Olivia Goldhill:
A lot of these drugs were invented - LSD in 1930s, 1938 Psilocybin exists in nature, and magic mushrooms has actually been used for thousands of years, particularly by indigenous communities. MDMA was synthesized in the 1950s. So, they've existed for a while and then they were outlawed in the U.S. in 1971 by President Nixon. These drugs were declared Schedule 1, meaning of no medical use. There was really a prohibition on research for a long time, and then they very, very slowly started up again and gradually the results from those studies were really pretty exciting, suggesting that various psychedelics looked like they were promising treatments for a host of different mental health conditions.

LuAnn Heinen:
That's Olivia Goldhill, an investigative reporter covering the health industry, including biotech, pharma, and inescapably the global pandemic for STAT, a media company, focused on finding and telling compelling stories about health, medicine, and scientific discovery. Before joining STAT, Olivia was a science reporter at Quartz and a features writer at *The Daily Telegraph* in London. She was an Aspen idea scholar in 2017.

I'm LuAnn Heinen and this is the Business Group on Health podcast, conversations with experts on the most important health and well-being issues facing employers.

My guest is Olivia Goldhill, and we'll talk about the race to legalize psychedelics as mental health drugs, which products, why now, and what it could mean for patients and payers. Olivia, welcome to the podcast.

Olivia Goldhill:
Hi, thanks so much for having me.

LuAnn Heinen:
I'm really looking forward to this. We're going to talk about psychedelics, something you've written about extensively. We're interested because approval of some of these compounds as legitimate drug therapies is being seriously considered by the FDA. Let's start with, what are psychedelics?

Olivia Goldhill:
Yes, so very broadly speaking, these are drugs that create altered states of consciousness, changes in your senses and emotions, thinking, and your experience of time. They are known in a general non-medical culture as recreational, sometimes spiritual drugs. MDMA, LSD, magic mushrooms, are all psychedelics and these are all the drugs that are also being studied now in clinical trials. For magic mushrooms, psilocybin is the main compound. The psychedelic compound there is in pretty advanced clinical trials. MDMA has already had the results from one Phase 3, which is the most advanced clinical trial. LSD recently also got approval for a Phase 2B, which there's still more studies to do beyond that, but it’s pretty sizeable. These same kind of psychedelic recreational drugs are now being studied from a clinical perspective.

LuAnn Heinen:
Would any of these drugs be dispensed without counseling and supervision on site?

Olivia Goldhill:
At the moment, it is still being worked out. Most of the clinical trials will look at these drugs in conjunction with therapists. There would be a medical team that would evaluate you before you have the psychedelics, but you would work with the therapist beforehand, during, and afterwards. There are people looking at, ideally in the future, could these drugs be accessible just in a standard doctor's office in the middle of some huge states. Like Texas, it might be hard to get a therapist to go everywhere and what kind of potential monitoring would there need to be in place to make that safe, both professional and potentially some kind of software. But, at the moment, yes, for the most part there are therapist oversight and definitely medical oversight, as well.

LuAnn Heinen:
Startups and funds focused on turning psychedelic compounds into approved medicines have raised, as I understand it, hundreds of millions of dollars. I even saw one estimate, it was a $2 billion forecast for 2021. Is that in the ballpark?

Olivia Goldhill:
Definitely. The psychedelic medicine market is expected to be valued at, I think, $7 billion by 2027. That's according to one set of analysis from Data Bridge Market Research. But there are four companies that have evaluation of a billion dollars each. A year ago the total market cap was probably around a billion dollars. The fact that there are now four separate companies worth that much, gives you a sense of how quickly it is growing.

LuAnn Heinen:
It's amazing. It's really amazing. Those are staggering numbers. Especially when the narrative arc for this category of drug is pretty stunning. When you think about these compounds were invented back in the early part of the 20th Century, I think, and they've been on quite a journey since then. Would you like to recap some of that for us?

