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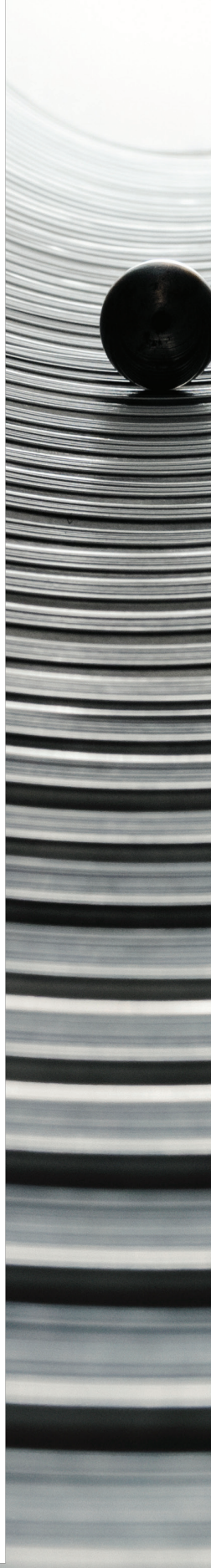


Counterpoint Global Insights

Psychedelics

EDGE | JULY 2022

WELCOME TO THE EDGE.
Morgan Stanley Investment Management's Counterpoint Global shares their proprietary views on a big idea that has the potential to trigger far-reaching consequences—ideas such as blockchain, autonomous vehicles, machine learning and gene editing.

Counterpoint Global's long-term ownership mindset emphasizes perspective, insight and thinking across categories, while our investment process focuses on identifying unique companies with sustainable competitive advantages. Through the EDGE, we share our framework for thinking about change and our process for recognizing patterns that may drastically alter the investment landscape over the longer term.

This work complements our team's more traditional, fundamental research to create a framework for long-term investing that is grounded in intellectual curiosity and flexibility, perspective, self-awareness and partnership.

Research into the potential therapeutic benefits of psychedelics is experiencing a renaissance. Psychedelics showed promise in treating mental illness as early as the 1950s, but research was essentially shut down in the 1960s. In 1970, the Controlled Substances Act classified psychedelics as Schedule 1 drugs, which have "no currently accepted medical use and a high potential for abuse." Now, a second wave of psychedelic research is underway, including a number of promising academic studies related to treating anxiety and depression. As a result, the use of psychedelics for medical purposes has renewed credibility and there is currently significant clinical trial activity for a number of psychedelic compounds that have a credible chance of achieving approval from the Food and Drug Administration (FDA). The potential market for psychedelic drugs is much larger than just patients with depression. Attention deficit hyperactivity disorder (ADHD), addiction, anxiety, and various chronic pain afflictions are likely to follow depression and post-traumatic stress disorder (PTSD) as indications approved by the FDA.

What is it?

Psychedelics are psychoactive substances that alter perception and mood. They affect numerous cognitive processes by promoting new pathways between neurons. Neurons are the fundamental cells in the brain and are connected to one another via synapses. These novel connections create specific psychological, visual, and auditory changes that alter the state of consciousness. The term "psychedelic" comprises hundreds of drugs, of which a few occur in nature and the majority are created in labs as synthesized derivatives of the classical psychedelics.

The classical psychedelics, including psilocybin, lysergic acid diethylamide (LSD), and dimethyltryptamine (DMT), have had the largest scientific and cultural influence. Contrary to what is implied by their designation as Schedule 1 drugs, they are generally considered physiologically safe and do not lead to addiction.[1] Widespread use of these drugs in the 1960s caused a severe backlash and heightened scrutiny, effectively halting all research. Current studies and trials strategically target sympathetic patient populations suffering from depression, trauma, or addiction and focus on the medicinal value of psychedelics rather than legalization and widespread access. At the same time that psychedelic drugs are in clinical trials seeking FDA approval for medical use, initiatives such as the Oregon Model seek to expand public access beyond medical treatment to include religious, spiritual, and recreational use.

Psychedelics offer a fundamental change in how mental health disorders are treated.

