



Founders Pledge

Psychedelic-Assisted Mental Health Treatments Cause Area Report

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Executive summary

Psychedelic drugs have the potential to revolutionise how we treat mental health conditions, from depression and anxiety to post-traumatic stress disorder (PTSD). So, how should philanthropists go about funding psychedelic-assisted mental health treatments? In this report, we answer this question, detailing the best projects to fund in this unique and promising space. The purpose of this research was to identify high-impact funding opportunities for people especially interested in improving the wellbeing of the current generation.¹

Psychedelic-assisted mental health treatments

In 2017, mental health problems, including substance use disorders, accounted for roughly 7% of the global disease burden, up from 4% in 1990.² Despite how much suffering they cause around the world, for many mental health problems, the best treatments available only have a limited effect. For example, for major depressive disorder (MDD), antidepressants and the most effective types of psychotherapy each have an estimated average standardised effect size of less than one third. This is equivalent to reducing patients' Hamilton Depression Rating Scale scores by about 1.6 points on average, on a scale that ranges from 0 to 50.³

Psychedelic-assisted mental health treatments have the potential to change this. They could one day help reduce the global mental health burden and tackle the lack of adequate treatment. They involve ingestion of a psychedelic substance such as psilocybin or MDMA in a safe setting, supervised by trained therapists, and are often combined with preparatory sessions prior to the active treatment sessions and integratory sessions in the

weeks following the treatment. Integratory sessions are non-drug psychotherapy sessions, which aim to address any difficulties that arose during or following the psychoactive sessions and to integrate lessons and understanding gained from these sessions into daily life.⁴ Psychedelic-assisted treatments are currently being tested for a variety of mental health problems, including major depressive disorder (MDD) and post-traumatic stress disorder (PTSD).

Intervention selection

Focusing on psychedelic-assisted mental health treatments, we identified three types of interventions to consider: direct treatment, academic research and drug development.

Drug development is a process that covers everything from the discovery of a brand new drug for treatment to this drug being approved for medical use.⁵ Of the three interventions considered, drug development seemed the most promising. We focused on drug development in the United States, Canada, Israel, the European Economic Area and the United Kingdom, as we know of nonprofit organisations taking psychedelic-assisted mental health treatments through the approval process in these places.

Funding opportunity analysis

When investigating where philanthropists' dollars could be put to best use, we considered funding opportunities at the two nonprofits currently working on drug development: Multidisciplinary Association for Psychedelic Studies (MAPS) and Usona Institute. We had detailed conversations with these organisations and other experts, and surveyed the

research literature on the psychedelic-assisted treatments they are advancing. We then determined how cost-effective the two funding opportunities are.

Usona is currently working on drug development for psilocybin, the active ingredient in magic mushrooms, as a treatment for depression in the US. Meanwhile, MAPS is carrying out drug development for MDMA-assisted psychotherapy for PTSD in the US, Canada and Israel, and soon also in Europe.

MAPS recently announced its Capstone Campaign, with the aim of raising \$30 million to make approval of MDMA-assisted psychotherapy a reality in the US, Canada and Israel and to start the commercialisation of this treatment. MAPS secured \$10 million of initial funding and a \$10 million matching pot to be unlocked if the remaining \$10 million is secured. Soon after we evaluated this funding opportunity, its funding gap was filled, so we turned our attention to MAPS's drug development programme in Europe.

Recommendation

We think Usona's drug development programme is similarly as impactful as our recommendations in other areas in the mental health and subjective well-being spaces, such as Action for Happiness' scale-up of their local community course⁶ and StrongMinds' treatment of women with depression.⁷ So, if you are passionate about improving mental health, we recommend you give to Usona's drug development programme alongside these other recommendations, especially if you are interested in 'riskier' interventions.

We came to the same conclusion about MAPS's drug development programme and Capstone Campaign for the US, Canada and Israel but this funding opportunity has now

been filled. We think that MAPS's drug development programme in Europe is less cost-effective than the Capstone Campaign. This judgement is driven partly by our cost-effectiveness models, which suggest that the European campaign is around one quarter as cost-effective as the Capstone Campaign. Additionally, we expect the wider benefits of MAPS's European drug development programme to be smaller than those of the Capstone Campaign as approval will come later in Europe and the first major approval will likely have the greatest wider benefits. Therefore, we think that the European programme presents a good funding opportunity for donors with a special interest in psychedelic-assisted mental health treatments but we would recommend it only in certain circumstances.

Funding opportunities vs nonprofits

To avoid confusion, especially when we are ranking funding opportunities in a particular cause area, we think it important to emphasise the difference between evaluating funding opportunities and nonprofits. Our research conclusions do not imply that one nonprofit does more important work than another, or that a particular cause is more worthy of support than another. They instead reflect our overall view of which funding opportunities at nonprofits *could currently use extra funds most effectively*.

This is because we aim to recommend to our members funding opportunities with a maximum *counterfactual* impact. That is, our goal is to recommend opportunities where extra funding by our members would make the largest difference compared to if they provided no extra funding. Paradoxically, this implies that if a nonprofit does high-impact

work but is *in addition* very successful at raising funds for that work, we should not recommend any funding opportunities at that nonprofit.

In the case of this research project, our current best guess is that both MAPS and Usona are doing high-impact work. However, one reason why we do not recommend MAPS's European drug development programme as highly as other funding opportunities in the mental health and subjective well-being space is that MAPS has an exceptional fundraising track record.

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1. Introduction

This report is the result of a Founders Pledge investigation of philanthropic funding opportunities in the area of psychedelic-assisted mental health treatments. The purpose of this project was to identify high-impact funding opportunities, comparable to those Founders Pledge recommends in our research reports on other cause areas.⁸

In the following sections, we describe the process we went through to investigate this area and how we arrived at our conclusions. Firstly, we give an introduction to mental health and psychedelic-assisted treatments as a cause, and why we decided to prioritise it within the larger psychedelics space. We then explain why we considered drug development to be the most promising intervention in psychedelic-assisted mental health treatments. We share our reasons to prioritise looking into Usona's and MAPS's drug development programmes as funding opportunities, and our analysis of these opportunities. We then explain what we recommend to donors interested in this space. Lastly, we give the limitations of this research project.

Overview of mental health disorders

In 2017, mental health problems, including substance use disorders, accounted for roughly 7% of the global disease burden, up from 4% in 1990.⁹ These statistics provide a lower bound to the true importance of mental health as a cause because standard estimates of the global disease burden understate the burden of mental health. This is because these estimates are based on people's judgement of health rather than broad well-being,¹⁰ and in

particular on comparative judgements by people who have not necessarily experienced these mental health problems themselves.^{11,12}

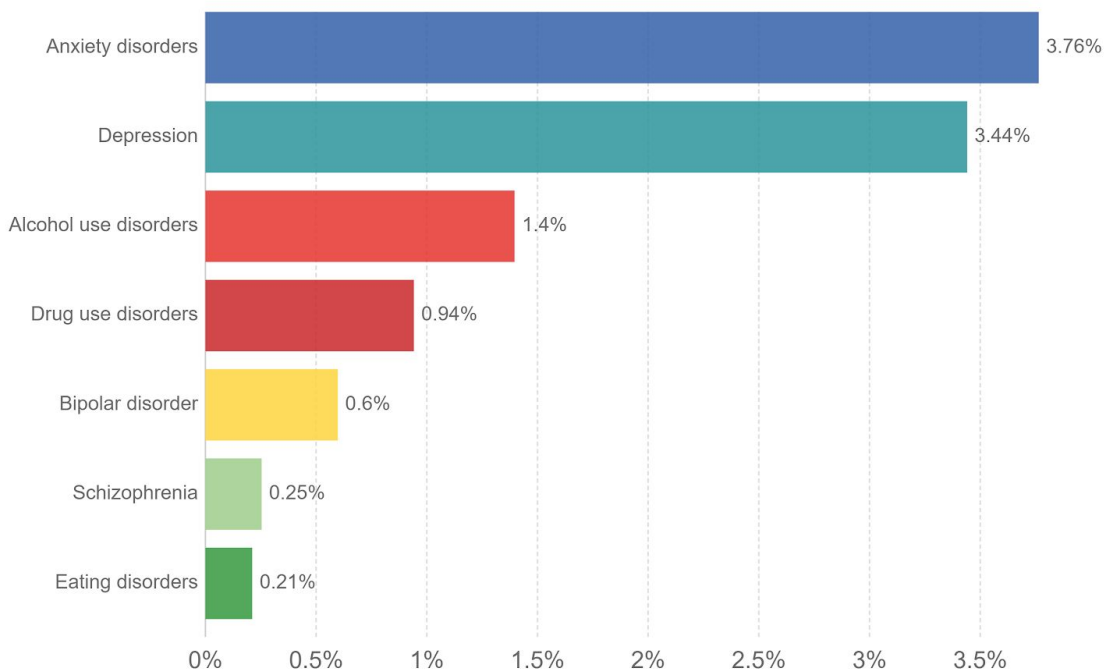
The most prevalent mental health disorders globally are anxiety disorders and depression, as shown in Figure 1.¹³

Figure 1. Global prevalence of mental and substance use disorders, 2017

Prevalence by mental and substance use disorder, World, 2017



Share of the total population with a given mental health or substance use disorder. Figures attempt to provide a true estimate (going beyond reported diagnosis) of disorder prevalence based on medical, epidemiological data, surveys and meta-regression modelling.



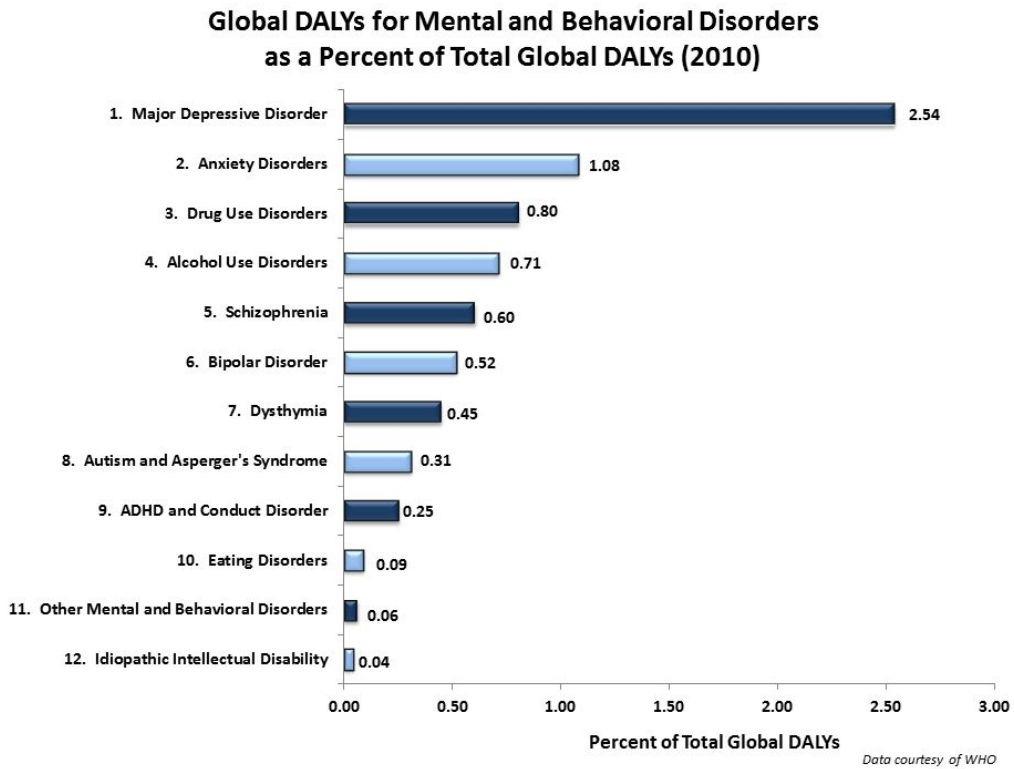
Source: IHME, Global Burden of Disease

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Source: Our World in Data, [‘Mental Health’](#)

Although more people suffer from anxiety than depression, depression is estimated to cause more suffering, as measured by disability-adjusted life years (DALYs) and shown in Figure 2.¹⁴ DALYs measure the burden of disease by accounting for the premature death (mortality) that it causes and for the years lived with illness (morbidity) it causes: a DALY burden can stem from premature death or from short-term or long-term ill-health. The disability weights of different diseases range from 0 to 1 (no disability to 100% disabled). One DALY can be thought of as one lost year of healthy life.

Figure 2: Global DALYs for Mental and Behavioral Disorders as a Percent of Total Global DALYs (2010)



Source: [NIMH » Global DALYs Contributed by Mental and Behavioral Disorders](#), accessed 16 March 2020

For many mental health problems, the best treatments currently available only have limited effect. For example, for major depressive disorder (MDD), antidepressants and the most

effective types of psychotherapy each have an estimated average placebo-controlled effect size of less than a third of a standard deviation.^{15,16}

The impacts of the COVID-19 pandemic on mental health are yet to be understood fully but it is clear that the disease and accompanying physical distancing measures have taken and will very likely continue to take a toll on people's mental health.¹⁷ As a result, the current and future global mental health burden will likely be even larger than previously expected.

