# CHANGING MINDS: PSYCHEDELICS AS LEGITIMATE MEDICINE

**Stephanie A. Sirota**
Partner
Chief Business Officer

**Connor Williams**
Senior Research Analyst

## Changing minds: Psychedelics as legitimate medicine

**Stephanie Sirota:** Welcome to the RTW podcast. I'm your guest host, Stephanie Sirota, Partner and Chief Business Officer leading the Strategic Partnerships team at RTW Investments. Today, I'm speaking with Connor Williams, the Senior Research Analyst at RTW responsible for research in neurological disease. Connor, thanks for being with us today.

**Connor Williams:** Great to be here.

## The development of psychiatric drugs

**Stephanie Sirota:** The earliest written accounts of depression date back to Mesopotamia, when it was thought that depression was caused by demons.

Then the Ancient Greeks and Romans thought it was both biological and psychological, and they prescribed exercise, diet, baths, massage, music, and medication. Now, they might have been on to something, but as we know, holistic therapies are especially tough to ensure compliance from the patient.

So it's down to the efficacy of the drugs. Most people today think about depression emerging on the scene as a disease with the advent of breakthrough pharmaceuticals in the mid-20th century with the MAOI, monoamine oxidase inhibitors. Let me just test your history here. Tell us about that class of drugs.

**Connor Williams:** Yeah. What's actually really cool about any drug that affects the brain is that a lot of them were discovered by serendipity. So, the first antidepressant was actually being developed as a drug to treat tuberculosis.

And they found in the patients they gave it to that it had this surprising effect on mood. And that was the first monoamine oxidase inhibitor and that started this kind of snowball where the monoamine oxidase inhibitors led to tricyclics and then led to this class of drugs, SSRIs, which have been the mainstay of antidepressant therapy for decades.

**Stephanie Sirota:** Prozac was developed by Eli Lily, and it was the most prescribed antidepressant because it worked, and it had this relatively clean side effect profile. But then it feels like there has been a desert of innovation.

**Connor Williams:** Psychopharmacology is this constant series of booms and then busts. So you have the 1950s and '60s where you first start getting psychopharmacological medicines.

You had this explosion in all these different drugs over the ensuing decades, where we went from monoamine oxidase inhibitors to again tricyclics and then SSRIs.

There's Prozac, which is fluoxetine, and Celexa, which is citalopram. Then its successor drug, Lexapro. SSRIs, they ultimately all work the same way. They're selective serotonin reuptake inhibitors.

If you're a patient that either doesn't respond to an SSRI, which happens all the time—we have millions of people that are treatment resistant in the U.S. —or you're a patient that gets unacceptable adverse events on an SSRI, you're kind of out of luck. It became a situation where patients weren't getting any better as we made more and more drugs.

Payers and physicians kind of caught on. And they said, "You know, why am I going to prescribe this branded drug that works just the same way as this generic drug? Am I really going to jump through all these insurance hoops to get a drug that's the same?"

And the answer was, "No." And so, what was a blockbuster market, every drug was a multi-billion-dollar drug, you now have these last straggler drugs that exist, and they haven't even crossed a billion dollars.

As pharmas were more risk averse in psychiatry because they couldn't figure out anything else that worked, they exited the space. And so, you had this period of time where nothing was really being made until biotechs started stepping in to kind of pick up where pharma left off.

## Treatment resistant patients in the U.S. and the international market

**Stephanie Sirota:** When you say treatment-resistant patients, does your research extend to patient populations globally?

**Connor Williams:** If you fail two adequate lines of antidepressants, you're said to be treatment resistant.

Your odds of getting better once you're treatment resistant go down markedly. In the U.S., treatment-resistant depression is a defined term, and there are now different medtech approaches and new pharmacotherapies to treat that. Outside the U.S., it's often hard for new psychiatric drugs to get to market.