History

Knowledge of psychedelic plants predates written text, and they have been used in religious and therapeutic contexts for thousands of years all over the world. Psychedelics are known for their ability to alter consciousness and their capacity to open the mind. They entered mainstream awareness in the U.S. in the 1960s and were largely associated with the counterculture movement. During this period, researchers published more than a thousand clinical papers and several dozen books on the benefits of psychedelic drugs in a therapeutic context, attracting the interest and support of many psychiatrists. Despite mounting evidence that clinical use of psychedelics could help many patients, public perception grew more negative as the recreational use of psychedelics became widespread. This dim view of psychedelics led the federal government to designate them as Schedule 1 drugs. This decision effectively stopped all research for the next 30 years. However, in the last 15 years several academic institutions have conducted small studies exploring the potential of psychedelics to address a number of medical indications, including treatment-resistant depression and PTSD. The impressive results of these small studies have generated great interest in further exploring the potential of psychedelic therapy.

[1] Source: Nichols, David E. "Psychedelics." Pharmacological reviews vol. 68,2 (2016)

Compounds

Numerous psychedelic compounds are in early studies and clinical trials today. Psychedelics such as psilocybin, DMT, and mescaline are found in nature while others, including LSD, are synthesized in a lab. Most of these psychedelics have different chemical structures but cause remarkably similar effects.

Initial commercial focus is on three compounds, two of which have been studied more extensively than the other. The first is the classical psychedelic psilocybin, which has attracted the greatest academic interest for the treatment of depression. Second is the psychedelic empathogen hybrid methylenedioxymethamphetamine (MDMA), which has shown great potential to treat PTSD. MDMA is the furthest along of the compounds, currently in Phase 3 clinical trials and expected to be approved by the FDA in 2023.

The third noteworthy psychedelic is 5-MEO-DMT. Originally discovered in the venom of a Sonoran Desert toad, the drug is now predominantly synthesized in the lab for medical use. While lacking in extensive anecdotal studies and research, this psychedelic is of particular interest due to its very short duration time of roughly 15 to 30 minutes compared to the six hour-plus experience of a classical psychedelic. While the inhalation of DMT has an onset measured in seconds and effects measured in minutes, the experience is significantly more intense than its longer-acting peers. DMT can cause users to enter a hallucinatory realm fully detached from reality, characterized by hyperbolic geometry and described as defying visual or verbal description. In addition, the company furthest along in developing 5-MEO-DMT to treat depression does not plan to include therapy as part of treatment. This substantially reduces the time and cost burden to the patient and clinician.

Mechanisms of action

Magnetic resonance imaging (MRI) scans show that a brain on psychedelics functions completely differently than one during ordinary consciousness. While the mechanism of action is not fully understood, we know that the primary effect of psychedelics comes from the brain's serotonin 5-HT2A receptors. The hypothesis is that activating these receptors allows the brain to "reset," leading to remission of the symptoms of depression that can last for months after a single psychedelic treatment.

Psychedelics bind to these serotonin receptors and shut down the Default Mode Network (DMN), which governs our sense of identity. This disrupts the traditional patterns of thinking and enables the activation of new neural pathways. The result is a shift of consciousness and perception. The psychedelic state has been compared to the mind of a baby, with billions of synaptic connections yet to be pruned as patterns of thought are established. This altered state of perception and fluid sense of identity have profound implications for mental illness rooted in rigid thought patterns such as depression and anxiety. The result is a patient who is able to shift to a different state of awareness that is often effective in reducing depressive symptoms drastically.

Why it's disruptive

The ability to perceive reality in a new way can change the life of a clinically depressed patient. The realizations a patient has with psychedelic medicine are subsequently integrated through therapy, potentially ending the self-perpetuating cycles of depressed thought. While multiple pharmacological and nonpharmacological options exist to treat mental illness, there have been no truly new psychiatric drug treatments since the 1980s, when Prozac and other selective serotonin reuptake inhibitors (SSRIs), the most common type of antidepressants, came to market. Unfortunately, many patients do not respond to these medications or don't like how they feel when on them. Unlike SSRIs, which dull or mask the symptoms of depression and must be taken chronically, psychedelic-assisted therapy can change a patient's fundamental outlook over the course of one to a handful of sessions. The specifics of dosing, setting, and the particular psychedelic compound are still to be determined and are likely to vary by individual.

