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COMPANY NOTE | EQUITY RESEARCH | April 28, 2021

**Healthcare: Biotechnology**

**Initiation of Coverage**

# Cybin Inc. | CLXPF - $1.48 - OTCMKTS | *Buy*

| Stock Data | |
|---|---|
| 52-Week Low - High | $0.19 - $2.24 |
| Shares Out. (mil) | 146.72 |
| Mkt. Cap.(mil) | $216.54 |
| 3-Mo. Avg. Vol. | 463,420 |
| 12-Mo.Price Target | $10.00 |
| Cash (mil) | C$64.4 |
| Tot. Debt (mil) | C$0.0 |

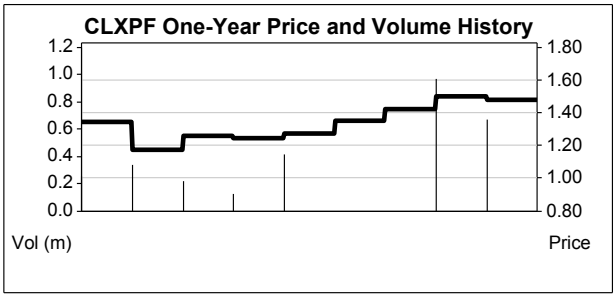
**Revenue ($ millions)**

| Yr Mar | —2021E— | —2022E— | —2023E— |
|---|---|---|---|
| | | Curr | Curr |
| 1Q | 0.0E | 0.0E | - |
| 2Q | 0.0E | 0.0E | - |
| 3Q | 0.0E | 0.0E | - |
| 4Q | 0.0E | 0.0E | - |
| YEAR | 0.0E | 0.0E | 0.0E |

*Initial listing on the Canadian NEO exchange: November 10, 2020*

**EPS $**

| Yr Mar | —2021E— | —2022E— | —2023E— |
|---|---|---|---|
| | | Curr | Curr |
| 1Q | (0.08)E | (0.07)E | - |
| 2Q | (0.08)E | (0.07)E | - |
| 3Q | (0.08)E | (0.07)E | - |
| 4Q | (0.08)E | (0.07)E | - |
| YEAR | (0.31)E | (0.28)E | (0.41)E |
| P/E | NM | NM | NM |




## CLXPF: Reinventing Psychedelics

We are initiating coverage of Cybin Inc. with a Buy rating and $10/share price target. Cybin develops alternative formulations and versions of existing psychedelic drugs.

**FOUND WAYS** Overlooked by the pharmaceutical industry, Cybin found, in our opinion, ingenious ways to improve potency and delivery of psychedelic drugs by reformulation and by exploring deuterated analogues. Along the way the company created novel intellectual property to fend off competition.

**BEATING an SSRI** According to a recent study by Imperial College London, psilocybin may actually be superior to an SSRI, escitalopram in patients suffering from major depressive disorder. However, each psilocybin treatment session may last 6-8 hours, when administered orally. Cybin's sublingual formulation bypasses the stomach, as the drug enters the bloodstream through the oral mucosa for faster onset of action.

**PRECEDENTED DEUTERATION** Cybin also explores a tried and tested strategy of replacing hydrogen atoms with deuterium to alter the pharmacokinetic profile of psychedelics. The half-life of short-acting tryptamines could be significantly extended. Combined with delivery by inhalation, sublingual route or orally disintegrating tablets, deuterated drugs could bypass liver metabolism for faster action and tighter dose control.

**CLOSELY FOLLOWING COMPASS** Cybin is a step behind COMPASS Pathways (CMPS - Buy) developing psilocybin for refractory depression. The company is about to enter Phase 2 trials with its sublingual film formulation.

**LARGE, UNFORTUNATELY** TRD impacts over 1% of the population, unfortunately. With a relatively small, 5% penetration, Cybin could achieve ~ $8B in sales in the U.S. and EU5 combined, according to our calculation.