**Stephanie Sirota:** Because of the strict payment regimes?

**Connor Williams:** In Europe, governments would prefer to give patients cheaper generic drugs. You see all the time in psychiatry that drugs just don't get to market in Europe.

There is a drug called Nuplazid, which treats Parkinson's disease psychosis, and it's available in the U.S.

But it was never brought to Europe. And it sets up this strange scenario where the only other drugs we can use for Parkinson's disease psychosis are atypical antipsychotics. And atypical antipsychotics increase mortality by a significant margin.

So in Europe, these patients with no other option are being given antipsychotics because they're cheap, but it's not actually the best outcome for these patients.

**Stephanie Sirota:** Some of the medtech solutions like TMS and ECT— can you talk a little bit about those?

**Connor Williams:** You might think that it's infrequent that people don't respond to antidepressants. But it's actually quite common.

**"There are probably 2 million people in the U.S. with treatment-resistant depression."**

You can go to a psychiatrist and oftentimes they'll give you certain medical devices that treat your depression.

TMS, or transcranial magnetic stimulation, lets out a magnetic field, which then causes electrical stimulation in your brain. It's very analogous to an older technology called electroconvulsive therapy or ECT.

**Stephanie Sirota:** That sounds scary.

**Connor Williams:** It's what you think of in horror movies. You think of someone in a psychiatric ward electrocuting a patient and it making them functionally a zombie. Even though there's massive stigma around it, it's probably the most effective antidepressant therapy we have.

And there are so many stories out there of patients with treatment-resistant depression who will take a course of ECT, and their lives will be changed. Even if it wasn't underutilized, we have 2 million treatment-resistant patients in the U.S. We couldn't possibly be giving ECT to all of them.

## The need for new depression treatment drugs

**Stephanie Sirota:** Clearly, there is a need for new drugs. J&J's Spravato/esketamine drug came on the scene. It's a nasally administered drug. I think people are interested that it's ketamine or a form of it.

**Connor Williams:** So Spravato is actually esketamine. In the same way, Johnson & Johnson didn't develop ketamine, because that's a very old compound. It would have been very hard to get any exclusivity around it.

Instead, they developed an enantiomer that they say has better properties. It was one of the first drugs for treatment-resistant depression. Patients take this nasal spray in a clinic.

It is a way for giving relief to these patients that really had no other option.

**“That drug's just passed doing a billion dollars a year in sales. And it's probably on track to be a multi-billion-dollar blockbuster in interventional psychiatry.”**

**Stephanie Sirota:** Is Spravato a psychedelic drug?

**Connor Williams:** Ketamine mostly works as an NMDA antagonist so it's more of a dissociative anesthetic, even though people think of it as a psychedelic because of its psychotomimetic properties.

**Stephanie Sirota:** How have SSRIs and psychedelics historically been manufactured?

**Connor Williams:** They're found in nature all the time. You have peyote cactus that contains mescaline, obviously psilocybin is produced by magic mushrooms.

And you even have toads in the Sonoran desert that make 5-methoxy DMT and all sorts of naturally occurring psychedelic compounds that are out there.

In the 1960s, you had people like Timothy Leary advocating for them, studying them. Eventually, he got pushed out of Harvard as a consequence of his research, but then he became part of the counterculture. Now, of course, that had downstream consequences where these drugs became outlawed and that became really hard to study the effects of psychedelics. So you had this dark age in psychedelic research where there are very few studies between the 1970s and kind of the early '90s, because it was so hard to get around restrictive scheduling laws.

**Stephanie Sirota:** And you had a dark age of innovation after the end of the incrementally beneficial SSRI drugs.

**Connor Williams:** You have this perfect storm for no new psychiatric drugs and the compounds that maybe have promise, you're not allowed to study.

## The rise of psychedelics & the impact of regulations and policies

**Stephanie Sirota:** When did this whole sector go from something that was part of the counterculture movement to actually a legitimate class of drugs that was worthy of your attention?