History of psychedelics

Psychedelics cause thought, auditory and visual changes and altered states of consciousness by acting as agonists on particular serotonin receptors.¹⁸ Humans have used psychedelics for thousands of years, for example, in the form of magic mushrooms, whose active ingredient is psilocybin, ayahuasca, whose psychedelic ingredient is DMT, and a variety of mescaline containing cacti. Medical research of psychedelics only began in the late 1800s with the discovery of mescaline in the peyote cactus.¹⁹ Albert Hofmann first synthesised LSD in 1938, but it was not until five years later when Hofmann accidentally ingested some that medical psychedelic research really took off.²⁰ Over the following two decades, psychiatrists used LSD to treat pain, as well as a wide range of mental health problems, such as anxiety, depression and social anxiety.²¹ Recreational use of psychedelics also increased, culminating in the banning of psychedelic substances in most countries in the late 1960s, and the slowing of medical research.

With the banning of LSD and other psychedelics, other drugs—notably MDMA—emerged or reemerged. LSD, psilocybin, DMT and mescaline are all classic psychedelics, which work through similar biological mechanisms and exhibit somewhat similar effects.²² MDMA

differs from the classic psychedelics. For example, it rarely causes visual perception changes and affects dopamine and norepinephrine levels as well as serotonin levels.²³ MDMA produces a gentler, more euphoric state than classic psychedelics, increases feelings of empathy and bonding, relieves depression while active and helps users to process emotional trauma.²⁴ MDMA was first synthesised in 1912 by German pharmaceutical company, Merck, but Alexander Shulgin and David Nichols published the first report into the psychoactivity of MDMA in humans in 1978.²⁵ Psychotherapists and psychiatrists used MDMA widely in the 1970s and 1980s until, as with LSD, it became popular for recreational use. The Drug Enforcement Administration in the US declared MDMA as a Schedule I drug in 1985, prompting the formation of the Multidisciplinary Association for Psychedelic Studies (MAPS), one of the organisations considered in this report.²⁶ The Schedule I ruling means that MDMA has no currently accepted medical use and a high potential for abuse.²⁷

The resurgence of psychedelic research started in 1990 with the study of DMT in healthy volunteers.²⁸ MDMA became increasingly hard to study due to its use at rave parties and high profile deaths, so researchers instead used classic psychedelics, such as psilocybin.²⁹ The 2000s saw the study of psilocybin for OCD and for occasioning mystical experiences.³⁰ Research into MDMA for treating PTSD began in 2000, with a study sponsored by MAPS in Spain, which was shut down due to a political backlash.³¹ Since 2010, the study of classic psychedelics and MDMA has picked up pace,³² as we edge closer to the approval of psychedelic-assisted treatments for alleviating mental illnesses.

Psychedelic-assisted mental health treatments

Psychedelic-assisted treatments might help reduce the mental health burden and lack of adequate treatment in the US, Canada, Israel and Europe. They are currently being tested as treatments for a variety of mental health problems, including depression,³³ end-of-life anxiety and depression,³⁴ post-traumatic stress disorder (PTSD),³⁵ obsessive-compulsive disorder (OCD),³⁶ tobacco dependence,³⁷ and alcohol dependence.³⁸ They involve ingestion of a psychedelic substance in a safe setting, supervised by trained therapists, and are often combined with preparatory and integratory sessions.

The psychedelic substances most commonly used for therapeutic purposes include psilocybin, LSD, DMT and MDMA. As mentioned above, unlike psilocybin, LSD and DMT, MDMA is not a classic psychedelic. MDMA-assisted psychotherapy is also different from other psychedelic-assisted treatments. Elements of psychotherapy play an important role in MDMA-assisted psychotherapy sessions,³⁹ whereas in psilocybin treatments, for example, the therapist primarily provides psychological support.⁴⁰

For an overview of the history and application of psychedelic-assisted mental health treatments and psychedelics more broadly, we recommend the book *How to Change Your Mind* by Michael Pollan.⁴¹

The safety of psychedelic use

Psychedelics are not without risk, but controlled usage in a medical setting does not pose significant risks. Psychedelics are among the safest drugs we know of if used sparingly and with the right precautions.⁴² David Nutt, professor of neuropsychopharmacology at

Imperial College London, and a previous member of the UK Committee on Safety of Medicines, writes about psilocybin and LSD in his book *Drugs Without the Hot Air*:⁴³

“It’s virtually impossible to die from an overdose of them; they cause no physical harm; and if anything they are anti-addictive, as they cause a sudden tolerance which means that if you immediately take another dose it will probably have very little effect.”

However, there are mental health risks associated with the use of classic psychedelics. Researchers at the Johns Hopkins Center for Psychedelic & Consciousness Research recommend that patients who either (i) currently have, (ii) have had in the past, or (iii) have first- or second-degree relatives who have any of the following disorders be excluded from trials using psychedelics: schizophrenia or other psychotic disorders, bipolar I, bipolar II. Risks of psychosis among patients with no personal or family history of psychotic disorders are reportedly low, however.⁴⁴

The physical safety of MDMA is not as clear as it is for classic psychedelics such as LSD and psilocybin: there is evidence that frequent use of MDMA can cause neurotoxic damage,⁴⁵ though this is difficult to verify due to confounding factors.⁴⁶ The potential for dependence on MDMA is not entirely clear.⁴⁷ Controlled use of MDMA in a clinical setting does not pose significant risks as the purity, dose and frequency of MDMA sessions can be controlled. Outside such settings, though, use of MDMA could pose significant risks to users. There is a risk that clinical use of MDMA could prompt patients to self-medicate in unsupervised settings where the risks cannot be adequately controlled.

Other interventions in the psychedelics space

Non-mental-health benefits

There are a few studies that suggest psychedelic use could be beneficial for people who do not suffer from any particular mental health problem. For example, psychedelics can bring about highly meaningful experiences,⁴⁸ and might increase prosocial attitudes and behaviour,⁴⁹ and subjective well-being.⁵⁰ However, after a quick survey of the studies on healthy people and conversations with field experts, we decided to prioritise looking into psychedelic-assisted mental health treatments over interventions that would benefit healthy people. This was mainly for the following reasons.

The evidence on increased prosocial attitudes and behaviours and improvements in subjective well-being is weak. We found only one experimental study that used direct subjective well-being measures before and after taking a psychedelic, and it found no statistically significant improvement.⁵¹ That said, two studies—a prospective⁵² and an unpublished⁵³ one—found improvements on a composite well-being scale and multiple studies found self-reported, self-attributed improvements of subjective well-being, i.e. participants stated that they think the psychedelic experience improved their well-being and prosocial behaviour and attitudes.^{54,55,56,57} It is unclear to what extent reports of psychedelics improving well-being and prosocial behaviour and attitudes translate into actual positive change though. Self-reported improvements in well-being are encouraging but should be treated cautiously: the study that did measure subjective well-being directly also found self-reported improvements in well-being, despite no statistically significant improvement in subjective well-being (i.e. people said that the psychedelic experience

improved their well-being but when measured directly, there was no statistically significant improvement in their subjective well-being).⁵⁸

It is less clear whether or to what extent it would be beneficial to increase the other outcome measures that have been studied, such as anti-authoritarianism,⁵⁹ nature-relatedness,⁶⁰ openness,^{61,62} and other personality traits.⁶³ Additionally, the evidence on psychedelics increasing these outcome measures is often weak as well.

Finally, even if making psychedelics available for healthy people has a high positive impact, focusing on psychedelic-assisted mental health treatments is plausibly among the best strategies to get there. Approval of psychedelic-assisted mental health treatments by the US Food and Drug Administration (FDA) would by itself lead to rescheduling of psychedelics to be a less-controlled substance. This would, for example, make research on healthy people easier. Additionally, psychedelic-assisted mental health treatments becoming widely available would likely further reduce stigma on psychedelics and increase positive attention, which could crowd in more philanthropic funding and change the attitudes of relevant actors, such as governments and regulatory bodies.

Advocacy for decriminalisation and/or regulated legalisation

Given the remaining stigma and legal restrictions on psychedelic use, advocacy to relieve some of the existing legal barriers to responsible (supervised) use could be a potentially impactful intervention in the psychedelic space.

However, given the current state of the evidence (discussed below) it seems premature to invest in regulated legalisation or decriminalisation advocacy. There are other potential benefits to people no longer being arrested for psychedelic use but those alone seem

unlikely to make this among the highest-impact causes to invest in, and fall largely outside the scope of this research project and within the more general cause area of drug liberalisation. Additionally, there are extra risks to drug liberalisation advocacy, such as risks of increased misuse of psychedelics, reincreased stigma, and politicisation of the issue.

Microdosing

Another psychedelics intervention that is often suggested as potentially promising is microdosing: taking psychedelics in very low doses. Here, however, the evidence is even sparser.⁶⁴ We currently see no reason to think this will have benefits comparable to those of higher-dose psychedelic-assisted mental health treatments, as there is reason to believe that with classic psychedelics, the latter benefits are mediated by ‘mystical-type’ experiences,⁶⁵ which microdosing doesn’t occasion. Furthermore, we don’t know much yet about the risks of prolonged microdosing,⁶⁶ and from a legal perspective, making microdosing available for healthy people seems much further away than psychedelic-assisted mental health treatments.

Is there evidence psychedelic-assisted mental health treatments work?

Overview

There have been a number of studies investigating the effects of psilocybin as a treatment for depression and MDMA-assisted psychotherapy as a treatment for PTSD, respectively.

These studies have shown promising initial results but it is important to interpret these results with care. This section explains how we assessed the efficacy of these treatments.

We are concerned here with the *standardised* effect size of these treatments. This means that an effect size of 0.5, say, corresponds to an average reduction in depression or PTSD of half of a standard deviation. For example, if the standard deviation of those receiving treatment for depression on the Hamilton Depression Rating Scale (HAM-D) is 5 points, and the effect size of psilocybin treatment on depression is 0.3, then the treatment reduces HAM-D scores by 1.5 points, on average. To begin with, we are interested in the effect sizes shortly after treatment. We then consider the retention rates of the benefits, i.e. the extent to which the benefits of the treatments persist over time.

It is important to recognise that studies in psychology and psychiatry—especially those that rely on self-reported measures—are often misleading. Perhaps as many as 40% of social science studies fail to replicate in large sample, high-quality studies and those that do often have effect sizes reduced by approximately 50%.⁶⁷ Relatedly, there is evidence that large scale pre-registered replications of psychology studies tend to find significantly smaller effect sizes than meta-analyses (perhaps as much as 3 times smaller), which in turn find smaller effect sizes than single studies.⁶⁸ In psychiatry specifically, a paper that selected 83 highly cited studies claiming effective psychiatric treatments found that “40 had not been subject to any attempt at replication, 16 were contradicted, 11 were found to have substantially smaller effects and only 16 were replicated”, with effect sizes overestimated by a factor of 2.3 on average.⁶⁹

Due to these concerns, we can rarely take the results of studies that test the efficacy of treatments at face value. We took two approaches to estimating the effect sizes of the treatments: a Bayesian estimate and a non-Bayesian estimate, which are explained below.

We focused on psilocybin for depression and MDMA-assisted psychotherapy for PTSD because (i) there are nonprofits currently taking these treatments through approval processes in need of funding and (ii) these are the psychedelic treatments with the largest evidence base. However, other psychedelic substances could prove effective for treating some mental health illnesses.

Classic psychedelics besides psilocybin act in similar ways to psilocybin, with promising preliminary results from studies of LSD for anxiety⁷⁰ and DMT in the form of ayahuasca for depression.⁷¹ The brevity of DMT-induced experiences could make DMT (not in the form of ayahuasca) an especially cost-effective treatment if it is similarly effective as psilocybin, due to reduced costs. However, as discussed in section 2, we expect drug development to be significantly more cost-effective than direct treatment and it is not obvious that DMT drug development will be similarly beneficial if psilocybin drug development has already been successful. In addition, small observational studies suggest that the psychedelic ibogaine could be effective for treating opioid use disorders.^{72,73} Opioid use disorders account for almost 15 million DALYs per year worldwide,⁷⁴ which is about half of the global DALY burden due to drug use disorders (excluding alcohol).⁷⁵ The evidence base for ibogaine is still weak and there are concerns over the safety of ibogaine after deadly incidents of cardiac arrest.⁷⁶ However, ibogaine could prove an effective treatment taken in appropriate doses. MAPS is looking to start drug development with a Phase 1 dose-response safety study with ibogaine for opioid dependence.

Bayesian analysis

We carried out a form of statistical analysis known as *Bayesian analysis* to estimate the effect of psilocybin as a treatment for depression and MDMA-assisted psychotherapy for PTSD. We believe that Bayesian analysis is the best way to form judgements under uncertainty.⁷⁷ This involves specifying a *prior probability distribution* (or 'prior' for short), which represents our beliefs about how effective the intervention is at improving depression or PTSD, before taking into all the evidence for the intervention. We then took the highest quality evidence into account which, combined with our prior probability distributions, results in a *posterior probability distribution* (or 'posterior' for short) for the effect size of psilocybin treatment and MDMA-assisted psychotherapy.