**VALUATION** We arrive at our 12-month price target of $10/share (USD) by assessing the after-tax, risk-adjusted NPV of potential future cash flows from the TRD indication and including a technology value for earlier programs. The probability-adjusted, fully taxed (21%) NPV (15% discount rate) of potential cash flows through 2035 is $2B or $9/share, in our calculation. Adding $200MM ($1/share) estimated technology value yields $2.2B or $10/share for the company, corresponding to our 12-month price target. Factors that could impede shares from reaching our price target include failure of Cybin's drugs to demonstrate significant efficacy benefit or found to be unsafe, leading to the discontinuation of the programs.

## SUMMARY

Cybin is a leading biotechnology company focused on progressing psychedelic therapeutics by utilizing proprietary drug discovery platforms, innovative drug delivery systems, novel formulation approaches and treatment regimens for psychiatric disorders. Cybin Inc. is headquartered in Toronto, Canada.

## KEY POINTS

**Initiating coverage of Cybin Inc. with a Buy rating.** Cybin is developing alternative formulations and derivatives of psychedelic drugs.
**Our Buy thesis on the shares of Cybin is based on the following:**

- **70-Year History** Psychedelic drugs have been researched by academics for treating mental illness for over 70 years.
- **Proper Clinical Research** Cybin intends to develop its drug candidates by conducting clinical trials acceptable to regulatory agencies.
- **Stands Out** The pharmaceutical industry largely ignores psychedelic drugs discovered in the middle of last century because of the lack of patent protection. Cybin found ingenious ways to alter formulations and develop deuterated analogues of psychedelics, creating novel intellectual property.
- **Drug-Assisted Psychotherapy** Cybin, along with others, explores the one-time (or very infrequent administration) of psilocybin-assisted psychotherapy. "Integration" or follow up reconciliation of the drug experience is an integral part of optimal therapy. The combined approach is unprecedented from the medicinal and regulatory perspective. There are willing regulators on both sides of the Atlantic to explore these uncharted territories. The FDA went as far as designating five different programs as Breakthrough Therapy between 2013 and 2019.
- **Beating an SSRI** In a recent publication by the Imperial College London, psilocybin beat a conventional antidepressant SSRI escitalopram in terms of response and remission rates in patients with depression. As opposed to daily administration (escitalopram), psilocybin was taken twice over a six-week period. Cybin is about to initiate a Phase 2a trial with a sublingual formulation of psilocybin (CYB001) in the same patient population.
- **Blockbuster Potential** According to a recent survey, over 1% of Americans suffer from TRD, translating to 3.6MM patients.[1] With pricing of $20,000/patient and a 5% market penetration the revenue opportunity is in excess of $5B, in our calculation. With a contribution of $3B from the EU5 market, the combined market potential is >$8B for CYB001 in TRD alone.

**Expected Newsworthy Events/Value Drivers for the Next 12-18 Months**

| | |
|---|---|
| Listing on NASDAQ | 2Q21 |
| Initiate Phase 2a and Phase 2b trials for CYB001 in patients with MDD | 2021 |
| File an IND for deuterated tryptamine (CYB003) for Alcohol Use Disorder | YE21 |

