant efficacy). In short, psilocybin treatment looks favorable compared to Lexapro in terms of both compliance scheduling and the minimum effective dose required to decrease depression scores.

I wonder if more frequent, smaller doses of psilocybin treatments, such as 2-3 days apart, could demonstrate superior efficacy in future studies. This kind of microdosing schedule,

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[3] Notably, however, its response rates only tend to average around 50-60%, compared to placebo

[4] An 8-week trial evaluating lexapro treatment with a different but strongly correlated depression score survey reported an average reduction of 3.3 points (vs a 6 point reduction in the current trial lexapro treatment group). All else equal, the reduction point difference for lexapro treatments in the two different trials suggests that a placebo effect and the potential effect of the adjunctive psychological support treatment may have inflated the depression score improvement.

taking small amounts of psilocybin a couple times a week (in the range of 1.8 to 5.4 mg psilocybin, too small to experience psychedelic properties), is associated with improved psychological health and wellbeing in self-report studies led by psychedelic research pioneer, James Fadiman. However, results from another participant-blinded naturalistic study suggests that the benefits of microdosing on general psychological health could be due to a placebo effect. Either way, there have yet to be more rigorous microdosing clinical trials specifically for treatment of depression.

The trial demonstrates how conclusions from a study are determined by the outcome results as well as post-hoc interpretations of said results. In this study, the lack of a statistically significant treatment effect was likely due to the small size of the study; the secondary outcomes that unilaterally favored psilocybin suggest there may have been a meaningful, overlooked difference between the treatments. If we interpret this trial as a noninferiority study, the between-group difference demonstrated psilocybin's efficacy and was not a negative trial. And the actual observed treatment effect, while statistically small, may have clinically significant implications.

What this trial also illustrates is how science navigates unmapped territory. There are persistent knowledge gaps in the dose and frequency for an optimal psychedelic intervention for depression, let alone how the drug works to seemingly alleviate both depression severity symptoms and improve psychological well-being. For that, I am on the lookout for when the research group publishes its follow-up analysis of brain-imaging data between the two treatment groups, which may provide further understanding of how psilocybin aids depression symptoms and secondary outcomes related to psychological growth.

- Peter

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