**Connor Williams:** In psychiatry, people will show us open-label data and it can be hard to tell that it's real. But with psychedelics, the effect size was so enormous, it was very hard for people to ignore.

As the war on drugs started to die down, you had certain academic groups at NYU and in other places that started studying magic mushrooms also out of Imperial College London. And they'd find in these very early, often open-label studies that the effects on depression of particularly psilocybin, which was most studied at the time, were profound.

And they were very much outside the range of what you'd expect for a placebo. What really started the snowball began with drugs like Spravato, as well as another drug called Epidiolex. And these are both scheduled substances. In the case of Epidiolex, it's cannabidiol, and of course, for Spravato, it's ketamine. What Johnson & Johnson and GW Pharma proved is, if you do find a legitimate medical use for these drugs, they can be rescheduled and they can be sold.

And so, between a legitimate way to make scheduled drugs medicine, between increasing academic research, you started having these biotech companies founded.

Often, the initial ones were in Europe or listed in Canada, and they started trying to find ways to bring these potentially paradigm-shifting medicines to market.

**Stephanie Sirota:** How were some of these early companies and how were some of these early entrepreneurs funded?

**Connor Williams:** They often weren't even founded by biotech founders. So you ended up with this company and investor phenotype that's maybe very alien to us here.

You have these companies that they were developing psychedelics, but maybe they were arguing that it had to be administered with concomitant psychotherapy.

**“I remember a banker calling me, and he was almost laughing when he called me. And he said, ‘You know, this very strange European company, they're telling me that they're talking to you about this illegal compound. And I just couldn't imagine that you would ever take this thing seriously.’”**

**Stephanie Sirota:** And you said, "Yeah."

**Connor Williams:** Right. And I said, "Yeah, no, I'm actually taking a serious look, because the therapeutic effects were real." It's hard to deny when you see the early, particularly double-blind data that these aren't transformative for the practice of psychiatry in the future.

**Stephanie Sirota:** How has this affected the regulatory space?

**Connor Williams:** Initially one of the roadblocks to investment was, "Can we even reschedule these drugs once they have legitimate data? And can they be sold and distributed in the U.S.?"

The second question, particularly for psychedelics became, because of their cultural baggage, their profound mind-altering effects, how is someone going to get one of these drugs across the line?

The FDA is really leaning in, and they've even produced guidance documents for these biotechs to really help them design a development program that the FDA is going to be able to approve and get across the line.

The FDA took the same view that we had, which is, the FDA is there to regulate drugs. They're not there to regulate therapists.

**Stephanie Sirota:** What impact has the IRA's pill penalty had on psychedelics?

**Connor Williams:** Even before the IRA, in the U.S. we had this preferential treatment of biologics.

So, if you get any biologic approved in the U.S., you get what's called biologic exclusivity. And that lasts for 12 years. In the world of small molecules, you only really get seven-and-a-half years of a much weaker form of exclusivity.

In psychiatry we're stuck with small molecules. That's the only way we can get into the brain, but there are all sorts of laws that are drafted that favor modalities that can't help us.

And in the same way, the IRA has what's called the pill penalty, an idea that small molecules are given a shorter period before negotiation compared to biologics. And this basically is telling pharmas and biotechs that the government will reward you more for developing an advanced modality, which is fine.

But what that also says in a way is, "We're going to protect you less if you develop drugs for brain diseases where biologics can't really go as easy." In intellectual property law, you can patent a molecule you invent, but you can't patent one you find in nature. So oftentimes, a way to get around that is to patent the method of use of the molecule.

If we were developing a naturally found psychedelic that we found today, we might patent the method of using that molecule in treatment-resistant depression. But what made it even harder for psychedelics is a lot of these effects they have in psychiatric disease were already described in literature, so you couldn't file a patent. This made actually this first generation of psychedelic companies have an even harder time raising money from institutional biotech investors, because it was much harder for any investor to gain confidence that they'd be able to defend their innovation.