[1] https://www.psychiatrist.com/read-pdf/29169/

## OVERVIEW: CNS DISEASES & TREATMENT OPTIONS

- **Depression** is classified as a mood disorder that may bring long-lasting symptoms including sadness, low energy, loss of appetite, and a lack of interest in things that used to bring pleasure. It may lead to serious health complications, including suicide[2].
    - Definitions of Depression Disorders:
        - **Major depressive disorder (MDD)**[3] is among the most common psychiatric disorders. In the U.S., ~7% of adults have at least one major depressive episode in a given year. Current treatments include therapy, medication, diet, and exercise. The most common medications include antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).
        - **Bipolar disorder**[4] is characterized by the development of a manic, or energized mood episode, which is often preceded or followed by episodes of depression. Common medications include mood stabilizers such as lithium to manage manic episodes and antidepressant SSRIs for treating depression episodes.
        - **Treatment-resistant depression (TRD).** Once two different regimens of antidepressants have been tried without improvement, the illness of MDD or bipolar disorder is termed treatment-resistant[5]. About 30% of people with MDD are resistant to conventional treatments.
            - For TRD to be diagnosed, objective clinical scales, such as the Hamilton Depression Rating Scale[6] and the Inventory of Depressive Symptomatology[7] and retrospectively using treatment history forms such as the Antidepressant Treatment History Form (ATHF)[8] can be helpful in tracking the course and understanding the level of treatment resistance.
            - TRD has a significantly higher economic burden for patients who are hospitalized[9]. For TRD patients, the hospital length of stay is longer and cost of hospitalization is higher than those of non-TRD patients, causing about $3,000 greater annual combined hospital cost[10]. Combined with expenses for medication, TRD was associated with a ~30% higher cost burden vs. non-TRD patients[11]. Effective and affordable treatments could substantially reduce the hospital and economic burden of patients.

[2] https://www.mayoclinic.org
[3] https://www.mayoclinic.org
[4] https://www.mayoclinic.org
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- Existing Treatment Options

  - **Traditional Pharmacological and Psychotherapy Approaches**

**Augmentation.** Augmentation includes adding a second medication on top of a first-line pharmacotherapeutic option. Three main augmentation strategies include: lithium, T3 and second-generation antipsychotics[12].

- *Lithium*, a naturally occurring salt, was traditionally used for treating bipolar disease. The best evidence for augmenting antidepressant pharmacotherapy with lithium comes from studies involving tricyclic antidepressants (TCAs)[13]. However, less evidence exists for augmentation of current first-line antidepressant serotonin reuptake inhibitors (SSRI) pharmacotherapy[14].

- *Triiodothyronine (T3)* is a thyroid hormone, which is known to have an elevation effect on mood. Similarly to lithium, the initial T3 studies were performed in augmentation of TCA pharmacotherapy. In general, it is better tolerated than lithium[15].

- *Second-Generation Antipsychotics*. Unlike lithium and T3, second-generation antipsychotics (SGAs), including quetiapine[16], aripiprazole[17], olanzapine[18] and risperidone[19] have been used in combination with SSRI treatment, which is approved by the FDA. They have some effects on serotonin receptors, thus may be effective combining with SSRI/SNRIs.

- *Ketamine.* Ketamine is a widely investigated N-methyl-D-aspartate (NDMA) antagonist and rapid acting antidepressant (RAAD)[20]. Its antidepressant effects are noted around three hours after the IV infusion is discontinued and continued over approximately 5–7 days, leading to a significant reduction in suicidal ideation in TRD patients. Recently, an intranasal form (esketamine) has been developed by Janssen. Its combination usage with an oral antidepressant has been approved by the FDA for restricted use of treating TRD.

[12] Zhou X, Ravindran AV, Qin B, Del Giovane C, Li Q, Bauer M, Liu Y, Fang Y, da Silva T, Zhang Y, Fang L, Wang X, Xie P. Comparative efficacy, acceptability, and tolerability of augmentation agents in treatment-resistant depression: systematic review and network meta-analysis. J Clin Psychiatry. 2015 Apr;76(4):e487-98. doi: 10.4088/JCP.14r09204. PMID: 25919841.
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**Optimizing, combining and switching classes of antidepressants.** The majority of MDD patients would initially start on selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) as first-line treatments.

- Older classes of antidepressants, including *tricyclic antidepressants (TCA)*[21] [22] *and monoamine oxidase inhibitors (MAOIs)*[23] [24], are reserved for trials of medication once SSRI/SNRI options have been exhausted

**Psychotherapy.** Psychotherapy is applied alone, or in combination with pharmacological treatment[25]. It can also be used to address a comorbid diagnosis of MDD and other psychiatric disorders[26].