Further details of our Bayesian analysis can be found in the Appendix. This is only the second time we have used Bayesian inference in our research, and we recognise our method still has many flaws and approximations that could be improved upon. We plan to make these improvements with each iteration of using it, in order of practical relevance. For example, in this second iteration, we have improved, among other things, the method for choosing our priors, the accuracy of our discounting process and the presentation of our calculations. Bayesian statistics and Bayesian reasoning are preferable to non-Bayesian alternatives because the former provide a formal framework for combining all information from prior beliefs with new evidence to determine how likely it is that various events will occur (in this case, how likely it is that the effect sizes take various possible values). It also constitutes a transparent form of reasoning. However, it can be

difficult to implement well, especially with uncertain data, so we made additional effect size estimates which did not use a Bayesian methodology.

We primarily used five studies of classic psychedelic treatments in our analysis of psilocybin treatment and four studies of MDMA-assisted psychotherapy. In each case, we used the two studies that we think offer the strongest evidence as our evidence in our Bayesian analysis and selected our prior based on the other studies and information about other psychedelic-assisted mental health treatments and other treatments for depression and PTSD. Choosing priors can be difficult and often has a degree of subjectivity but it should be guided by evidence as far as possible. Our choices are based primarily on intuitive judgements based on the track record of several comparable interventions, e.g. drugs that went through the FDA approval process which had similar promise at the time. Four researchers and three external reviewers with relevant expertise used a process outlined in the Appendix to provide prior estimates.

As noted above, we have general concerns about the effect sizes reported in experimental studies. We accounted for these concerns in our prior probability distributions and discounts we made to our posterior probability distributions. These concerns led us to be sceptical of the evidence considered when choosing the prior and of the direct evidence used to update to posteriors.

Evidence for psilocybin as a treatment for major depressive disorder

Prior probability of effect size

We chose our prior primarily by taking into account studies of the effectiveness of psilocybin for treating depression and end-of-life anxiety in cancer patients and ayahuasca for treating treatment-resistant depression:^{78,79,80}

Study	Description	Design	Dose	Therapy	Reported effect
Grob et al. 2011	A pilot study of psilocybin treatment for end-of-life anxiety and depression in cancer patients	Randomised, double-blind, placebo-controlled (250mg niacin), crossover trial, sample size: 12	0.2 mg/kg	No therapy, preparation or integration was provided to participants	2 weeks post-treatment : 0.78 on the Beck Depression Inventory (BDI)
Ross et al. 2016	Studied psilocybin treatment for end-of-life anxiety and depression in cancer patients	Randomised, double-blind, placebo-controlled (250mg niacin), crossover trial, sample size: 29	0.3 mg/kg	Psychotherapy, preparation, integration and evaluation were provided to participants	6 weeks post-treatment : 1.07 BDI; 1.32 on the depression portion of the Hospital Anxiety and Depression Scale
Palhano-Fontes et al. 2019	Studied the effects of the psychedelic ayahuasca (whose active ingredient is DMT) on treatment-resistant depression	Randomised, double-blind, placebo-controlled, sample size: 29	0.36 mg/kg DMT	Some preparation but not much integration, evaluation or further psychological support was provided to participants	1 week post-treatment : 0.98 on the Hamilton Depression Rating Scale (HAM-D)

The reported effect sizes of these studies are surprisingly high: the current best treatments for depression have an effect size of only about 0.3.^{81,82} All else equal, this gives reason for optimism.

However, these studies have many limitations. For instance, none of the trials studied the effects of psilocybin on typical people with depression: the first two studied end-of-life anxiety of cancer patients as well as depression and the latter studied the effect of DMT (rather than psilocybin) on *treatment-resistant* depression (as opposed to major depressive disorder more generally).⁸³ Furthermore, the number of participants in each study was small. As mentioned above, there are good reasons to be sceptical of reported effect sizes in psychology and psychiatry studies in general. Given particular concerns about these studies, this led us to be especially sceptical of the reported effect sizes.

Overall, these studies gave us reason to expect a small but positive effect of psilocybin for treating depression, though with lots of uncertainty. The mean of our prior for the effect size is 0.23, with variance 0.09. Units are standardised, meaning that we expected a drop in depression of 0.23 standard deviations as a result of the treatment. For more details on how we chose our prior, please see the Appendix on our Bayesian analysis.

Direct evidence

We took two studies as evidence to combine with our prior to form our posterior distribution.^{84,85,86} We selected these because they used psilocybin (as opposed to a different psychedelic substance) and either studied effects on depression in particular (in the case of Carhart-Harris et al.) or had a relatively large sample and better control (in the case of Griffiths et al.).

Study	Description	Design	Dose	Therapy	Reported effect
Griffiths et al. 2016	Studied the effects of psilocybin treatment on end-of-life anxiety and depression in cancer patients	Randomised, double-blind, low-dose placebo (0.02-0.04 mg/kg psilocybin) controlled, crossover trial, sample size: 51	0.3-0.4 mg/kg	Preparation and integration were provided to participants	5 weeks post-treatment : 1.3 on the GRID-Hamilton Depression Rating Scale (GRID-HAMD-17)
Carhart-Harris et al. 2016 and Carhart-Harris et al. 2018	Studied psilocybin for treatment-resistant depression in an open-label feasibility trial	Randomised, open-label, no control, sample size: 12	10 mg, followed by 25 mg 7 days later	Psychological support and therapy were provided to participants	1 week post-treatment : 2.3 HAM-D; 1.01 HAM-D adjusting for the placebo effect

Note that the Carhart-Harris et al. effect size is calculated without any control group.

Adjusting for a placebo response equivalent to that of antidepressants,^{87,88} the effect size was 1.01.⁸⁹

There are limitations to the studies, which led us to discount the estimated effect size. We emphasise that our aim is to predict the effect sizes of psilocybin treatment as accurately as possible. Some of the following limitations are not direct criticisms of the quality of the studies but are inevitable limitations of studies of this kind:

Griffiths et al. 2016

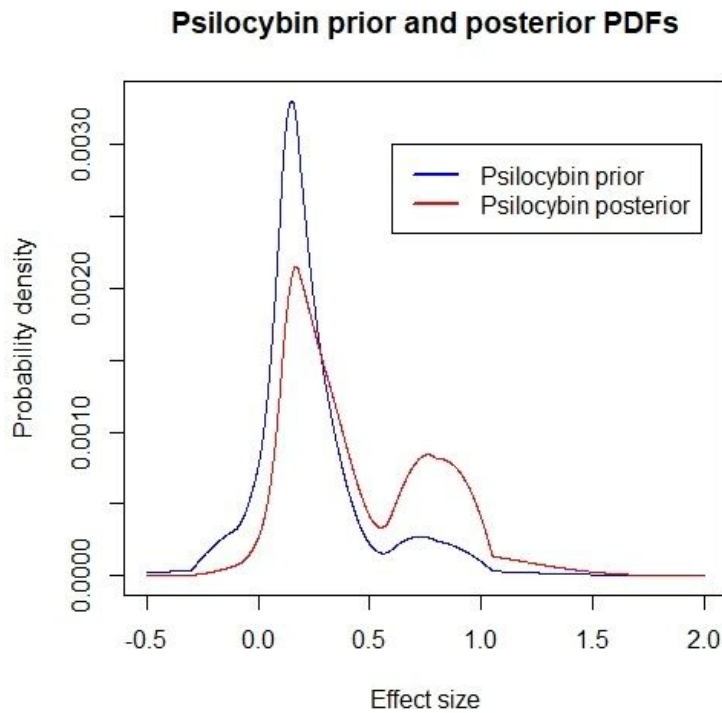
- End-of-life anxiety and depression rather than major depressive disorder (MDD)
 - Only 18 out of 51 participants were diagnosed with MDD, and it might be that this intervention works better for a subgroup of patients with end-of-life depression than for the average MDD patient
 - It is unclear whether this sample selection bias would increase or decrease the average effect, but it increases uncertainty about the study results
- Therapy likely run to a higher standard in the study than when scaled up
 - It is likely that the therapy was higher quality in the study than it will be at scale
- Study volunteers more likely to respond well than an average MDD case
 - Study volunteers might be especially open to psychedelics and susceptible to benefits from psilocybin treatment
- Participants knowing that they are part of a study
 - Knowing that one is part of a study can bias self-reported measures
 - For instance, there is a risk of social desirability bias
- Other risks of replication failure
 - As explained above, there are strong reasons to treat study results with caution, due to risk of replication failure

Carhart-Harris et al. 2018

- Treatment-resistant depression rather than MDD
 - It is unclear whether this sample selection bias would increase or decrease the average effect, but it increases uncertainty about the study results
- Therapy likely run to a higher standard in the study than when scaled up
 - It is likely that the therapy was higher quality in the study than it will be at scale
- Study volunteers more likely to respond well than an average MDD case
 - Study volunteers might be especially open to psychedelics and susceptible to benefits from psilocybin treatment
- Participants knowing that they are part of a study
 - Knowing that one is part of a study can bias self-reported measures
 - For instance, there is a risk of social desirability bias
- No placebo/control group
 - We adjusted the reported effect size estimate to partially account for this but we further discounted the estimated effect size because we could not fully account for it there
- Other risks of replication failure
 - As explained above, there are strong reasons to treat study results with caution, due to risk of replication failure

The overall discounts for Griffiths et al. 2016 and for Carhart-Harris et al. 2018 were 71% and 81%, respectively. Further details are on the BA discounts tab of our cost-effectiveness analysis. See the Appendix on Bayesian analysis for the details and justification of our method of discounting. Figure 3 displays the prior and posterior of our Bayesian analysis.

Figure 3. Psilocybin Bayesian analysis



Source: Computed in R.⁹⁰

Since both studies used as evidence in our Bayesian analysis were limited in significant ways and had small samples, our Bayesian update is fairly small compared to the reported effect sizes. The mean of our posterior for the effect size of psilocybin is 0.45, corresponding to a 2.19 point reduction on the HAM-D scale. From this analysis, we estimate that there is a 55% chance that psilocybin treatment is as good as or better than

standard treatments for depression (effect size of 0.3) and that conditional on this being the case, the mean of our posterior is 0.68 (90% CI: 0.32-1.13).

We are only considering the benefits in the case in which the effect size is greater than or equal to 0.3 because we do not expect the case in which it is less than this to make a significant difference to our final cost-effectiveness estimate (i.e. we expect cost-effectiveness to be dominated by the case in which the effect size is at least 0.3) and it would require a separate analysis. This is because an effect size less than 0.3 would make psilocybin treatment for depression less likely to be approved by the FDA, unlikely to replace current best treatments and be rolled out widely and a lot less value if rolled out widely (even though it could still be useful for certain patients and as an additional treatment).

Non-Bayesian approach

The Bayesian approach is desirable because it offers a principled and formal method of incorporating all relevant information to answer the question of how likely something is, given the evidence. However, it is difficult to implement well in practice, especially when we cannot interpret study results at face value. Therefore, we also estimated the effect size using a different approach.

Our non-Bayesian estimate is based on the results of a meta-analysis which combines the four psilocybin studies, Goldberg et al. 2020.⁹¹ The meta-analysis found a controlled Hedge's g effect size of 0.83. Because Carhart-Harris et al. 2018 has no control group, it was not included in this calculation.

For reasons given above, we think that even meta-analyses are very likely to overstate effect sizes. Considering general information about the effect sizes found in large sample, high-quality studies compared to single studies and meta-analyses, we estimated the effect size as a proportion of that reported in Goldberg et al. 2020. This resulted in an estimated effect size of 0.22. Further, we estimated a 28% chance that the effect size is at least as large as standard treatments for depression (0.3) and that, conditional on being at least 0.3, the effect size is 0.45 (90% CI: 0.31-0.76). See the Non-Bayesian effect size sheet in our cost-effectiveness model and the appendix for details and explanation.

Overall judgement

We combined these estimates by taking the average to use in our cost-effectiveness model. This resulted in an estimated effect size of 0.57, conditional on the effect size being equal to or greater than 0.3 and a 41% chance that the effect size is at least 0.3.

Evidence for MDMA-assisted psychotherapy

Prior probability of effect size

We chose our prior primarily by considering two small, pilot studies of MDMA-assisted psychotherapy for treating PTSD:^{92,93,94}

Study	Description	Design	Dose	Reported effect
Mithoefer et al. 2011 and Mithoefer et al. 2013	A pilot study of MDMA-assisted psychotherapy for treatment-resistant PTSD	Randomised, double-blind, inactive placebo, sample size: 20	125 mg + optional 62.5 mg	Between group effect size of 1.24
Oehen et al. 2013	A pilot study of MDMA-assisted psychotherapy for treatment-resistant, chronic PTSD	Randomised, double-blind, active placebo, sample size: 12	Treatment: 125 mg + 62.5 mg (n = 8) Placebo: 25 mg + 12.5 mg (n = 4)	Mean and SD CAPS-IV score 3 weeks post-treatment imply between group Hedges' g = 0.9

As with the psilocybin/ayahuasca studies, we have to take care not to take the study results at face value. However, these results are slightly more reliable for our purposes because they both tested the use of MDMA in psychotherapy for PTSD, whereas the studies considered for psilocybin tested a different but related compound (DMT-containing ayahuasca) or as a treatment for a different but related condition (end-of-life anxiety and depression, or treatment resistant depression).

The mean of our prior for the effect size is 0.36, with variance 0.15. For more details on how we chose our prior, please see the Appendix on our Bayesian analysis.