**“And if you're bringing a psychedelic to market, not only are you bringing a drug that comes with cultural baggage, that will change patients' lives, you'll also bring something to market that's going to change psychiatrists' lives. ”**

They're going to have to transform their whole practices to be able to work around this molecule that requires in some cases a psychotherapist. It requires you to logistically schedule the psychotherapist to come in with the doctor, with the patient, at the same time.

If you have to change the face of psychiatry, you better have a long exclusivity, because it could take a very long time for that drug to really make its return on investment.

## New areas of study in psychedelics

**Stephanie Sirota:** Well, if there are other indications that psychedelics can treat, then maybe that can extend some of this longevity. What other areas and what other studies are taking place?

**Connor Williams:** So, in psychiatry there's this great tradition of broadening drug labels.

There are antipsychotics like Abilify that are approved not only to treat schizophrenia but also bipolar disorder and Tourette disorder.

And they can be used as adjunct treatments for depression. So you start looking at psychedelics, there's promising data in addiction, so alcohol abuse disorder, generalized anxiety disorder, PTSD, and anorexia nervosa. You could end up with a class of drugs that really changes the face of many diseases, not just treatment-resistant depression.

## The valuation of psychedelics and what it means for investors

**Stephanie Sirota:** So for all the investors who are listening, walk me through the valuation of psychedelics. It had a big run-up— that coincided with the COVID biotech trade that really attracted a lot of money into the sector. And then the bubble burst for psychedelics in October of 2021.

**Connor Williams:** Psychedelics had a particularly bad year in 2021. You had Compass, which before data was a multi-billion-dollar company and after data, it just slowly slid over the ensuing years.

Compass is founded on a very simple idea, that you can take the active moiety in a magic mushroom, psilocybin, and use it to treat depression.

And they ended up picking up enough excitement that they ran a very large Phase 2b study.

Compass presented their Phase 2b data, and you saw the stock drop down very precipitously on that day. When we looked at the data, we saw a drug which had a 6.6 point MADRS delta.

It's much better than Spravato. But to generalists, this way missed their expectations. And similarly, in psychiatry all the time, you see increased rates of suicidality in clinical trials.

In fact, almost all antidepressants right now have a label for increased suicidality, a big black box warning at the top. And for COMP360, in that trial, they saw increased suicidality that was actually dose dependent. Almost all psychiatric drugs already cause some degree of suicidality. When we look at all historical natural history data of use of psilocybin, there is no other mention of suicidal ideation.

As far as we're concerned, COMP360 their version of psilocybin can still profoundly transform patients' lives and probably outdo Spravato.

**Stephanie Sirota:** What's happening in the private space? You know, we can talk about a company developing MDMA for PTSD. Maybe a good Silicon Valley-backed company called Lykos that you can maybe walk through.

**Connor Williams:** When the bubble burst, people saw this as a valuation reset, and people started to get involved in the space again. Around the same time, a company called Lykos was basically a spinout of an older charity called MAPS. And they were taking all of MAPS's research for MDMA, used to treat PTSD, and trying to put it in this commercial vehicle to get the drug approved. Last year, people were getting pretty excited about the potential for the first psychedelic-adjacent compound to get approved.

Eventually, due to deficiencies in the package, certain experiments they didn't conduct, certain clinical trial practice that maybe went awry, they were ultimately rejected by the FDA.

**"These psychedelic biotechs have really viable products that can really change patients' lives, but negative news flow just led to people fleeing the space."**

**Stephanie Sirota:** Is that one of the major negative catalysts that we saw last year for the broader psychedelic space?

**Connor Williams:** Oh yeah. As soon as that event happened, you saw almost every psychedelic biotech down day after day after day. And that just increased cost of capital and it makes it harder for these companies to get across the line.