Olivia Goldhill:
Yes. A lot of these drugs were invented, LSD in 1930s, 1938 Psilocybin exists in nature, and magic mushrooms has actually been used for thousands of years, particularly by indigenous communities. MDMA was synthesized in the 1950s. So, they've existed for a while and then they were outlawed in the U.S. in 1971 by President Nixon. As part of that ruling, was part of the war on drugs and criminalization of a lot of drugs, but he stated as part of that legal classification, these drugs were declared Schedule 1, meaning of no medical use. Because of that, it was incredibly hard for researchers to study the drugs. If they have been blanketed as medically useless, why study them. So, there was really a prohibition on research for a long time, a couple of decades I think, with no studies whatsoever in the U.S. Then they very, very slowly started up again in the late 1990s, starting to get very small studies in the early 2000s and gradually the results from those studies were really pretty exciting, suggesting that various psychedelics looked like they were promising treatments for a host of different mental health conditions. More and more trials have been done slowly getting larger. 2016 was starting to see larger Phase 1 studies that then became the groundwork for these clinical trials, with for-profit companies seeing the potential to invest and bring drugs to market, as well as non-profits that are interested. So MDMA already has one Phase 3 trial, and will likely have the results from another within a year or so, and two Phase 3 trials, plus some of the background studies could be grounds for approval and Psilocybin is a couple of years after that.

The FDA has given these drugs, these treatments, called breakthrough therapy designation, which just means it will get something of a fast track through the drug approval process and is a sign that the FDA is really open to these treatments. The one psychedelic that has been approved, S-ketamine from Johnson and Johnson, is a version of ketamine or a modified version of ketamine. The FDA is open to it. The clinical trials are advancing pretty quickly. You can never say for certain, of course you have to see what the studies show and what the results are, but it looks increasingly likely that more and more of these psychedelic drugs will be approved in the coming year.

LuAnn Heinen:
Let's just go back and revisit some of the turning points in that story that you outlined. I mean, there were the early days of kind of consciousness raising in the 60s, 70s. There was this sort of party drug use that came a little bit late later, and then these really fell out of favor. Criminalization, stigmatization, researchers couldn't even research them, couldn't even mention it. To now, Johns Hopkins University was one of the first to really, I think, get grants and come out with positive studies on some of these classes of drugs and now Harvard and other major universities, NIH is behind it, FDA is seriously looking at it. There's been a polarizing debate over psychedelics. How do you explain that?

Olivia Goldhill:
I guess I'll give you two responses. The first is, I think it's pretty incredible that these drugs represent the first new medical breakthrough in mental health treatment and depression treatment for more than three decades. A lot of people don't realize that ever since Prozac was invented, other anti-depressants or variations on that and psychedelics represent an entirely new way of treating mental health that is potentially hugely effective and could make a massive difference for a large number of people. If you look at the range of conditions being studied, depression, post-traumatic stress disorder, anxiety disorder, if the results continue to be as strong as they are, these drugs could really help a lot of people and be major breakthroughs. The other thing I wish people understood is nothing in medicine, psychedelics included, is black and white. These drugs were demonized for so long and declared medically useless, so that they couldn't even be studied and were seen as incredibly dangerous.

I just think that's not productive. Very clearly if you're just looking at the studies being developed, some of these drugs definitely do have medical potential, but then the flip side of that is there can also be people who think psychedelics are going to cure everyone, and they're absolutely amazing, and everyone should be doing them all the time. That's actually also really dangerous and therapists talk about some patients having a disappointment reaction. If you think about who's going into clinical trials, for example, for treatment resistant depression, they're people with really long-term chronic, mental health conditions who haven't had relief from elsewhere, and they really pushed to be in these clinical trials, and they think that one session is going to absolutely change everything. That kind of level of expectation can be quite difficult to meet and I just think with all drugs, you have to be careful, you have to evaluate, you have to look at the individual and the context and how they're being used and the therapist helping them, and with everything there has to be a level of nuance. I wish people were open to that and neither absolutely for, or absolutely against, psychedelics.

LuAnn Heinen:
Let's talk about how just that groundswell and the role that advocates played, the role that investors played, or was it really just about the scientific evidence?