Direct evidence

We took two studies as evidence to combine with our prior to form our posterior distribution.^{95,96} We selected these because they had somewhat larger samples and both used active placebos (low doses of MDMA).

Study	Description	Design	Dose	Reported effect
Mithoefer et al. 2018	Studied the effects of MDMA-assisted psychotherapy for chronic PTSD in military veterans, firefighters and police officers	Randomised, double-blind, active placebo, sample size: 26	Treatment: 75 mg (n = 7) or 125 mg (n = 12) Placebo: 30 mg MDMA (n = 7)	Cohen's d: 2.8 for 75 mg group, 1.1 for 125 mg group, both compared with 30 mg group
Ot'alora et al. 2018	A pilot study of MDMA-assisted psychotherapy for treatment-resistant, chronic PTSD	Randomised, double-blind, active placebo, sample size: 27	Treatment: 100 mg (n = 9) or 125 mg (n = 12) Placebo: 40 mg MDMA (n = 6)	Cohen's d: 0.37 for 100 mg group, 0.42 for 125 mg group, both compared with 40 mg group

Again, there are limitations to the studies, which led us to discount the estimated effect size. We emphasise that our aim is to predict the effect sizes of MDMA-assisted psychotherapy as accurately as possible. Some of the following limitations are not direct criticisms of the quality of the studies but are inevitable limitations of studies of this kind:

Mithoefer et al. 2018

- Patients were military veterans, firefighters, and police officers rather than general PTSD population

- This sub-population might respond differently to MDMA-assisted psychotherapy than the general PTSD population, so this increases uncertainty about the results
- Therapy likely run to a higher standard in the study than when scaled up
 - It is likely that the therapy was higher quality in the study than it will be at scale
- Study volunteers more likely to respond well than an average PTSD case
 - Study volunteers might be especially open to psychedelics and susceptible to benefits from MDMA-assisted psychotherapy
- Participants knowing that they are part of a study
 - Knowing that one is part of a study can bias self-reported measures
 - For instance, there is a risk of social desirability bias
- Other risks of replication failure
 - As explained above, there are strong reasons to treat study results with caution, due to risk of replication failure

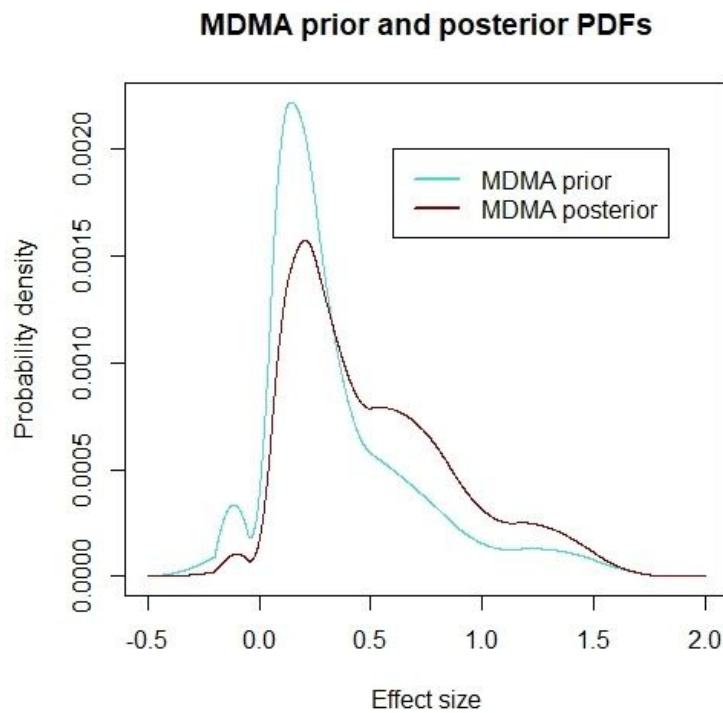
Ot'alora et al. 2018

- Therapy likely run to a higher standard in the study than when scaled up
 - It is likely that the therapy was higher quality in the study than it will be at scale

- Study volunteers more likely to respond well than an average PTSD case
 - Study volunteers might be especially open to psychedelics and susceptible to benefits from MDMA-assisted psychotherapy
- Participants knowing that they are part of a study
 - Knowing that one is part of a study can bias self-reported measures
 - For instance, there is a risk of social desirability bias
- Other risks of replication failure
 - As explained above, there are strong reasons to treat study results with caution, due to risk of replication failure

The overall discounts for Mithoefer et al. 2018 and for Ot'alora et al. 2018 were 74% and 68%, respectively. Further details are on the BA discounts sheet of our cost-effectiveness analysis. See the Appendix on Bayesian analysis for the details and justification of our method of discounting. Figure 4 displays the prior and posterior of our Bayesian analysis.

Figure 4. MDMA-assisted psychotherapy Bayesian analysis



Source: Computed in R.⁹⁷

The mean of our posterior for the effect size of MDMA-assisted psychotherapy is 0.51, corresponding to a 8.92 point reduction on the CAPS-IV scale. From this analysis, we estimate that there is a 63% chance that MDMA-assisted psychotherapy has an effect size of 0.3 or more, and that conditional on this being the case, the mean of our posterior is 0.72 (90% CI: 0.32-1.37).

We are only considering the benefits in the case in which the effect size is at least 0.3 for similar reasons to doing so for psilocybin and to make it easier to compare our analyses of psilocybin treatment and MDMA-assisted psychotherapy. However, the 0.3 benchmark is not as relevant to PTSD treatments as it is to depression treatments.

Non-Bayesian approach

Our non-Bayesian estimate for MDMA-assisted psychotherapy is based on the pooled analysis of six MDMA studies, Mithoefer et al. 2019.⁹⁸ The analysis found a Cohen's d effect size of 0.8.

For reasons given above, we think meta-analyses are very likely to overstate effect sizes. Considering general information about the effect sizes found in large sample, high-quality studies compared to single studies and meta-analyses, we estimated the effect size as a proportion of that reported in Mithoefer et al. 2019. This resulted in an estimated effect size of 0.23. Further, we estimated a 30% chance that the effect size is at least 0.3 and that, conditional on being at least 0.3, the effect size is 0.46 (90% CI: 0.31-0.73). See the Non-Bayesian effect size sheet in our cost-effectiveness model and the appendix for details and explanation.

Overall judgement

We combined these estimates by taking the average to use in our cost-effectiveness model. This resulted in an estimated effect size of 0.59, conditional on the effect size being equal to or greater than 0.3 and a 46% chance that the effect size is at least 0.3.

A limitation of these estimates is that effect sizes are calculated by comparing a 75 mg+ MDMA treatment group to a low dose MDMA-psychotherapy control, both of which receive psychotherapy. This is good in that the studies are well-controlled but it means that reported effect sizes only state the effect of a moderate-to-large dose of MDMA with psychotherapy beyond low dose MDMA-psychotherapy rather than the full effect size of moderate-to-large dose MDMA-assisted psychotherapy. In contrast, psychotherapy is not as important a part of the psilocybin treatment, so our effect size estimates compared to a placebo control—and therefore our cost-effectiveness estimates—might not be directly comparable. However, we tested whether this affected our conclusions by using a similar adjustment that we made to the Carhart-Harris et al. 2018 effect size for psilocybin (as the study has no control group). We considered the uncontrolled pre-post effect sizes for MDMA-psychotherapy minus a placebo response. We do not have good data on how large the placebo response is likely to be, so we considered a range of values from (0 to 0.8 SDs) and found that our conclusions are not affected across this range.

The interim analysis of MAPS's first of two Phase 3 studies has shown promising results, with at least a 90% chance that the study will obtain statistical significance, with an effect size of 0.56 or greater.⁹⁹ We have not accounted for this formally in our analysis but keenly await publication of the full results. We note, however, that even Phase 3 studies are prone to overstate effect sizes and so we should not interpret the results of this study as the effect size of the treatment at scale.

2. Intervention selection

Focusing on psychedelic-assisted mental health treatments, we identified three types of interventions to look into: direct treatment, academic research, and drug development. Of these, we decided to focus on drug development. We'll consider our reasoning for each intervention type in turn.

Direct treatment

Donors could directly fund psychedelic treatments. Surveying the research literature on psychedelic-assisted mental health treatments, we found that a lot of different treatments are being studied and that the evidence suggests psychedelic-assisted mental health treatments as a category is promising. However, for most individual treatments the evidence is still relatively weak, and it is generally unclear whether they are more effective than the best alternative treatments available. Furthermore, the treatments are expensive, costing thousands of dollars for a course of treatment.^{100,101} Given these costs, to be competitive with other recommendations we have made in the mental health and subjective well-being spaces, such as StrongMinds¹⁰² and Action for Happiness,¹⁰³ funding psychedelic-assisted mental health treatments directly would have to avert more than 1 disability-adjusted life year (DALYs) per average participant. This seems very unlikely.

As an example comparison, the current best alternative treatments for depression other than psychedelic treatments have an effect size of only 0.3 standard deviations.^{104,105}

Assuming pooled standard deviation is the same as in the studies of psilocybin, this is equivalent to a reduction in HAM-D score of 1.5 points, which is roughly equivalent to averting about 0.04 DALYs if effects persist for a year. For depression,

psychedelic-assisted treatments would have to be about a hundredfold more effective than the current best treatments available for direct treatment funding to be competitively cost-effective with our other recommendations. Indeed, in our Bayesian and cost-effectiveness analysis of [psilocybin treatment](#) and [MDMA-assisted psychotherapy](#), we ended up estimating the cost-effectiveness for direct treatment funding to be only 76 and 30 DALYs per million dollars averted respectively, compared to our estimate of approximately 400 DALYs per million dollars averted for Action for Happiness.

In addition to not likely being cost-effective from a philanthropic perspective, psychedelic-assisted mental health treatments are still illegal in many countries. No treatment has yet been approved for use in the United States, most countries of the European Union or the United Kingdom, where the majority of the research on psychedelic-assisted mental health treatments is happening. There are countries where one can legally perform psychedelic-assisted mental health treatments, for example, Jamaica¹⁰⁶ and the Netherlands,¹⁰⁷ but the available treatments there are not integrated with the medical system. This means there is no independent quality and risk control, and it's less likely the treatments will reach those who need it most.

Overall, direct treatment seems unlikely to be cost-effective because treatments are very expensive, there are few opportunities to fund legal psychedelic treatments, and the evidence base for psychedelic treatments is still fairly weak, so we cannot be confident in their effectiveness for treating mental health problems.

Academic research

The lack of strong evidence in support of individual psychedelic-assisted mental health treatments suggests that funding further high-quality academic research into their effectiveness is a promising option. We had conversations with multiple funders of research and research institutes and concluded there are indeed a lot of research projects that could use funding.

Moreover, most progress in researching psychedelic-assisted mental health treatments in the past 20 years has been funded philanthropically.¹⁰⁸ Governments still generally seem reluctant to fund research on psychedelic-assisted mental health treatments (and psychedelics more generally), which indicates a larger potential counterfactual impact for philanthropists who step in and fill the gap. However, there are some signs this might be changing, with the American National Institute of Mental Health funding more research in the past 10 years for example.¹⁰⁹

To assess the impact of funding further research, the main question we asked was: will funding a particular research project make it significantly more likely that either 1. effective psychedelic-assisted treatments reach the people that need them or 2. we learn which psychedelic-assisted treatments are ineffective, so no funding is wasted on further research and rollout of those treatments. We compared the likelihood of these outcomes to the potential benefits of drug development (discussed below) and found drug development to be a more attractive funding opportunity for the following reasons:

- There are already many ongoing and upcoming high-quality studies^{110,111,112,113} on psychedelic-assisted mental health treatments, and there are likely more of those

to follow, given the new philanthropic funding that has recently come into the area.¹¹⁴ It seems prudent to await the results of these research projects to determine which treatments and interventions, including drug development, to (de)prioritise.

- Assuming that one wants to fund something now, there is a much weaker case for academic research leading to people benefiting from psychedelic-assisted treatments at scale than for drug development. There are many more intermediate steps from funding academic research to that point, and these steps would likely include drug development.
- Lastly, drug development requires high-quality trials as a part of it, and academic studies do not automatically qualify as a substitute for these studies. All else equal, this is a reason to prefer studies as part of drug development to those that are only part of an academic research agenda.

Overall, although there could be high impact academic research projects requiring funding—especially research that governments are reluctant to fund—we think that the best funding opportunities are more likely to be within drug development.

Drug development

Among the three interventions we considered, drug development seemed the most promising. This is the process that covers everything from the discovery of a new drug for treatment to this drug being approved for medical use.¹¹⁵ We mainly focused on drug development in the United States and the European Union, as these are the places where

we are aware of nonprofit organisations working on taking psychedelic-assisted mental health treatments through the approval process. They also each have relatively large populations which would get access to the treatments. In the United States, the Food and Drug Administration (FDA)¹¹⁶ is in charge of authorising new drugs, whereas for the European Union this is (mostly) done by the European Medicines Agency (EMA).¹¹⁷

We think drug development is currently the most promising intervention for the following reasons:

- It is the most straightforward and potentially the only way to make psychedelic-assisted mental health treatments available at scale
 - FDA approval is tightly linked with health insurance coverage, both private and public.¹¹⁸ For EMA approval roughly the same holds, although the situation is slightly more complicated due to differing health insurance systems in different countries.¹¹⁹ Given the relatively high costs of the treatment, health insurance coverage is necessary to make it widely available.
- Drug approval will likely unlock other progress in psychedelic-assisted treatments
 - It will contribute to reduced stigma in society at large. For example, it seems likely that people will be less sceptical and negative about psychedelic use if they have a friend or relative for whom a psychedelic-assisted treatment improved their mental health.