- **Brain Stimulation**

Multiple modalities of brain stimulation therapies have been investigated and applied in the treatment of TRD. They are not the first line of therapy, but used when several options of pharmacotherapy and/or psychotherapy failed**.**

**Electroconvulsive Therapy (ECT).** ECT applies high frequency electrical pulses to either the non-dominant right hemisphere or bitemporally, resulting in pyramidal cell firing with the subsequent generalization of cortical activity to produce a generalized, tonic-clonic seizure[27].

- Applied two to three times per week, 6-18 sessions in total, it has been shown that ECT can yield superior efficacy of treating TRD compared with antidepressant medications[28].

**Repetitive Transcranial Magnetic Stimulation (rTMS).** Unlike ECT, rTMS is applied non-invasively. It has focused pulses of an electromagnetic coil being repetitively discharged over the scalp to stimulate cortical neurons, altering neural excitability without causing a seizure. rTMS has been approved as a treatment and its efficacy has been established over the past two decades and affirmed in several large meta-analyses[29] [30]. It comes with various forms, including the following:

[21] Thase ME, Rush AJ, Howland RH, Kornstein SG, Kocsis JH, Gelenberg AJ, Schatzberg AF, Koran LM, Keller MB, Russell JM, Hirschfeld RM, LaVange LM, Klein DN, Fawcett J, Harrison W. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. Arch Gen Psychiatry. 2002 Mar;59(3):233-9. doi: 10.1001/archpsyc.59.3.233. PMID: 11879161.
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- Conventional high frequency rTMS focused on the left dorsolateral prefrontal cortex (DLPFC)[31].
- Deep rTMS applied to deeper areas of the cortex[32].
- Theta-burst stimulation approximated the endogenous theta frequency emitted by the brain and induced cortical plasticity[33].
- Accelerated rTMS protocols to induce multiple rTMS sessions daily[34]

**Deep brain stimulation (DBS).** In a DBS procedure, a permanent neurosurgical implant is placed in the brain to activate and silence specific regions. The implant stimulates the target areas repetitively, including the subgenual cingulate cortex (SCC)[35]. Studies have shown DBS in SCC yield a 92% response rate two years after the implantation[36].

**Magnetic seizure therapy** discharges repetitively to induce focal synchronous activity in the targeted cortical region, resulting in a generalized seizure similar to ECT[37]. Unlike ECT, it is focally discharged thus resulting in significantly fewer cognitive side effects. Several treatment sessions are necessary to result in significant therapeutic effects.

**Vagus nerve stimulation (VNS)** modulates brain activity via stimulation of the tenth cranial nerve, the vagus nerve, aiming to alter various networks of the brain for treating TRD[38]. The implanted VNS system is composed of a pulse generator, an electrode attached to the left vagus nerve in the neck and a system delivers pulsed electrical signals to the vagus nerve[39]. The FDA approved VNS as an adjunctive long-term therapy for TRD in patients who failed to respond to four or more different therapies[40].

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- Limitations Associated with Existing Treatments

  - **Side Effects Associated with Pharmacological Approaches.**

    - Before SSRIs and SNRIs entered the market, tricyclic antidepressants (TCAs) were the standard pharmacological treatment for depression. TCAs were largely replaced by SSRIs from the 1990s, with the hope that SSRIs would be more efficacious and safer than TCAs.

    - However, safety and tolerability concerns related to SSRIs and SNRIs have increased.[41][42] Side effects include dry mouth, gastrointestinal side effects, hepatotoxicity, seizure, and weight gain[43]. Side effects are especially profound in TRD patients due to prolonged medical treatment.

  - **Stigma Associated with ECT.**

    - Despite strong clinical evidence supporting its therapeutic efficacy, due to its invasive nature, ECT has suffered from extensive stigma, where it was seen as a punishment as a form of behavioral control[44]. The stigma has resulted in ECT being used by less than 0.25% of individuals with MDD in the U.S[45].