Olivia Goldhill:
The science definitely came first. A lot of those early trials were supported and funded by non-profit organizations, MAPS, Heffter Institute, Usona Institute and are the three main ones. MAPS is decades old. They have been operating and advocating for more research for long, long periods where it looked like it wasn't goings to happen. So, definitely there was advocacy behind funding the research and studying psychedelics is pretty extensive just because they are Schedule 1 drugs. It means you have to use highly specialized labs to create them in very, very pure standards. It's called GMP, good manufacturing practices standards. For some of these trials, I think it would cost around $7,000 a gram to produce the level of highly specialized Psilocybin, which is not what it would cost should these drugs be approved, but is an indication of the expense. So, definitely non-profits behind them, but Johns Hopkins and Imperial College in London and probably NYU, as well, were some of the first universities. Starting around 2010, maybe 2013 or 2016, that's when studies started to get bigger, you'd maybe have quite prestigious professors at these universities looking into them.

The first for-profit company, COMPASS Pathways, they launched in, I can't remember if it was 2017, 2018, but they were the first for quite a while. Really, it's only in the past year or so that more and more companies have got involved, have got investment. It used to be quite difficult. Peter Theil was an early investor in COMPASS Pathways. There have been big names who have been involved for a while, but I think stigma used to be a major challenge for people when they were fundraising, and that's much less the case now, you know, the stigma is fading. I will say, Michael Pollan's book, *How to change Your Mind*, was a huge success, and I think that was a turning point in how popular culture saw psychedelics and potential for these drugs. I think that was probably a turning point in cultural acceptance.

LuAnn Heinen:
That book came out in 2018 was a *New York Times* Number 1 best seller.

Olivia Goldhill:
Yes, hugely popular.

LuAnn Heinen:
In addition, let's not forget the role that veterans have played as advocates in the drive to legalize psychedelics, particularly for benefits easing post-traumatic stress, anxiety experiences, tied to their military service.

Olivia Goldhill:
Absolutely. The most advanced trials and psychedelics at the moment is MDMA as treatment for post-traumatic stress disorder. Veterans suffer terribly from post-traumatic stress disorder and it has massive impact and there's a large amount of interest from veterans in these potential treatments. Currently in the U.S., there is even compassionate use for MDMA, meaning that if you have PTSD and other treatments don't work, you could be allowed to have excess MDMA treatment. I think Israel is another one of the countries at the forefront of this research, also where PTSD and MDMA, I believe it is legal there, and again I think, speaks to they have a large number of soldiers and veterans and the trauma experience by people there. There's definitely a strong link and veterans stand to benefit quite considerably to have this groundbreaking new treatment for post-traumatic stress disorder.

LuAnn Heinen:
Let's dive into the conditions that these therapies would benefit and also who would these drugs not be for. There are contraindications that are already known. We know first is post-traumatic stress disorder and you've mentioned treatment resistant depression, generalized anxiety disorder.

Olivia Goldhill:
Yes, MDMA for post-traumatic stress disorder, Psilocybin is being studied for both treatment depression disorder and Psilocybin also for major depressive disorder. So, both depression, it's just kind of a different way of determining who would be eligible and for treatment resistant disorder you have to have had tried other treatments and had them not be successful such as anti-depressants. LSD for generalized anxiety disorder, that's the Phase 2B trial that just got approval recently. Then there are smaller studies kind of looking at a whole collection of different mental health conditions, so anorexia, addiction, OCD, alcoholism. John Hopkins, one of the first universities to research this, in 2019 got a pretty major $17 million grant for a center devoted to psychedelics. A lot of the thinking behind some of their research is that this is a new mental health paradigm and potentially these drugs could be useful for a huge collection of different mental health related conditions. They're also looking into, and these are very early stage studies, but things like Alzheimer's disease and Lyme disease, but I think potentially these drugs could be useful for quite a range of different conditions.

LuAnn Heinen:
These are completely different from any type of drug currently used to treat mental health.

Olivia Goldhill:
Yes, very, very different. As we're saying that we don't understand the specifics even of how antidepressants work, mental health and the drugs used as treatment, they are something of a mystery. But yes, antidepressants, you take them over a considerable period. A lot of people might be on them for years or decades. Psychedelics are intended, you know, in clinical trials it's often three sessions, which would be weeks or months apart, but they're very fast acting and the sessions can take six hours. Psilocybin has an effect for that length of time and you're under supervision for that length of time, but immediately after it, you would start to feel the effects. So, they work very differently. It's often around, kind of, changing your perspective and rewriting personal narrative and they work in conjunction with therapies. So you would have a therapist with you often when you are taking the psychedelic and definitely afterwards to try and integrate some of the experiences. A lot of people refer to this as psychedelic-assisted therapy, rather than just the psychedelics working by themselves.