- With an improved reputation, other funders are more likely to enter the field, both philanthropic and non-philanthropic, and there is likely to be (even) more research interest.
- Drug approval allows for off-label prescription:¹²⁰ doctors will be able to prescribe evidence-based psychedelic-assisted mental health treatments that use the same drug, but for different conditions than the one for which the drug was originally approved. Such treatments would not have to go through the full approval process for this to happen. They are, however, less likely to be covered by health insurance,¹²¹ and we would expect them to be prescribed to a lesser extent.
- After approval, the nonprofit in question can fund further work on the same or other psychedelic-assisted treatments by selling the drug and the treatment.
- Drug development involves high-quality clinical trials that will teach us more about the benefits and costs of psychedelic-assisted mental health treatments
 - If this were the only purpose, it would be cheaper to fund the research directly, but this information is still a good side benefit.
- There has been little initiative so far from for-profit pharmaceutical companies to develop psychedelics and make psychedelic-assisted mental health treatments available at scale

- The exception here is COMPASS Pathways,¹²² which is currently going through both the FDA and EMA process for psilocybin as a treatment for treatment-resistant depression.
- There are nonprofit organisations that are currently going through the drug development process
 - These are the Multidisciplinary Association for Psychedelic Studies (MAPS),¹²³ which is developing MDMA-assisted psychotherapy for PTSD both in the US and EU, and Usona Institute,¹²⁴ which is developing psilocybin as a treatment for major depressive disorder (MDD) in the US.

Drug development seems the most promising type of intervention at this time because it offers high leverage opportunities: FDA and EMA approval will likely be necessary in order for psychedelic-assisted mental health treatments to be available at scale, approval would bring other benefits (e.g. allowing for off-label prescription), and high-quality clinical trials involved in the drug development process would provide more information on the effectiveness of these treatments.

3. Funding opportunity analysis

We considered funding opportunities at the two nonprofits currently working on drug development: MAPS and Usona Institute. We had conversations with these organisations, conversations with other experts, and surveyed the research literature on the psychedelic-assisted mental health treatments they are advancing. We then completed a full Bayesian and cost-effectiveness analysis of the two funding opportunities. Based on this analysis, we concluded that we should recommend Usona's drug development programme alongside those we recommend in related cause areas, such as mental health in low-income countries and subjective well-being.¹²⁵

We came to the same conclusion about MAPS's drug development programme and Capstone Campaign for the US, Canada and Israel but this funding opportunity has now been filled. We think that MAPS's drug development programme in Europe is less cost-effective than the Capstone Campaign. Therefore, we think that the European programme presents a good funding opportunity for donors with a special interest in psychedelic-assisted mental health treatments but we would recommend it only in certain circumstances.

Usona Institute's psilocybin drug development programme

What does Usona do?

Usona is a US-based non-profit medical research organisation that carries out and supports research into psychedelic treatments. Usona began Phase 2 research of psilocybin as a treatment for major depressive disorder in late 2019. After completing

Phase 2 trials, Usona aims to achieve FDA approval for psilocybin via Phase 3 research and to commercialise psilocybin, to make it available as a treatment for depression. We have evaluated Usona’s psilocybin drug development programme of psilocybin for depression, which is Usona’s primary programme.

Is there evidence the intervention works?

We have discussed the evidence for psilocybin as a treatment for depression in Section 1, and the process of drug development in section 2. We should note that drug development is a very ‘risky’ intervention: there is far from a guarantee that Usona will succeed, but if they do, the benefits may be large.

Is the intervention cost-effective?

We built a [cost-effectiveness model](#) for funding Usona’s drug development programme, including a Bayesian analysis for the effect size of psilocybin as a treatment for depression and a [Guesstimate model](#) to calculate a 90% confidence interval.¹²⁶ The spreadsheet contains explanatory notes and sources for the cost-effectiveness analysis, and we have included a more detailed description of our Bayesian analysis in the appendix.

Our rough model considers the benefits of speeding up the roll-out of psilocybin as a treatment for depression. We chose this over a model that considers whether roll-out happens at all. This is for a few reasons:

- Usona expects to be able to raise the necessary funds themselves eventually, even without us recommending them.¹²⁷

- Even if Usona were unable to raise the funds, we would expect another organisation to develop psilocybin as a treatment for depression at a later point in time, if it is indeed an effective treatment, especially because other companies (most notably MAPS, Compass Pathways) are already making progress on drug development for psychedelic-assisted mental health treatments in parallel.

Our model suggests that funding Usona’s drug development programme would have the following cost-effectiveness in terms of health benefits for people receiving psilocybin treatment:

Metric	Lower bound of 90% Confidence Interval, using Guesstimate	Expected cost-effectiveness estimate, using Guesstimate	Upper bound of 90% Confidence interval, using Guesstimate	Best guess point estimate, using Google Sheets (for comparability with previous estimates)
DALYs-equivalent per million dollars	-9	668	4,540	497
Cost per DALY	-\$108,814	\$1,497	\$220	\$2,012

Note that although we expect this funding opportunity to avert a large number of DALYs, there is a non-negligible chance that it will have a negative impact. This is because we have accounted for costs, such as future treatment costs that could have been spent on other healthcare interventions, and these could outweigh the benefits. For this reason, as

well as the high uncertainty in our estimates, this funding opportunity might appeal most to donors with a relatively high risk tolerance.

Our Guesstimate model accounts for uncertainty better than our Google Sheets model, providing an estimate of expected cost-effectiveness as well as a 90% confidence interval for cost-effectiveness. Previously, we made our cost-effectiveness estimates of funding opportunities in the mental health and subjective well-being space in Google Sheets^{128,129} and such estimates are not easily compared with our Guesstimate model for this funding opportunity. Therefore, we also made a cost-effectiveness model in Google Sheets (right hand column above) to make it easier to compare this funding opportunity with previously evaluated funding opportunities.

Is it a strong organisation?

Usona is a relatively young organisation, founded in 2014, so it has not yet had time to build a robust track record.¹³⁰ However, Usona has quickly grown in size, established its own chemistry laboratories and started Phase 2 psilocybin research.¹³¹

The FDA has granted Usona drug development programme Breakthrough Therapy Designation, which serves as a formal acknowledgment of the FDA's confidence in early evidence and psilocybin's potential as a therapy for depression.¹³² This designation provides Usona with early and intensive FDA guidance to accelerate FDA approval.

Usona was co-founded by Malynn Utzinger, MD, and Bill Linton, founder of the global life science research company, Promega Corporation. Despite its youth as an organisation, Usona has a strong and experienced staff and boards of scientific and clinical advisors.¹³³

Usona has been transparent in its communication with us, providing detailed, informative replies to our queries.

Is there room for funding?

Within its psilocybin drug development programme, Usona is currently seeking funding to complete phase 2 clinical trials and to prepare for phase 3. Usona has a funding gap of \$6.5 million to fill before the end of 2020. In our cost-effectiveness analysis, we have estimated the cost-effectiveness of filling this funding gap but Usona will be able to productively absorb additional funding in the coming years for completing phase 3 clinical trials and for the commercialisation of psilocybin treatment if phase 2 trials are successful. Usona estimates that it will need between \$18 million and \$30 million to complete phase 3, and will require additional funding beyond that for commercialisation.

What are the main uncertainties?

There are many uncertain judgements and assumptions we had to make in our analysis.

These are the ones we think are most relevant to our conclusions:

- Retention rates of benefits
- Cost-effectiveness of counterfactual healthcare spending
- Funding gap
- Years approval is advanced
- Probability of another donor stepping in

- Fraction of patients receiving treatment at scale

See the notes in our [cost-effectiveness model](#) for more details on how we arrived at our chosen values for these variables.

Multidisciplinary Association for Psychedelic Studies (MAPS)'s MDMA drug development programme

What does MAPS do?

MAPS is a US-based non-profit working to benefit people from the careful uses of psychedelics and marijuana. MAPS was founded in 1986 shortly after the US Drug Enforcement Administration's criminalisation of MDMA.

We have evaluated MAPS's MDMA drug development programme via MDMA-assisted psychotherapy for PTSD. MAPS is currently undergoing Phase 3 research, which could lead to approval of MDMA-assisted psychotherapy in the US, Israel and Canada. Following the approval and commercialisation of MDMA-assisted psychotherapy in these countries, MAPS will seek approval of MDMA-assisted psychotherapy for PTSD from the European Medicines Agency, starting its globalisation campaign.

Is there evidence the intervention works?

We have discussed the evidence for MDMA-assisted psychotherapy in Section 1, and the process of drug development in section 2. We should note that drug development is a very 'risky' intervention: there is far from a guarantee that MAPS will succeed, but if they do, the benefits may be large.

Is the intervention cost-effective?

We built a [cost-effectiveness model](#) for funding MAPS's drug development programmes, including a Bayesian analysis for the effect size of MDMA-assisted psychotherapy for PTSD and Guesstimate models to calculate a 90% confidence interval ([MAPS Europe CEA](#), [MAPS US, Canada & Israel CEA](#)).¹³⁴ The spreadsheet contains explanatory notes and sources for the cost-effectiveness analysis, and we have included a more detailed description of our Bayesian analysis in the appendix.

Our rough model considers the benefits of speeding up the roll-out of MDMA-assisted psychotherapy. We chose this over a model that considers whether roll-out happens at all.

This is for a few reasons:

- We expect MAPS to be able to raise the necessary funds themselves eventually, even without us recommending MAPS, given its strong fundraising track record.
- Even if MAPS were unable to raise the funds, we would expect another organisation to develop MDMA-assisted psychotherapy for PTSD at a later point in time, if it is indeed an effective treatment, especially because other companies (most notably Usona, Compass Pathways) are already making progress on drug development for psychedelic-assisted mental health treatments in parallel.

MAPS recently announced its Capstone Campaign, raising \$30 million to reach approval of MDMA-assisted psychotherapy in the US, Canada and Israel and to start the commercialisation of this treatment. MAPS secured \$10 million of initial funding and a \$10 million matching pot that will be unlocked by securing the remaining \$10 million. We initially evaluated this funding opportunity. At the time we carried out this analysis, MAPS had a

\$4.4 million funding gap remaining as part of this campaign so our analysis estimates the cost-effectiveness of filling this funding gap by September 10 2020. This funding opportunity has recently been filled so we also evaluated MAPS’s drug development programme in Europe.

Our model suggests that funding MAPS’s drug development programmes would have the following cost-effectiveness in terms of health benefits for people receiving MDMA-assisted psychotherapy:¹³⁵

Metric	Lower bound of 90% Confidence Interval, using Guesstimate	Expected cost-effectiveness estimate, using Guesstimate	Upper bound of 90% Confidence interval, using Guesstimate	Best guess point estimate, using Google Sheets (for comparability with previous estimates)
DALYs-equivalent per million dollars (US, Canada, Israel)	-4	679	5,450	398
Cost per DALY (US, Canada, Israel)	\$272,784	\$1,473	\$183	\$2,514
DALYs-equivalent per million dollars (Europe)	-27	177	1,480	85
Cost per DALY (Europe)	-\$37,594	\$5,650	\$676	\$11,732

Note that although we expect these funding opportunities to avert a large number of DALYs, there is a non-negligible chance that they will have a negative impact. This is

because we have accounted for costs, such as future treatment costs that could have been spent on other healthcare interventions, and these could outweigh the benefits. For this reason, as well as the high uncertainty in our estimates, this funding opportunity might appeal most to donors with a relatively high risk tolerance.

Our Guesstimate model accounts for uncertainty better than our Google Sheets model, providing an estimate of expected cost-effectiveness as well as a 90% confidence interval for cost-effectiveness. Previously, we made our cost-effectiveness estimates of funding opportunities in the mental health and subjective well-being space in Google Sheets^{136,137} and such estimates are not easily compared with our Guesstimate model for this funding opportunity. Therefore, we also made a cost-effectiveness model in Google Sheets (right hand column above) to make it easier to compare this funding opportunity with previously evaluated funding opportunities.