Unmet need

The number of mood disorders and suicide-related events has increased significantly in the last decade, exacerbated by the stress of modern life and the isolation brought on by COVID. Major Depressive Disorder and other mental health disorders can be debilitating and life threatening. Suicide is now the second-leading cause of death for people aged 10 to 34 years.[2] The number of people diagnosed with depression has increased drastically over the past decade. According to The Substance Abuse and Mental Health Services Administration, an estimated 52.9 million adults, or in one in five, suffer from a mental health illness in the U.S. Mental Health America reports that 46 percent of Americans meet the criteria for a diagnosable mental health condition at some point in their life, and half of those people will develop conditions by the age of 14. Depression is now one of the leading causes of disability, and the global cost to treat mental health illness is anticipated to reach $6 trillion by 2030.[3]

Unfortunately most people, including those with access to care, are not getting better. Many patients simply do not respond to current treatment options. Psychedelic therapies are an alternative approach to treating mental health that target unmet needs and redress the lack of innovation in the field. Various psychedelic compounds may also have the ability to treat addiction, chronic pain conditions like fibromyalgia, and even ADHD. Studies to determine their efficacy in these areas are underway now.

[2] Source: National Center for Health Statistics, CDC, December 2020.

[3] Source: World Health Organization, September 2021.

Problem they solve

Psychedelics offer a fundamental change in how mental health disorders are treated. Instead of aiming to mask or mute symptoms with chronic drug intake, they reset the mind with one or several treatments. Recent studies suggest that these positive effects have considerable durability, showing efficacy up to a year later. They also have an immediate effect in contrast to the onset time of four to 12 weeks for current treatments such as SSRIs for depression and anxiety. SSRIs treat depression by increasing levels of serotonin in the brain. Serotonin is one of the chemical messengers that carry signals between neurons. Despite being the best option available, SSRIs are not very effective and help only about 25 percent of patients who take them. Psychedelic medicine or assisted therapy could be the next course of treatment in cases where SSRIs fail. Early research by doctors affiliated with Johns Hopkins, New York University, and UCLA has shown psychedelic-assisted therapy to be effective and relatively durable with only one to a few treatments. These studies have been so promising that the FDA has designated both MDMA and psilocybin as breakthrough therapies. This designation allows researchers to expedite the development and review of drugs that are intended to treat a serious condition. To qualify, preliminary clinical evidence must indicate that the drug is safe and has the potential to demonstrate substantial improvement over available therapies.

Potential markets

Research indicates the potential for a wide array of mental health disorders. Psychedelic drugs are currently being investigated for the treatment of everything from depression to cluster headaches to Alzheimer's disease. Scientists are also studying psychedelics for their beneficial effects for pain-related diseases, with the belief they can beneficially alter psychological mechanisms and neural pathways associated with persistent pain. Because psychedelics reorganize neural networks in the brain, they have the potential to target pain through changes in the brain's structure and function. Beyond mental illness and pain-related diseases, psychedelics have the potential to treat any disease where new neural pathways might improve function.

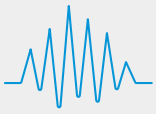
Challenges

While promising, psychedelics face numerous roadblocks to adoption. The most immediate challenge is navigating clinical trials and achieving FDA approval before advancing to administration and treatment protocols. To succeed, infrastructure and clinician support must be available and scalable. For example, therapists need specific training in order to administer psychedelic medicine, which is time consuming and not widely available. The treatment facility is also very important because it establishes the setting in which a patient will have their experience. Setting can shape the experience positively or negatively. These factors will add to the costs and complexity of providing psychedelic-assisted therapy.