You did mention before and I forgot to answer about who is this not for. I think a lot of the research is very cautious about not enrolling people who have a first degree relative with psychosis, such as schizophrenia or people themselves with schizophrenia, or maybe being in a manic state, that's a population for whom there's a lot of caution around using these drugs. There can be contraindications around if you have very high blood pressure as well, or cardiovascular conditions, potentially even. We don't know if that's because of the drugs themselves or maybe just a sense of anxiety that can come on, depending on how the psychedelic experience goes. It's definitely not going to be for everyone. Also, I think a lot of people say, if you are in the middle of a very challenging experience, it could be difficult to have psychedelic treatment. It might be more something to wait until you're at a more stable place afterwards, and if you have symptoms then of post-traumatic stress disorder, to consider it. So, not for absolutely everyone, but these drugs are very safe in terms of physical side effects. There aren't very many contraindications, so there's a pretty wide population of people who could potentially be using them.

LuAnn Heinen:
So interesting though, just some of the differences that you called out. First of all, a huge attractor is this not quite one and done, but short-term therapy. It's not a chronic for everything, like so many current medications are. I mean, that's got great appeal, and then you're talking about like the length of time in therapy, one-on-one, or in the session, hours at a time. We don't really have a model for that, how that works must be a lot of training involved, and also it seems a greater unpredictability.

Olivia Goldhill:
I think that's really interesting, and I think that's something a lot of institutions are thinking about, and I really hope we'll continue to think about, because it's not just the drug and the impact of the drug on the person, but the impact of the therapist, too. How do you train them? How do you make sure it can be standardized? There's variations in quality, of course, there's also potential for misconduct, and how do you evaluate for that and prevent it from happening? I think the role of the therapist is absolutely crucial with the patient during the session, but then also what generally tends to happen is it's called integration work afterwards, so you'll meet with the therapist, discuss what you learn during the psychedelic experience and how to make sense of it, how to integrate it into your life. It is still very much up for debate how these therapists will be trained. There are training programs under development. They have to be a licensed mental health professional, for example. I know there are some institutions that are considering that the therapist could work in two-person teams where one would be licensed and the other wouldn't. Then there are some companies, COMPASS for example is considering, would you not need to have a therapist with you during the psychedelic experience? You would still afterwards for integration work, but during the experience, could you be monitored remotely and have a therapist nearby if needed or kind of someone monitoring your responses, but not necessarily sitting with you all the time. There is still a lot of questions, I think, around exactly how the therapist will work at scale, which I think is hugely important.

LuAnn Heinen:
I wanted to ask you about potential end-of-life applications. I've also read about people who have anxiety near the end-of-life and have had very positive experiences with psychedelic therapy. Are you familiar with that?

Olivia Goldhill:
Yes, some of the earliest research was looking at end-of-life anxiety and depression and psychedelics as a way to help people, I guess, with the trauma, let's say if you have terminal cancer, and if it's terminal, making the most of your end-of-life and kind of connections with people. There was also a right-to-try law that was passed under the Trump Administration that said if you're terminally ill, patients could try drugs that are currently in clinical trials, but are unproven. There was a lawsuit, because psychedelics were not included in that, to say that they absolutely should be, and that people who are terminally ill should be able to have access to these clinical drugs.

LuAnn Heinen:
Pivoting back to the employer perspective, what are some things that employers might need to encounter or face down the road? I mean, companies in their benefits planning programs and with their PBM, pharmacy benefit manager and health plan partners, may think about is this a category or an area of treatment where we should create a Centers of Excellence program? What kind of prior authorization or criteria up front, which are provided by FDA, but what are the things that they should be thinking about as this may come to pass?