There are a number of reasons why we think that the European programme is less cost-effective than the Capstone Campaign. These include:

- [We estimate](#) that a smaller number of people suffer from PTSD in Europe than in the US, Canada and Israel
 - While the total population in Europe is larger, prevalence data suggest that the total population suffering from PTSD is lower¹³⁸
- We are more uncertain and less optimistic about the level and speed of take up of MDMA-assisted psychotherapy in Europe

- Following approval by the European Medicines Agency, we expect take up in the countries in which MAPS has Phase 3 sites to be similar to in the US, Canada and Israel but we expect take up in other countries to be lower and/or slower on average
- The European campaign, unlike the Capstone Campaign, has no matching pot
- We do not expect MAPS to raise funds as quickly as during the Capstone Campaign as this was a very large fundraising effort with a large matching pot but we still expect MAPS to be able to fundraise relatively well
- The wider benefits of the European programme are smaller
 - MAPS will be able to use European data as part of the approval process in some non-European countries but overall we expect the wider benefits of FDA approval in the US to be largest
 - This is mainly because, if successful, FDA approval in the US will be the first approval of a psychedelic medical treatment
 - The following section considers the wider benefits in more detail
- The estimated cost per treatment in Europe are slightly higher than in the US, Canada and Israel
- Approval and roll out in Europe are about 2-3 years behind the US, Canada and Israel, which introduces extra uncertainty

Taken individually, these reasons are each fairly small but overall (excluding the consideration of wider benefits, which are not modelled explicitly), they suggest cost-effectiveness about 4 times smaller. Given the additional uncertainty of the estimate of the European programme and the smaller wider benefits, the true difference in cost-effectiveness is likely even greater.

Is it a strong organisation?

MAPS was founded in 1986¹³⁹ and, in our understanding, has a longstanding positive reputation in the psychedelics research and advocacy space. MAPS has a strong track record and is furthest along in the drug development pipeline of every organisation developing psychedelic treatments. MAPS completed Phase 2 clinical trials of MDMA-assisted psychotherapy for PTSD in 2016 and started Phase 3 in late 2019 with the interim analysis of its first of two Phase 3 studies taking place in March 2020.

MAPS has a strong fundraising track record, having raised over \$70 million prior to the Capstone Campaign.¹⁴⁰ MAPS has successfully completed its Capstone Campaign, raising an additional \$30 million.

The FDA has granted MDMA-assisted psychotherapy Breakthrough Therapy Designation, which serves as a formal acknowledgment of the FDA's confidence in early evidence and MDMA-assisted psychotherapy's potential as a treatment for PTSD.¹⁴¹ This designation provides MAPS with early and intensive FDA guidance to accelerate FDA approval.

MAPS is able to leverage the data already collected for the FDA in its EMA approval application. The EMA will accept all the data gathered by MAPS for the FDA, requiring only one additional Phase 3 trial in Europe.¹⁴² As a result, the cost of EMA approval for MAPS will

be about one third of that of FDA approval. No other organisations have similar data to leverage, so MAPS is uniquely positioned to obtain EMA approval for MDMA-assisted psychotherapy efficiently.

MAPS has been very transparent in its communication with us, providing detailed, informative replies to our queries.

Is there room for funding?

MAPS is seeking \$26 million to reach approval by the European Medicines Agency (EMA). This will fund Phase 3 research for European Medicines Agency approval and the globalisation of MDMA-assisted psychotherapy. MAPS has currently raised \$2.3 million of this \$26 million campaign.¹⁴³

In our analysis, we evaluate the impact of raising \$5.7 million of the remaining \$23.7 million by July 1 2021.¹⁴⁴ This will leave \$18 million to raise to reach EMA approval. MAPS will also have costs for commercialisation Europe following EMA approval.

What are the main uncertainties?

There are many uncertain judgements and assumptions we had to make in our analysis.

These are the ones we think are most relevant to our conclusions:

- Retention rates of benefits
- Cost-effectiveness of counterfactual healthcare spending
- Years approval is advanced

- Probability of another donor stepping in
- Fraction of patients receiving treatment at scale, more so for MAPS than Usona (as Usona data used for MAPS)

See the notes in our [cost-effectiveness model](#) for more details on how we arrived at our chosen values for these variables.

We are also uncertain about how the impact of this funding opportunity will change over time. In particular, MAPS has ambitious fundraising goals for the European programme that might prove challenging to meet. While we judge that MAPS will likely raise the first \$5.7 million relatively swiftly, we expect that the following \$18 million could be much harder to raise. We will take a keen interest in following MAPS's progress and need for funding over the coming years and are open to revising our views as we see how MAPS's fundraising needs change.

The wider benefits of these funding opportunities

We think that our cost-effectiveness estimates capture a leading way in which these funding opportunities can be expected to have an impact. They also allow us to compare them with other funding opportunities we are recommending in similar areas, most notably Action for Happiness's scale-up of local community courses to improve well-being¹⁴⁵ and StrongMinds's treatment of women with depression.¹⁴⁶ However, there are a number of ways in which these funding opportunities could have wider benefits that are not accounted for in our cost-effectiveness analysis.

Easier use of psilocybin/MDMA as a treatment for other conditions

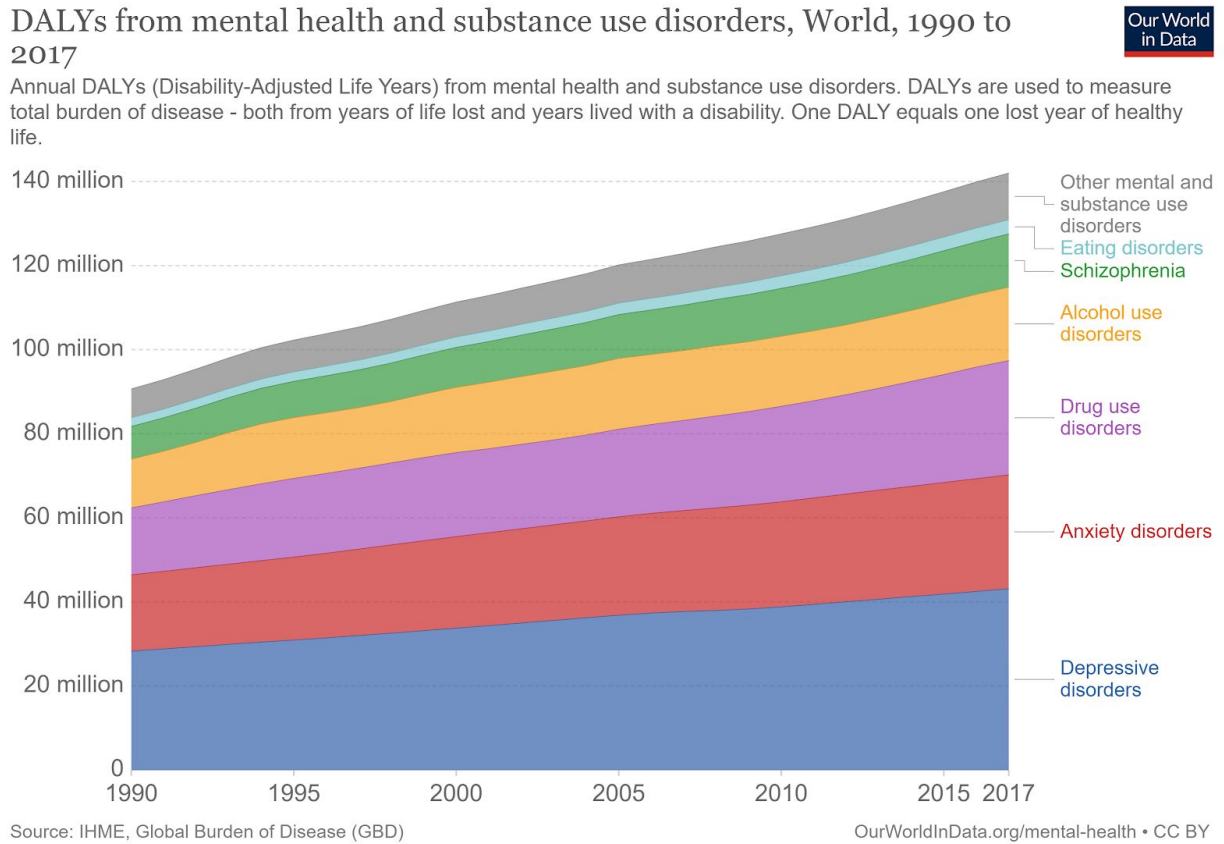
There's some initial research into the use of psilocybin and MDMA to treat a wide range of mental health and substance use disorders (MH&SUDs), suggesting that psilocybin and MDMA could have benefits beyond alleviating depression and PTSD. Indeed, many of the studies we draw on in our analysis of the effect size of psilocybin for depression measure the impact of psilocybin on end-of-life anxiety in cancer patients, as well as depression. More speculatively, initial and ongoing research suggests psilocybin could be effective as a treatment for a range of conditions, including addiction to alcohol, nicotine and other substances, OCD, anorexia, Alzheimer's Disease, and cluster headaches.

On the one hand, this suggests that the benefits of psilocybin could be much larger than the direct effects on depression. On the other hand though, evidence supporting most of these claims is still very sparse and it would be prudent to treat such claims sceptically.

The annual global DALY burden of MH&SUDs is about 140 million, of which about 30% (43 million) is due to depressive disorders.¹⁴⁷ Making the very optimistic assumptions that psilocybin is as effective at averting DALYs due to all MH&SUDs as it is for those due to depression and that psilocybin becomes as widely used for treating all MH&SUDs as it will for depression, this very roughly suggests that the total benefits of psilocybin could be at most 3 times greater than we have estimated for depression, in a given population.¹⁴⁸

However, given the sparsity of evidence for psilocybin as a treatment for other conditions, the true size of the additional benefits is likely to be much smaller. Additionally, such benefits would not be costless, so, for instance, a 3x increase in DALYs averted would not straightforwardly lead to a 3x improvement in cost-effectiveness.

Figure 5. DALYs from mental health and substance use disorders, World, 1990 to 2017



Source: Our World in Data, [‘Mental Health’](#)

The best-supported use of psilocybin besides depression is for anxiety and addiction. The global DALY burdens of anxiety disorders and drug use (excluding alcohol) disorders are 27 million each (19% of the DALY burden of MH&SUDs), and the burden of alcohol use disorder is 17 million (12%).¹⁴⁹ In total, these amount to 72 million DALYs, about half of the total

MH&SUDs DALY burden and about 1.7 times as large as the DALY burden of depressive disorders. This is significant but not overwhelming. Very optimistically, if psilocybin is as effective at alleviating DALYs due to anxiety, drug use and alcohol use disorders as it is at alleviating DALYs due to depression, this suggests the total DALYs averted is 2.7 times greater than estimated by direct effects on depression. We think that the true multiplier is probably much smaller though as we expect psilocybin to be less effective at averting DALYs due to these conditions due to sparser evidence. Additionally, it is still unclear how widely used psilocybin will be. On balance, it is possible that these wider benefits will be fairly large, so they are worth taking into account. However, it is unlikely that the wider benefits dominate other considerations.

Compared to MDMA, psilocybin is more promising from the perspective of off-label prescription and further research because there are more completed and ongoing studies on psilocybin for treating other conditions besides depression than there are for MDMA-assisted psychotherapy for other conditions besides PTSD. However, MDMA shows promise for treating some other conditions. For example, the FDA has approved a pilot study sponsored by MAPS of MDMA-assisted psychotherapy for eating disorders.¹⁵⁰ MAPS also has aspirations for sponsoring exploratory studies of MDMA for treating social anxiety, depression, alcoholism, couples therapy, fibromyalgia and irritable bowel syndrome.¹⁵¹

Successful approval crowds in funding for further studies on other psychedelics, unlocking or speeding up the approval of other psychedelic treatments

The success of other classic psychedelics as treatments for other conditions other than depression is highly correlated with the success of psilocybin as a treatment for other conditions since they act in very similar ways. Therefore, essentially the same argument applies here as in the previous section. The multiplier could be large but is very likely less than 3. These benefits are not (or are only very slightly) additional to the wider psilocybin benefits because other classic psychedelic treatments are unlikely to provide much value above and beyond psilocybin.

MDMA acts differently to psilocybin and other classic psychedelics, which suggests that MDMA approval would be less useful in unlocking other psychedelic treatments. However, we think it is reasonable to expect that MDMA approval would still crowd in some level of extra funding for other psychedelic treatments. Furthermore, we expect earlier successes to crowd in more funding than later ones (all else equal) and since MAPS is further along the drug development pipeline than Usona and will likely reach approval first, these benefits could be larger for MDMA approval than psilocybin approval. With the completion of the Capstone Campaign, MAPS has secured sufficient funding to reach FDA approval in the US, and soon after approval in Canada and Israel. This suggests that future donations probably will not have as large crowding in effects as donations to the Capstone Campaign.

Relatedly, it is important to consider the effects of the for-profit company Compass Pathways, which is running a drug development programme for psilocybin for

treatment-resistant depression. If Compass Pathways reaches FDA approval before MAPS or Usona, then these wider benefits due to MAPS or Usona could be diminished. However, Compass Pathways has not yet started Phase 3 studies so it is unlikely to obtain FDA approval of psilocybin before MAPS does so for MDMA.

Successful approval provides useful evidence and crowds in funding for psychedelics studies in other countries, unlocking or speeding up approval of these treatments in other countries

The global ramifications of FDA approval of psilocybin and MDMA could be very large. It is plausible that after FDA approval, other countries will approve psychedelic treatments. For instance, the studies used in FDA approval might help to advance approval in other countries and the hype surrounding successful FDA approval could crowd in additional funding to approve psychedelic treatments in other countries. For example, the European Medicines Agency has indicated to MAPS that it will accept data generated for the FDA, reducing the cost of EMA approval of MDMA-assisted psychotherapy for PTSD.¹⁵² Bringing forward FDA approval could therefore bring forward the approval of psychedelic treatments in various other countries.