  - **Lack of Strong Evidence of Alternative Brain Stimulations.**

    - Current evidence supports the therapeutic potential of electroconvulsive therapy (ECT), with less evidence for the more recently developed forms of brain stimulation including magnetic seizure therapy (MST), deep brain stimulation (DBS) and vagus nerve stimulation (VNS)[46].

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## HISTORICAL REVIEW OF ANTIDEPRESSANTS[47]

- **Monoamine Hypothesis and Monoamine Based Pharmacological Treatments**
  - Monoamine Hypothesis
    - In the 1950s, the monoamine hypothesis emerged and proposed that patients with depression have depleted concentrations of serotonin, norepinephrine, and dopamine[48]. Based on the hypothesis, various pharmacological treatments were designed for treating depression.
  - Monoamine Based Pharmacological Treatments (Figure 1)
    - **Monoamine oxidase (MAO) inhibitors.** MAOs responsible for the breakdown of serotonin, dopamine, epinephrine, and norepinephrine and sympathomimetic amines located in the presynaptic terminal[49]. Inhibition of MAO would increase the availability of the monoamine neurotransmitters in the presynaptic terminal when action potentials reach the synapse.
      - In 1953, Fox and Gibas synthesized iproniazid, a monoalkyl derivative of isoniazid, which was originally designed to be new antitubercular compounds[50].
      - In 1958, Loomer, Saunders, and Kline conducted a systematic clinical study of iproniazid on patients with depression. Significant improvement was shown in 70% of these subjects[51]. Thus, iproniazid became the first approved pharmacological treatment for depression. However, Iproniazid is a non-selective irreversible MAO inhibitor, which led to safety concerns and led to its exit from the U.S. market.
      - In the 1990s, reversible and selective MAO-A inhibitors moclobemide [Manerix®] and brofaromine [Consonar®]) were developed[52]. Currently, moclobemide is available in over 50 countries worldwide, while not in the U.S.
    - **Tricyclic antidepressants (TCA)** are characterized by their three benzene ring molecular cores. They have a diverse pharmacological profile, with inhibiting presynaptic norepinephrine and serotonin reuptake transporters, and blocking postsynaptic adrenergic α1/2, muscarinic and histamine H1 receptors[53].

[47] Hillhouse, T. M., & Porter, J. H. (2015). A brief history of the development of antidepressant drugs: from monoamines to glutamate. Experimental and clinical psychopharmacology, 23(1), 1–21. https://doi.org/10.1037/a0038550
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- In 1959, imipramine (Tofranil®) was approved by the FDA for the treatment of MDD. Compared with MAO inhibitors, it has much less serious side effects[54].

- **Selective serotonin reuptake inhibitors (SSRIs).** In the late 1960s, realizing the significant role of serotonin in MDD, researchers were actively seeking compounds selectively targeting the serotonin pathway. SSRIs are much more selective for inhibiting serotonin reuptake over norepinephrine at their uptake transporter proteins, with minimal binding affinity for other postsynaptic receptors[55].

    - In 1974, the first report of an SSRI was published suggesting that **fluoxetine** has antidepressant properties[56]. It was approved by the FDA in 1987 and was launched in 1988 under the trade name **Prozac®**[57].

    - After the launch of Prozac, several other SSRIs were developed and approved by the FDA, including sertraline [Zoloft®], citalopram [Celexa®], paroxetine [Paxil®], and escitalopram [Lexapro®])[58].

- **Atypical antidepressant drug bupropion**. Bupropion is an atypical antidepressant whose binding profile differs from other antidepressant drugs, which was approved by the FDA in 1989 for treating MDD[59]. It is primarily a dopamine-norepinephrine reuptake inhibitor with highest binding affinity for dopamine transporters and much less selectivity for norepinephrine transporters[60], along with no binding affinity for serotonin transporters or other pre- and postsynaptic receptors[61]. Clinical results have shown that bupropion is as efficacious as other antidepressants for treating MDD[62]. It is also better tolerated than other antidepressants[63].