Olivia Goldhill:
Yes, I think a good amount of it, I am expecting, hoping, will come from the FDA and from the rep just in terms of things like how the therapist should be trained. I think it is generally important that this is integrated in health care, generally. Maybe there would be discussions with physicians and with other therapists. A lot of people say you wouldn't necessarily go for this treatment without talking with your existing health care team, but generally speaking, this is the first new model of mental health treatment for 30 years, more than 30 years since Prozac was approved, all the other antidepressants are kind of variations of the same thing. I think if these drugs are approved and if the trials go well, it's potentially hugely helpful to a really large number of people and it's definitely worth considering how they can be offered to people and how insurance can cover it, as well.

LuAnn Heinen:
Which reminds me of something else I've read is that the individual of the patient mindset is really important, that there's some preparation even before you show up with the therapist in the session, either remotely or in person. Are you familiar with that concept of mindset and preparation?

Olivia Goldhill:
Yes, so this is kind of how the experience is very much part of, you know, talking with a therapist in general and depending on the patient needs. That's definitely the kind of thing that you would talk to therapist about ahead of time and there can be therapists especially trained and in tune to responding to different conditions. I think the setting of the room, as well, is very important. You want the patient to be able to choose the lighting and the music and the relaxation. It is, I think, generally a good thing for the patient to be feeling relaxed and calm and safe and comfortable before the experience starts, and that the therapist has an understanding of some of the issues to be talked about. I will say from having spoken to therapists, that for a lot of patients visits the psychedelic experience itself is not necessarily fun or pleasurable. It can be confronting or very upsetting memories. It can be a very difficult experience, but that is still beneficial, and that sometimes patients who have difficult psychedelic experiences will say it helped them the most, just to reconfront those old traumas. Yes, all of that work before and afterwards can help prepare a patient and then make sense of it.

LuAnn Heinen:
Interesting how a whole new informed consent is needed for this. What else haven't we spoken about, but should?

Olivia Goldhill:
One thing that's very interesting in this space, is typically when a company is developing a drug, they invest quite a lot into the clinical trials, and then when it's approved, they tend to have IP over it so that they set the price and have the monopoly on the market and bring in rewards for themselves and the investors. Psychedelics are really interesting and unusual, because as we talked about, psychedelics exist naturally, it was both synthesized nearly a century ago. MDMA was synthesized decades ago and LSD decades ago. So, all of these drugs are in the public domain, meaning there's not a straightforward patent you can do on them. There are very interesting attempts to patent the creation of drugs, like different methods of creating the drugs or even one company, COMPASS Pathways, they put in a patent placeholder application that kind of looked at patenting the particular environment where psychedelics took place, what the colors of the room was like, and the materials were like, which was seen as pretty controversial, who knows if that patent will actually be put in or approved.

LuAnn Heinen:
With a market of couple billion dollars, going up to projected $7 billion in a few years, it seems that investors must be fairly confident this strategy is going to yield fruit.

Olivia Goldhill:
There have been challenges as well, legal challenges, especially on Psilocybin. I think that remains to be seen, what gets approved there, what IP is available there. I think there's definitely the sense that there will be a market and companies will be able to offer those drugs, and that will be lucrative. Whether or not you'll be able to successfully patent some of the kind of oldest existing drugs, I think, is still being figured out. People talk about second generation, third generation psychedelics. Second generation, for example, we talked about how long Psilocybin is, like six hours, if you could modify it so that the effects were just one hour, that would be a lot more cost effective and easier to roll out. Those are some of the second generation drugs. And then third generation, entirely new molecules. There's definitely, I think, a sense that this space is going to keep growing, with a lot of room for investment and improvement, and in some of those later drugs, there's a lot more room for patents that are kind of more secure.

LuAnn Heinen:
Thank you so much, Olivia. It was fascinating to connect with you today. Really enjoyed the conversation.

Olivia Goldhill:
Yes, it was really great to talk with you. Thank you so much for all your questions.

LuAnn Heinen:
I've been speaking with Olivia Goldhill, investigative reporter at STAT and the author of *The Shroom Boom, The meteoric rise of the psychedelic medicine industry*, a report published in 2021, exploring the use of psychedelics as a medical therapy. You can learn more about her work@stat.com, https://www.oliviagoldhill.com/ and @OliviaGoldhill on Twitter.

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