## Discovering GH Research and its novel approach to TRD

**Stephanie Sirota:** Well, all is not so glum, because maybe this is a good segue into a company that we have long backed, GH Research. Maybe tell us a little bit about that. It's an $850 million market cap company. It's up 100% year-to-date on the positive news on their Phase 2b results that just came out.

**Connor Williams:** GH Research is a company we actually invested in right as the psychedelic bubble came to an end. They were a private company when we found them. I stumbled across one of their patent filings, which was a method of using their compound, 5-methoxy DMT in treatment-resistant depression. We ended up supporting their cross-over round.

So they took this compound—5-methoxy DMT. It can get to the brain really quick, you inhale this drug out of a bag that a little machine fills. And you have your psychedelic trip. And then you come back down, and hopefully you can go on with your day.

**Stephanie Sirota:** How long is that experience?

**Connor Williams:** Between ten and 15 minutes long. When you compare that to psilocybin, which is a six-to-eight-hour trip or LSD, which is closer to ten hours, that is a much faster throughput.
And when they came out with their Phase 2b data, it was, at least to my memory, the biggest drug effect I think I've ever seen in psychiatry in my life. It was, I think a 15.5 point difference versus placebo on the MADRS scale, which is a scale we use to measure depression.

**"Over 50% of patients were in remission, which is basically unheard of to date in psychiatry."**

**Stephanie Sirota:** They were in remission after how many treatments? Just one?

**Connor Williams:** Right, after the first dose.

**Stephanie Sirota:** After one successful—

**Connor Williams:** At seven days. Psychedelics, which hold the promise of once-a-month dosing or longer, you can also help the psychiatrist, because then they have more room to treat more patients.

GH we thought was an innovation on many fronts. They had a method of use patent. They had the opportunity to have a really short duration of treatment.

They had the opportunity to help out the psychiatrist's office, and on top of all of that, this was founded by real biotech guys that have developed drugs before. So, we knew they'd really go out of their way to tick all of the boxes that maybe some of the initial companies didn't.

**Stephanie Sirota:** So of the patients that have gone into remission, what are some of the long-term studies showing?

**Connor Williams:** The question of, "Are psychedelics more durable than Spravato?" that's pretty settled. Almost every study that's measured it has shown a response of at least a month.

In almost any scenario, it's an improvement over standard of care.

**Stephanie Sirota:** Coming up soon, you're going be sitting with Dr. Valcheva, the CEO of GH Research, who's very kindly visiting us from company headquarters in Ireland. Maybe tell us a little bit about that.

**Connor Williams:** GH has really had their work cut out for them for the last couple years. You know, unlike most drug companies where they're just developing their drug, which is often in pill form, these guys are developing a drug-device combo.

One of the funniest experiences I've ever had in this office is I was going through their original patent. They describe their inhalation device called the Volcano Medic. It's actually this device that people use to inhale cannabis.

And I was seated at my desk, and I asked one of the analysts, "Have you ever heard of this?"

And he told me, "Yeah, no, Connor, you can go down to the store on the corner right now, right here, and see a version of it."

I almost actually went out to buy one and deconstructed it on my desk in the office to figure out how to make it. That was one of the more interesting ways I've done diligence in my life.

**Stephanie Sirota:** I'm going to have to ask you this. Have you tried any of the psychedelics?

**Connor Williams:** I've met so many people that have done them, particularly people that have started these companies. And they're so evangelical about these compounds and maybe for good reason, because they can change people's lives.

If you ask me today, have I done them? No. In the future, you know, who knows? Maybe I'll go on holiday to Jamaica at some point, but I think until we're done investing, I'm purely data driven here.

**Stephanie Sirota:** Thank you so much, Connor. This has been a fascinating look into a very important and very exciting new class of drugs and hopefully will bring a great deal of hope to patients.

**Connor Williams:** Thanks for having me.

---

## CONTACT US FOR FURTHER INQUIRIES

RTW Investments, LP
40 10th Avenue, Floor 7
New York, NY 10014
(646) 597-6980

Find more information at:
rtwfunds.com