- **Serotonin-norepinphrine reuptake inhibitors (SNRIs).** Similar to TCAs, SNRIs inhibit the reuptake of serotonin and norepinephrine by targeting the serotonin and norepinephrine transporters[64]. However, unlike TCAs, SNRIs have minimal affinity towards adrenergic (α1, α2, and β), histamine (H1), muscarinic, dopamine, or postsynaptic serotonin receptors[65].

[54] Fangmann P, Assion HJ, Juckel G, González CA, López-Muñoz F. Half a century of antidepressant drugs: on the clinical introduction of monoamine oxidase inhibitors, tricyclics, and tetracyclics. Part II: tricyclics and tetracyclics. J Clin Psychopharmacol. 2008 Feb;28(1):1-4. doi: 10.1097/jcp.0b013e3181627b60. PMID: 18204333.
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[65] Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, Shaw JL, Thompson L, Nelson DL, Hemrick-Luecke SK, Wong DT. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. Neuropsychopharmacology. 2001 Dec;25(6):871-80. doi: 10.1016/S0893-133X(01)00298-6. PMID: 11750180.

- In 1993, **Venlafaxine,** an inhibitor selectively targeting the serotonin and norepinephrine transporters was introduced to the U.S. market.

- After venlafaxine got approved, several other SNRIs including **duloxetine** [Cymbalta®] and **milnacipran** [Savella®]) have been approved for the treatment of MDD[66].

- **Atypical antidepressant drug vortioxetine.** In 2013, **vortioxetine** (Brintellix®) was approved by the FDA for the treatment of MDD. Vortioxetine has a high binding affinity for several serotonin receptors[67]. It also has slight receptor affinity for dopamine and norepinephrine transporters[68]. Its clinical efficacy and tolerability of vortioxetine are comparable to other antidepressants, with a low risk for sexual dysfunction and weight gain[69] and potentially cognitive functioning improvement[70].

- **Glutamatergic Systems and Major Depressive Disorder**

  - Glutamate Dysfunction in MDD:

    - Although there are seven classes of antidepressant drugs targeting various monoamine neurotransmitters, patients with treatment-resistant depression failed to respond, suggesting that dysfunctioning of monoamine signaling plays a modulatory role rather than a major direct role in MDD[71]. Thus, research has shifted on non-monoaminergic based targets for treatment-resistant depression, including the glutamatergic system[72].

    - Clinical results have found differences in plasma glutamate and glutamine in patients with MDD as compared to healthy individuals[73]. Using proton magnetic resonance spectroscopy researchers found reduced metabolic glutamate/glutamine exchange (Glx) in subcortical and cortical brain regions of MDD patients, including hippocampus[74] and anterior cingulate cortex[75].

  - Glutamate Based Pharmacological Treatments (Figure 1)

    - **Noncompetitive NMDA receptor antagonists**

      - **Ketamine** is a noncompetitive NMDA receptor antagonist that binds to the phencyclidine site inside the ion channel. In 2000, ketamine was first used in a proof of concept randomized, double- blind study to