The total DALY burden of MH&SUDs in the US is 12.74 million, about 9% of the global burden, naively suggesting that the DALYs averted beyond the US could be 11 times as large as those averted in the US.¹⁵³ Considering just DALYs due to depression, the burden in the US is about 6% of the global burden, naively suggesting that DALYs averted due to depression outside the US could be 17 times larger than within the US. However, these rough calculations are extremely speculative and many countries will be unlikely to

approve psychedelic treatments in the near future, so we expect the actual global benefits to be much smaller than these naive calculations suggest.

These wider benefits would also come with extra costs (e.g. to fund studies for approval and treatment costs), which would have to be accounted for carefully to estimate the wider net benefits. Nonetheless, while we remain very uncertain about the extent of the global benefits, we think that there is scope for large gains.

Again, we expect earlier successes to crowd in more funding than later ones (all else equal), so this consideration is probably a larger bonus for MDMA approval than psilocybin approval.

Other possible benefits

Other wider benefits that we think could come about but which we think are probably much smaller and/or more speculative than those considered above include:

- A reduction in criminal prosecution of people who use psilocybin or MDMA
- More evidence on whether and how these treatments work
- More general subjective well-being benefits
- An increase in altruistic behaviour
- An increased in nature-relatedness
- An increase in creativity and innovation

4. Conclusion and recommendation

We think Usona's drug development programme is competitive with our recommendations in other areas, such as Action for Happiness' scale-up of their local community course¹⁵⁴ and StrongMinds' treatment of women with depression.¹⁵⁵ We hence recommend Founders Pledge members to give to Usona's drug development programmes alongside these other recommendations, especially those members more interested in 'riskier' interventions.

We came to the same conclusion about MAPS's drug development programme and Capstone Campaign for the US, Canada and Israel but this funding opportunity has now been filled. We think that MAPS's drug development programme in Europe is a good funding opportunity for donors with a special interest in psychedelic-assisted mental health treatments but that it is less cost-effective than the Capstone Campaign.

Our main line of reasoning is as follows:

- We have arrived at similar cost-effectiveness estimates for the health benefits of Usona's and MAPS's Capstone Campaign funding opportunities as we have arrived at for Action for Happiness's programme: all are estimated to be on the order of hundreds of DALYs per million dollars, using our latest methodology.
- However, we are a lot more uncertain about the cost-effectiveness model¹⁵⁶ we have used for Usona and MAPS: the model is more complicated and requires many more subjective judgements and assumptions. It is highly sensitive to those judgements and assumptions being erroneous. This means we should put less

weight on our cost-effectiveness estimates for Usona and MAPS than we do on those for Action for Happiness.

- In addition, improving mental health is not the main focus of Action for Happiness' programme: it is aimed at improving subjective well-being foremost and has evidence supporting its effectiveness at doing that.¹⁵⁷
- However, the indirect positive effects of Usona's and MAPS's drug development are plausibly (much) larger than those of Action for Happiness's courses. We are very uncertain about whether this holds and to what extent, but it's important enough for us to conclude that Usona's and MAPS's Capstone Campaign programmes should be recommended on par with Action for Happiness's programme, and by extension¹⁵⁸ with StrongMinds' programme.
- The judgment that MAPS's European drug development programme is less cost-effective is driven partly by our cost-effectiveness models, which estimates expected cost-effectiveness of 191 disability-adjusted life years (DALYs) per million dollars for the European programme compared to 738 for the Capstone Campaign. Additionally, we expect the wider benefits of MAPS's European drug development programme to be smaller than those of the Capstone Campaign as approval will come later in Europe and the first major approval will likely have the greatest wider benefits. Therefore, we think that the European programme presents a good philanthropic funding opportunity for some donors but we would recommend it only in certain circumstances.

5. Limitations

This research project has multiple caveats and limitations. The following are the most important ones for our readers to be aware of:

- There is an important difference between evaluating funding opportunities and nonprofits. Our research conclusions do not represent a judgement of whether a particular nonprofit does more important work than another. They only reflect our view of which funding opportunities at nonprofits could currently use extra funds most effectively.
- This is only the second time we have used a Bayesian approach in our analysis, and we know there are still many limitations to our method, which we aim to keep improving with each new iteration.
- Our cost-effectiveness estimates have very wide 90% confidence intervals. Moreover, these confidence intervals do not capture all uncertainty: we have had to make many assumptions and judgements in the process of the analysis which we deem plausible though uncertain, including the choice of model. The cost-effectiveness estimates and confidence intervals should hence not be taken literally, and our conclusions should be taken as very uncertain.
- At each level of prioritisation throughout this project (cause, intervention, and funding opportunity) we have had to rely on heuristics and non-decisive argumentation to make decisions. This is essential for us to use our research time in the most effective way possible, but means that our conclusions carry extra

uncertainty. It could for instance be the case that there are high-impact opportunities in this area that we did not identify.

Appendix

Bayesian analysis

We used Bayesian inference to estimate the effect sizes of psilocybin as a treatment for major depressive disorder and of MDMA-assisted psychotherapy for PTSD. This enabled us to take all relevant information into account, without relying too heavily on only one or a few studies.

Within the Bayesian paradigm, we treat degrees of belief as probabilities, which obey the laws of probability. In Bayesian inference, we have a model, which depends on parameters, at least some of which we are uncertain about. In this case, we aim to predict the effect of psychedelic-assisted treatments on future patients. The effect on a future patient is given by the effect size plus random noise, which we treat as a random variable, with unknown mean. The effect on a future patient x is a random variable that depends on the parameter μ . We write $x \sim p(x|\mu, \sigma)$ to mean that x has a probability density given by $p(x|\mu, \sigma)$, which depends on given values of μ and σ .

The aim of Bayesian inference is to estimate the parameters μ and σ , though in this case, we assumed that σ was known. We begin with a prior for μ , which is a probability distribution $p(\mu)$. Given new data D , we revise our prior $p(\mu)$ to a posterior probability distribution $p(\mu|D)$ using Bayes' Theorem:

$$p(\mu|D) = \frac{p(D|\mu)p(\mu)}{p(D)} \propto p(D|\mu)p(\mu)$$

The term $p(D|\mu)$ is called the likelihood, which gives the probability of observing the data D , given the value of μ . Note that D is fixed and that μ is the variable here, so the likelihood need not be a probability distribution.

The posterior probability distribution for μ can be used to predict the effect on a future participant \tilde{x} :

$$p(\tilde{x}|D) = \int p(\tilde{x}|\mu)p(\mu|D) d\mu$$

This distribution is known as the posterior predictive distribution.

Below we describe our full Bayesian inference process, including a way to incorporate imperfect evidence. This is only the second time we have used Bayesian inference in our research, and we recognise our method still has many flaws and approximations that could be improved upon. We plan to make these improvements with each iteration of using it, in order of practical relevance. For example, in this second iteration, we have improved, among other things, the method for choosing our priors, the accuracy of our discounting process and the presentation of our calculations. The main advantages of the Bayesian approach over the non-Bayesian one are that the former takes into account more information and constitutes a more transparent way of doing the analysis..

Prior selection

We chose priors $p(\mu)$ for the mean reduction of depression and PTSD, informed by reference class comparison. Choosing priors is often subjective and difficult. Our choices are based primarily on intuitive judgements based on the track record of several

comparable interventions, e.g. drugs that went through the FDA approval process which had similar promise at the time. Four researchers and three external reviewers with relevant expertise used a process outlined below to provide prior estimates. Each researcher tried to carry out this process as independently as possible to avoid biasing each other, but complete independence was impossible given time and resource constraints in gathering all the information required to make a good judgment.

Each individual provided a median estimate of the effect size, as well as 50%, 80%, 90%, 98% and 99.8% confidence intervals, as far as possible ignoring information contained in the studies we used as Bayesian evidence (as this was accounted for formally in the Bayesian inference). We did this for psilocybin as a treatment for depression and MDMA-assisted psychotherapy for PTSD separately. We then took the median across all individuals for each input to generate a median and confidence intervals of our aggregate prior (i.e. the lower bound of the 50% confidence interval of our prior was the median of all the lower bounds of the 50% confidence intervals etc.).

This provided 11 points on the cumulative distribution function of our prior (2 per confidence interval, and the median). The cumulative distribution function is the function $F(x) = P(\mu \leq x)$, which is an increasing function with minimum value 0 and maximum value 1. We then converted these prior inputs into a full distribution by splining an increasing cubic equation between each point on the cumulative distribution function, as well as fixing $F(-4) = 0$ and $F(4) = 1$ (i.e. enforcing that the effect sizes must be between -4 and 4). The prior probability density can be derived from the cumulative distribution function. The full prior probability distributions were computed in R.¹⁵⁹

Undiscounted updating

Each of the studies is represented by data D . We assumed that the data is normally distributed around the true effect size, with mean μ and standard deviation σ . The normality assumption is partially justified by the Central Limit Theorem. We acknowledge that the relatively small sample sizes (19–51) introduce some error, but we don't expect this to significantly affect our analysis outcomes.

The normality assumption determines that the likelihood $p(D|\mu)$, as a function of μ , is a normal distribution with mean D and standard deviation σ_1 .¹⁶⁰ In each case, the mean D is taken as the standardised (Cohen's d) reduction in HAM-D score and the standard deviation σ_1 is the corresponding standard error. The table below contains the parameters of the likelihood for each study:

Study	D	σ_1
Griffiths et al. 2016	1.30	0.38
Carhart-Harris et al. 2018	1.01	0.33
Mithoefer et al. 2018 (75 mg)	2.8	0.81
Mithoefer et al. 2018 (125 mg)	1.1	0.5
Ot'alora et al. 2018 (100 mg)	0.37	0.51
Ot'alora et al. 2018 (125 mg)	0.42	0.51

We then computed the Bayesian update on the prior in R. The results of our Bayesian analysis can be found in the 'Bayesian effect size' sheets of our cost-effectiveness models.

Note that μ is the mean effect we predict on future participants (i.e. the effect size) so the posterior for μ gives our probability distribution for the effect size. The posterior predictive gives our probability distribution for the effect on a single future participant, which is less certain than the mean effect.

Discounting for limitations

The formal Bayesian inference process above treats the evidence as certainly correct but in practice, reported study results rarely reflect reality perfectly. In the case of these particular studies, the results were limited in several ways. As explained in the main report, we think that there are possibilities of bias, meaning that the true effect size of psychedelic-assisted treatments might have been lower than the reported effect sizes. Hence, rather than updating fully to the posterior, we accounted for the uncertainty of the evidence, as follows:

- Due to additional uncertainty about the study results, we increased the variances of the likelihoods, which resulted in weaker updates (i.e. weighting the prior more heavily relative to the likelihood than we otherwise would)
- For each study, we estimated how much we ought to discount between 0 (not at all) and 1 (completely discount)
- A discount of $\delta = 0$ would result in taking the study at face value, i.e. leaving the mean and variance of the likelihood unchanged

- A discount of $\delta = 1$ would result in completely disregarding the study and sticking with our prior, i.e. increasing the variance of the likelihood to infinity
- A discount of $\delta = 0.5$ would result in discounting the study such that the discounted posterior mean is half-way between the prior mean and the undiscounted posterior mean; we would do this by leaving the mean of the likelihood unchanged but increasing the variance until this is the case
- Four researchers provided discounts for each study and we took the median of these values for each study separately
- This process resulted in discounts of
 - = 0.71 for Griffiths et al. 2016
 - = 0.81 for Carhart-Harris et al. 2018
 - = 0.74 for Mithoefer et al. 2018
 - = 0.68 for Ot'abora et al. 2018

This means, for example, that our discounted posterior mean after updating on only Griffiths et al. 2016 was 29% of the way from our prior to the undiscounted posterior mean.

Combining updates

To arrive at a posterior mean that incorporates all the evidence present, we need to subsequently update on one study and then update the resulting posterior on the other.

For undiscounted Bayesian updating, the order in which we do that does not matter.

However, for discounted updating using Jeffrey's Rule the order can make a difference, as

this method is an approximation of ideal Bayesian updating that takes study limitations into account. In this case, the order of updating made a negligible difference.

This resulted in the following final posterior mean:

Treatment	Discounted posterior mean, given effect size larger than 0.3
Psilocybin treatment	0.68
MDMA-assisted psychotherapy	0.72

Destandardising

We needed the effect size as a reduction on the HAM-D scale for depression and CAPS-IV scale for PTSD as the input for our cost-effectiveness models. Since our posterior mean was standardised (i.e. tells us the effect size as a proportion of the standard deviation), we multiplied it by the pooled pre-intervention HAM-D standard deviation for psilocybin and the pooled pre-intervention CAPS-IV standard deviation for PTSD to arrive at our destandardised effect size estimates:

Reduction in HAM-D score	Reduction in CAPS-IV score
2.19	8.92

Non-Bayesian effect size estimate

We have effect sizes reported by meta-analyses but even these very likely overstate the true effect sizes at scale. Goldberg et al. 2020 reports a controlled effect size of 0.83 for psilocybin for depression (excluding Carhart-Harris et al. as it has no control) and Mithoefer et al. 2019 reports an effect size of 0.8 for MDMA-assisted psychotherapy for PTSD.