The first wave of psychedelic-assisted therapies last roughly six to eight hours and require clinic space and medical supervision during this period. In addition, there are follow-up therapy sessions. At the same time, the medical psychedelic community faces challenges from both the rising movement to decriminalize psychedelics and the challenge of overcoming a negative perception of psychedelics. Many clinicians and patients are wary of psychedelics as the result of years of negative press and Schedule 1 Drug status. The public will need to see psychedelic medicine as real medicine. Clinicians will have to rethink and expand their definition of what an antidepressant is and even how we should be treating depression. The competitive landscape also introduces headwinds for the commercial success of many of these companies. Even though most novel psychedelic compounds are patented, the drugs have similar chemical structures and, consequently, similar therapeutic effects, making it unclear how psychedelic companies will significantly differentiate their treatments and establish market share. Finally, the matter of reimbursement will be vital to achieve meaningful access and adoption. Once efficacy and duration are established, we will have a better idea of how psychedelic drugs and therapies will be priced and at what stage of treatment insurance companies will agree to reimburse patients.

Conclusion

Psychedelics have a long history of use in religious and ceremonial contexts around the world in addition to the treatment of numerous physical and mental conditions. Interest in and openness to psychedelics as medicine are increasing daily as the media's narrative has changed and promising research on their benefits continues to grow. Psychedelic-assisted therapy has the potential to literally rewire our brains through the creation of new neural pathways, allowing depressed patients to escape perpetual cycles of negative thought. Early results indicate that psychedelic therapy has the potential to fundamentally reshape how we think about and treat not only mental illness but a host of other conditions as well. In order for psychedelics to become mainstream, they will need to be validated in large-scale randomized controlled trials. Over the next few years, we might see the first psychedelic therapies pass FDA approval, giving clinicians additional tools to treat mental illness, and potentially the data to determine which psychedelic drugs would better treat certain indications and patients.



OTHER DISRUPTORS

Other themes the team is currently researching include

- Drones
- Quantum Computing
- CAR-T Therapy
- Automation/robotics
- Blockchain
- Autonomous vehicles

Counterpoint Global

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ARMISTEAD NASH	Business Services, Software	24	22	20
DAVID COHEN	Consumer	36	31	25
ALEX NORTON	Consumer, Industrials, Technology (ex Software)	29	24	24
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ANNE EDELSTEIN	Co-Head of Vitality, Health Care	13	6	6
JENNY LEEDS	Co-Head of Vitality, Health Care	8	5	5
ABHIK KUMAR	Software, Media	15	5	5
JOSHUA JARRETT	Director of Research, Generalist	19	4	4
RUOBING CHANG	Internet	12	8	4
ALEKS SAMETS	Payments	4	4	4
BETH FIFER	Health Care	12	3	3
MUHAMMADRAZA PANJU	Internet	5	3	3
PETE STOVELL	Generalist	30	3	3
MICHAEL MORITZ	Generalist	6	2	2
GINO GRAZIADIO	Generalist	<1	<1	<1
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DAN CALLAHAN	Consilient Research	19	4	4
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STAN DELANEY	Big Ideas, Emerging Themes	23	23	20
SASHA COHEN	Big Ideas, Emerging Themes	7	7	7
JUSTIN AMEZQUITA	Big Ideas, Emerging Themes	4	4	4
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DERRICK MAYO	Sustainability Research	19	10	3
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KERRY ANN JAMES	Head of Client Relations, Portfolio Specialist	27	7	3
PRAJAKTA NADKARNI	Portfolio Specialist	20	17	13
MICK MORAN	Portfolio Specialist	10	10	2
MCKENZIE BURKHARDT	Portfolio Specialist	21	21	21
XAVIER SALAZAR	Portfolio Analyst	6	6	2
KATHRYNE DOWNS	Portfolio Specialist ~ Global Endurance	12	12	2
EARL PRYCE	Portfolio Administrator	24	24	17
CHAYSE MORGAN	Portfolio Administrator	4	4	4
ERICA CASARENO	Portfolio Administrator	2	2	2
AMBER YANG	Business Management	14	6	3

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Years of Experience, Years with Firm and Years with Team are as of June 2024.

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