[66] Papakostas GI. Serotonin norepinephrine reuptake inhibitors: Spectrum of efficacy in major depressive disorder. Primary Psychiatry. 2009;16(Suppl 4):16–24.
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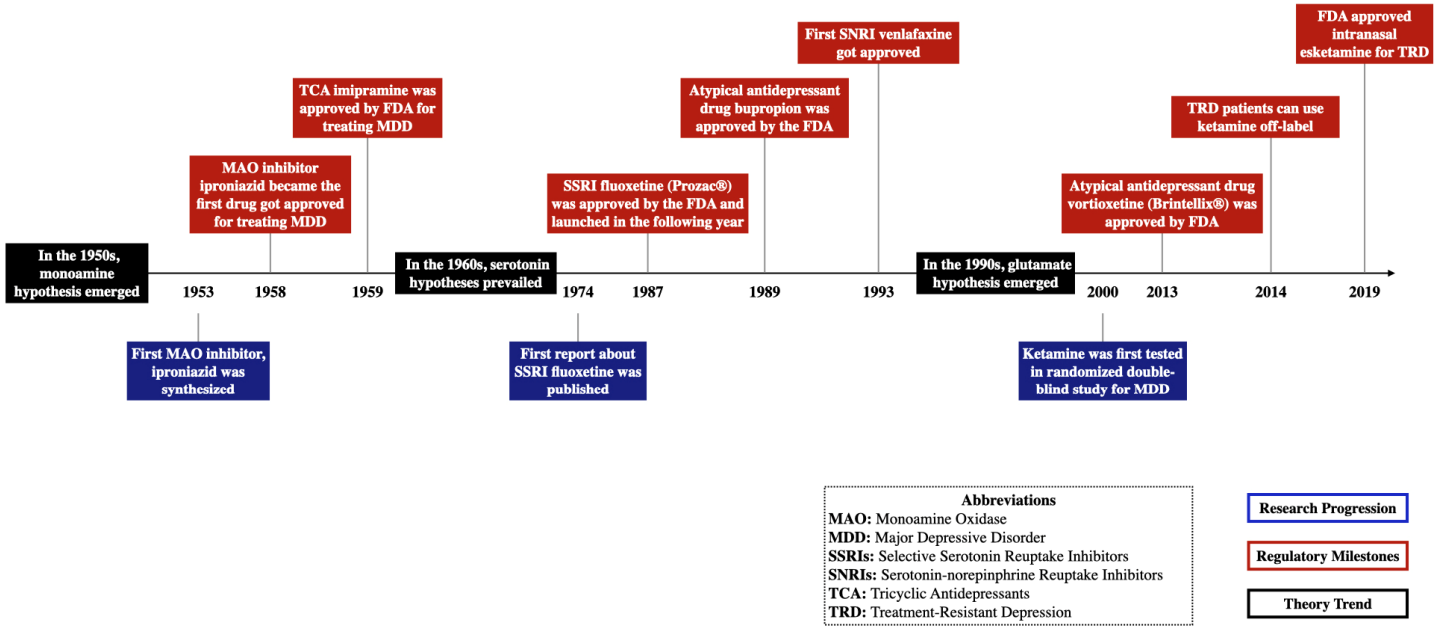
assess the effects of ketamine on MDD[76]. Ketamine displayed rapid antidepressant effect, which is superior to the 4-12 week delay with existing antidepressant drugs. With their doctors' prescription, patients with treatment-resistant depression can legally use ketamine off-label in medical ketamine clinics since 2014. In 2019, the FDA approved intranasal esketamine [SPRAVATO®] for TRD[77].

**Figure 1: Timeline of Antidepressant Development**




*Source: Hillhouse & Porter (2015)[78]; ROTH Capital Partners Research.*

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## PSYCHEDELICS: AN EMERGING MARKET OPPORTUNITY

- **A New Paradigm for Treating Mental Health and Wellness**

For years, mental unwellness has been a growing public health crisis. In our view, the recent COVID-19 pandemic has accelerated the deterioration of the world's collective mental health and well-being. Over 15% of the global population suffers from mental and substance use disorders[79]. The pandemic has exposed the wide gap between mental health needs and mental health resources, where depression, PTSD, and addictions are on the rise in many countries, as stress, worry, sadness, and loneliness are increasing worldwide. After years of prohibition, we believe psychedelics is making a significant resurgence driven by a movement of people initiating steps to change the way they live, work, and play, on top of governments and companies looking for ways to invest in prevention and better outcomes to lower healthcare costs.

- **Clinical Summary**

Beginning in the 1950s, academic researchers explored the therapeutic utility of psychedelic drugs in depression, anxiety, addiction, PTSD, just to name a few. Most of these studies, rather than formal clinical trials, were conducted in a limited number of subjects, using poorly defined instruments to detect benefit and lacked control groups. Studies were performed without the involvement of regulators. Following loss of governmental funding, research came to a screeching halt in the 1970s.