We estimate the effect size by estimating the following probabilities, where S is the actual effect size and d is the effect size reported in the meta-analysis:

- $p(0 \leq S \leq d/4)$
- $p(d/4 \leq S \leq d/2)$
- $p(d/2 \leq S \leq 3d/4)$
- $p(3d/4 \leq S \leq d)$

Given these estimates, we compute an approximation for the rest of the distribution by interpolating an increasing cubic equation between these points in the cumulative distribution function, as we did for our Bayesian prior. This was also computed in R.¹⁶¹ For simplicity, we assumed that the effect size is certainly between 0 and the reported effect size, though we do not think our results depend on this assumption.

Four researchers provided estimates for each of these probabilities and we took the median for each probability. The inputs and the results of this analysis are in the 'Non-Bayesian effect size' sheets of our cost-effectiveness models.

Endnotes

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20. "Then, in 1943, Hofmann synthesises a new batch of LSD, accidentally absorbs some crystals The History of Psychedelics in Medicine 3 and has the world's first LSD experience. A few days later he conducts a personal experiment. Monitored by colleagues he intentionally ingests 250 micrograms and famously cycles back to his house from the laboratory. LSD is investigated with phase one studies that demonstrate its low toxicity and safety for human consumption." Sessa.
21. "In the 1960s, psychiatry embraces LSD for a wide range of problems, including the "neuroses" (anxiety disorders), depression, social anxiety in autism and pain relief – as well as some dubious diagnoses including female frigidity and homosexuality." Sessa.
22. Matthew W. Johnson et al., 'Classic Psychedelics: An Integrative Review of Epidemiology, Therapeutics, Mystical Experience, and Brain Network Function', *Pharmacology & Therapeutics* 197 (2019): 83–102, <https://doi.org/10.1016/j.pharmthera.2018.11.010>.
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24. "Not a "classical" psychedelic, but rather an "entactogen" (a term coined by Nichols), MDMA produces a gentler, more euphoric state than LSD. It seems the perfect drug for post-trauma psychotherapy; shorter-acting and therefore more clinically manageable, MDMA increases feelings of empathy and bonding, as well as relieving depression and allowing users to access and process memories of emotional trauma." Sessa, 'The History of Psychedelics in Medicine'.
25. "And in 1912, the German pharmaceutical company Merck synthesises and patents 3,4 Methylenedioxymethamphetamine (MDMA), which is then shelved until the mid fifties ... Shulgin calls MDMA his "low-cal Martini" and together with chemist, David E. Nichols, publishes the first report into the psychoactivity of MDMA in humans." Sessa.
26. "[T]hroughout the 1970s and into the 1980s [Mylon Stolaroff] continues providing psychedelic therapy with unscheduled compounds; describing hundreds of sessions with MDMA and other newly emerging experimental drugs ... Psychotherapists in the early 1980s using MDMA, which was initially called "Empathy," are keen to keep it within the clinical community. But MDMA's growing popularity is impossible to hide. Rebranded as the more marketable "Ecstasy," MDMA spreads. ... In 1984, the DEA announces that it intends to make MDMA a Schedule One drug. ... Psychiatrist Rick Ingrasci,

having conducted 150 MDMA sessions with 100 patients with overwhelmingly positive results, testifies in favour of continued MDMA research. Nevertheless, in May 1985 the DEA places MDMA in an emergency Schedule One category for a one-year period pending further investigations, prompting Doblin to form The Multidisciplinary Association for Psychedelic Studies, MAPS.” Sessa.

27. “Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse. Some examples of Schedule I drugs are: heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote” ‘Drug Scheduling’, accessed 17 March 2020, <https://www.dea.gov/drug-scheduling>.

28. “In December 1990, Strassman starts his DMT pilot study on healthy volunteers to establish intravenous dosage, safety parameters and physiological measures. The project re-launches psychedelic medical research with humans, demonstrating that regulatory authorities can be persuaded to consider psychedelics again.” Sessa, ‘The History of Psychedelics in Medicine’.

29. “But now rave parties have emerged from their niche beginnings into massive large-scale events, and several high profile deaths of young people prompt crackdowns. In 1992, The History of Psychedelics in Medicine 11 Professor of Child and Adolescent Psychiatry at UCLA, Charles Grob, submits a proposal to use MDMA-assisted psychotherapy on patients with anxiety secondary to end-stage cancer and begins a physiological Phase One study. But efforts to obtain approval for the clinical study are rejected twice by the FDA, leading Grob to use psilocybin instead of MDMA.” Sessa, ‘The History of Psychedelics in Medicine’.

30. “With support from both, the Heffter Research Institute and MAPS, Delgado and Moreno plan a human clinical study with psilocybin for OCD. ... In 2006, Moreno and Delgado publish their psilocybin OCD study, showing the drug is well tolerated and causes impressive reductions in obsessive-compulsive symptoms. ... [In 2006], a team at Johns Hopkins University, lead by Roland Griffiths, veteran psychedelic researcher William Richards and Jesse Roberts of the Council of Spiritual Practice, describes its exploration of psilocybin as mystical agent.” Sessa.

31. “In Spain, in 2000, Dr. Jose Carlos Bouso gets approval for a MAPS-sponsored study looking at MDMA for PTSD. But after 1 year, having dosed just 6 of the planned 29 patients, a political backlash by the Spanish government shuts down the study.” Sessa.

32. “As we progress through 2016, the studies, conferences and articles continue to roll in faster than they can be summarised” Sessa.

33. R. L. Carhart-Harris, M. Bolstridge, C. M. J. Day, et al., ‘Psilocybin with Psychological Support for Treatment-Resistant Depression: Six-Month Follow-Up’, *Psychopharmacology* 235, no. 2 (2018): 399–408, <https://doi.org/10.1007/s00213-017-4771-x>.

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42. Bridget Huber, 'What Do We Know about the Risks of Psychedelics? « Michael Pollan', accessed 28 January 2020, <https://michaelpollan.com/psychedelics-risk-today/>.
43. 'Drugs Without the Hot Air by David Nutt | Waterstones', accessed 28 January 2020, <https://www.waterstones.com/book/drugs-without-the-hot-air/david-nutt/9781906860165>.
44. "In our research, individuals are excluded who have a current or past history of meeting DSM-IV criteria for schizophrenia or other psychotic disorders (unless substance-induced or due to a medical condition), or bipolar I or II disorder, which are the most important conditions to exclude for ensuring safety. We also exclude those with a first or second-degree relative with these disorders. ... In a survey of investigators who had administered LSD or mescaline, Sidney Cohen (1960) reported that only a single case of a psychotic reaction lasting more than 48 hours occurred in 1200 experimental (non-patient) research participants (a rate of 0.8 per 1000). Notably, the individual was an identical twin of a schizophrenic patient and thus would have been excluded under the proposed guidelines. Prolonged reactions over 48 hours were slightly more frequent in patients undergoing psychotherapy than in experimental non-patient participants, but still relatively rare, occurring at a rate of 1.8 prolonged reactions per 1000 patients." Matthew W. Johnson, William A. Richards, and Roland R. Griffiths, 'Human Hallucinogen Research: Guidelines for Safety', *Journal of Psychopharmacology (Oxford, England)* 22, no. 6 (August 2008): 603–20, <https://doi.org/10.1177/0269881108093587>.
45. "The neurotoxic potential of mephedrone appears to be low, whereas MDMA can cause long-term damage to the serotonergic system, although this needs further investigation." Jessica Paige Mead and Andrew Charles Parrott, 'Mephedrone and MDMA: A Comparative Review', *Brain Research*, 19 February 2020, 146740, <https://doi.org/10.1016/j.brainres.2020.146740>.
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Exposure to Other Drugs', *Addiction (Abingdon, England)* 106, no. 4 (April 2011): 777–86, <https://doi.org/10.1111/j.1360-0443.2010.03252.x>.

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48. "At 2 months, the volunteers rated the psilocybin experience as having substantial personal meaning and spiritual significance and attributed to the experience sustained positive changes in attitudes and behavior consistent with changes rated by community observers." R. R. Griffiths et al., 'Psilocybin Can Occasion Mystical-Type Experiences Having Substantial and Sustained Personal Meaning and Spiritual Significance', *Psychopharmacology* 187, no. 3 (August 2006): 268–83; discussion 284–292, <https://doi.org/10.1007/s00213-006-0457-5>.

49. "Psilocybin can occasion enduring trait-level increases in prosocial attitudes/behaviors and in healthy psychological functioning." Roland R. Griffiths et al., 'Psilocybin-Occasioned Mystical-Type Experience in Combination with Meditation and Other Spiritual Practices Produces Enduring Positive Changes in Psychological Functioning and in Trait Measures of Prosocial Attitudes and Behaviors', *Journal of Psychopharmacology (Oxford, England)* 32, no. 1 (2018): 49–69, <https://doi.org/10.1177/0269881117731279>.

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122. 'COMPASS - Navigating Mental Health Pathways', accessed 4 February 2020, <https://compasspathways.com/>.
123. 'Multidisciplinary Association for Psychedelic Studies - MAPS', accessed 4 February 2020, <https://maps.org/>.
124. 'Usona Institute', accessed 4 February 2020, <https://www.usonainstitute.org/>.
125. 'Research | Founders Pledge'.
126. <https://www.getguesstimate.com/> is a user-friendly and transparent online tool for creating probabilistic models. This allows for more accurate estimates than simple point estimates calculated in Google Sheets and allows us to calculate a 90% confidence interval. We have previously estimated the cost-effectiveness of funding opportunities in Google Sheets, so we included a Google Sheets estimate here to allow for comparisons with our previous analyses.
127. Communication with Usona, 4 November 2019
128. James Snowden, John Halstead, and Sjr Hoeijmakers, 'Mental Health Cause Area Report', *Mental Health*, n.d., 34.
129. Goth and Hoeijmakers, 'Charity Recommendation Report: Action for Happiness'.
130. 'Usona Institute | About', accessed 5 February 2020, <https://www.usonainstitute.org/about/#about>.

131. Communication with Usona, June 2020.
132. Communication with Usona, June 2020.
133. 'Usona Team', accessed 24 July 2020, <https://www.usonainstitute.org/usona-team/>.
134. <https://www.getguesstimate.com/> is a user-friendly and transparent online tool for creating probabilistic models. This allows for more accurate estimates than simple point estimates calculated in Google Sheets and allows us to calculate a 90% confidence interval. We have previously estimated the cost-effectiveness of funding opportunities in Google Sheets, so we included a Google Sheets estimate here to allow for comparisons with our previous analyses.
135. [US, Canada & Israel Guesstimate model](#); [Europe Guesstimate model](#).
136. James Snowden, John Halstead, and Sjr Hoeijmakers, 'Mental Health Cause Area Report', *Mental Health*, n.d., 34.
137. Goth and Hoeijmakers, 'Charity Recommendation Report: Action for Happiness'.
138. For sources, see the [Europe PTSD prevalence estimate sheet](#) of our cost-effectiveness model.
139. 'About - MAPS', accessed 4 February 2020, <https://maps.org/about>.
140. Conversation with MAPS, 24 June 2019.
141. 'FDA Grants Breakthrough Therapy Designation for MDMA-Assisted Psychotherapy for PTSD, Agrees on Special Protocol Assessment for Phase 3 Trials', MAPS, accessed 4 August 2020, <https://maps.org/news/media/6786-press-release-fda-grants-breakthrough-therapy-designation-for-mdma-assisted-psychotherapy-for-ptsd,-agrees-on-special-protocol-assessment-for-phase-3-trials>.
142. Communication with MAPS, 15 September 2020.
143. Communication with MAPS, 8 August 2020.
144. We could have instead evaluated the broader funding opportunity of raising all the funding required to reach roll-out in Europe, or somewhere in between. Our conclusions are not sensitive to how we define the funding opportunity.
145. Goth and Hoeijmakers, 'Charity Recommendation Report: Action for Happiness'.
146. Snowden, Halstead, and Hoeijmakers, 'Mental Health Cause Area Report'.
147. Ritchie and Roser, 'Mental Health'. <https://ourworldindata.org/mental-health>
148. Major depressive disorder is not the only depressive disorder, so the upper bound is probably a little higher. Realistically, the size of the benefits will be much lower than this anyway, so this does not matter very much.
149. Ritchie and Roser, 'Mental Health'. <https://ourworldindata.org/mental-health>
150. Private correspondence with MAPS (June 5 2020)
151. Private correspondence with MAPS (June 5 2020)

152. Private correspondence with MAPS (October 11 2019)
153. Ritchie and Roser, 'Mental Health'. <https://ourworldindata.org/mental-health>
154. Goth and Hoeijmakers, 'Charity Recommendation Report: Action for Happiness'.
155. Snowden, Halstead, and Hoeijmakers, 'Mental Health Cause Area Report'.
156. Note that this is a different consideration from the uncertainty we have incorporated *within* the model, which is reflected in the 90% confidence intervals for our estimates.
157. Goth and Hoeijmakers, 'Charity Recommendation Report: Action for Happiness'.
158. We recommend Action for Happiness's programme based on a direct comparison with StrongMinds' programme.
159. Code can be found [here](#).
160. Note that in this case, our likelihood is conveniently a probability distribution as a function of μ , due to the symmetry in the normal probability density function with respect to μ and D .
161. Code can be found [here](#).