Twenty years later, in the early 2000s, formal clinical trials, still sponsored by academics and non-profit organizations, got under way. In a seminal report, researchers provided the first controlled evidence for the rapid antidepressant effects of intranasal ketamine in 2014. In 2016, it was demonstrated for the first time that high-dose psilocybin reduces anxiety in terminally ill cancer patients. According to a publication in 2018, MDMA treatment led to an 80%$^{+}$ response rate in patients with PTSD. A Phase 3 trial is under way to corroborate these findings. A single dose of ibogaine was shown to be effective for the treatment of opioid withdrawal (2018).

Currently, three psychedelic active ingredients have been FDA granted Breakthrough Therapy Designation (BTD), which shortens the process of drug development and review by two years or 30% (Table 1). Today, there are numerous clinical trials being conducted by a growing number of companies to formally evaluate the benefit of psychedelic substances in CNS disorders worldwide.

**Table 1: Breakthrough Therapy Designation**

| Psychedelic Breakthrough Therapy Designations (BTD) | | | |
|---|---|---|---|
| Active Ingredient | Company | Designation | Year |
| Ketamine | Janssen | Treatment Resisitant Depression(TRD) | 2013 |
| Ketamine | Janssen | Major Depression Disorder (MDD) | 2016 |
| MDMA | MAPS | Post Traumatic Stress Disorder (PTSD) | 2017 |
| Psilocybin | COMPASS Pathways | Treatment Resisitant Depression (TRD) | 2018 |
| Psilocybin | Usona Institute | Major Depression Disorder (MDD) | 2019 |

*Source: FDA, Company press releases, and ROTH Capital Partners*

[79] http://www.healthdata.org/

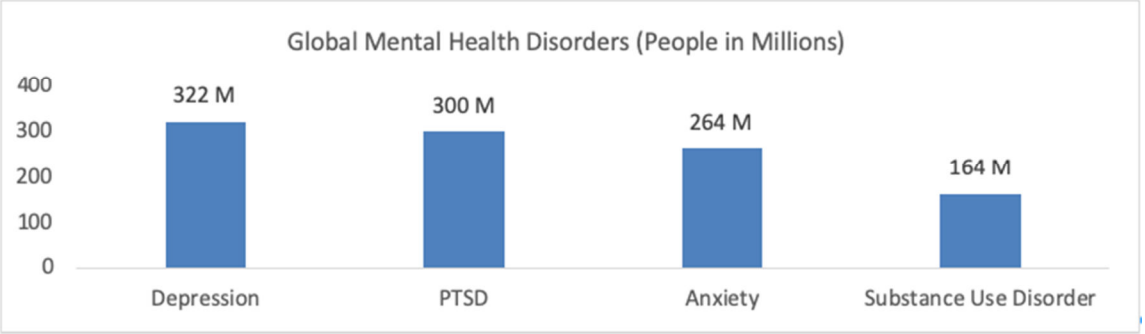
- **Role of Medicinal Psychedelic Drugs in Market of Mental Health**

Globally, the psychedelic market is expected to reach nearly $7B by 2027 according to Data Bridge Market Research. While $7B is relatively small compared to the entire market for mental health, psychedelic drugs will have carved out a small but important niche in treating treatment-resistant depression, PTSD, and addiction by 2027 (Figure 2). As acceptance in the U.S. and Canada begins to grow, we will see other countries adopt medicinal psychedelic programs.

The U.S. market for psychedelics is especially large. In 2019, 52 million adults lived with a mental illness in the United States according to NIMH. Of those people suffering from mental illness, only 45% received mental health services due to various factors from financial reasons to complicating side effects of treatment.

Psychedelic medicines, specifically second-generation psychedelics seek to target this group of people not receiving medical treatment due to negative side effects on their lifestyle or people with mental illnesses resistant to traditional mental health treatments. Overall, the mental health market is increasingly growing as more people begin to prioritize their mental health, searching for ways to increase their qualities of life.

**Figure 2: Psychedelic Mental Health Market Focus**



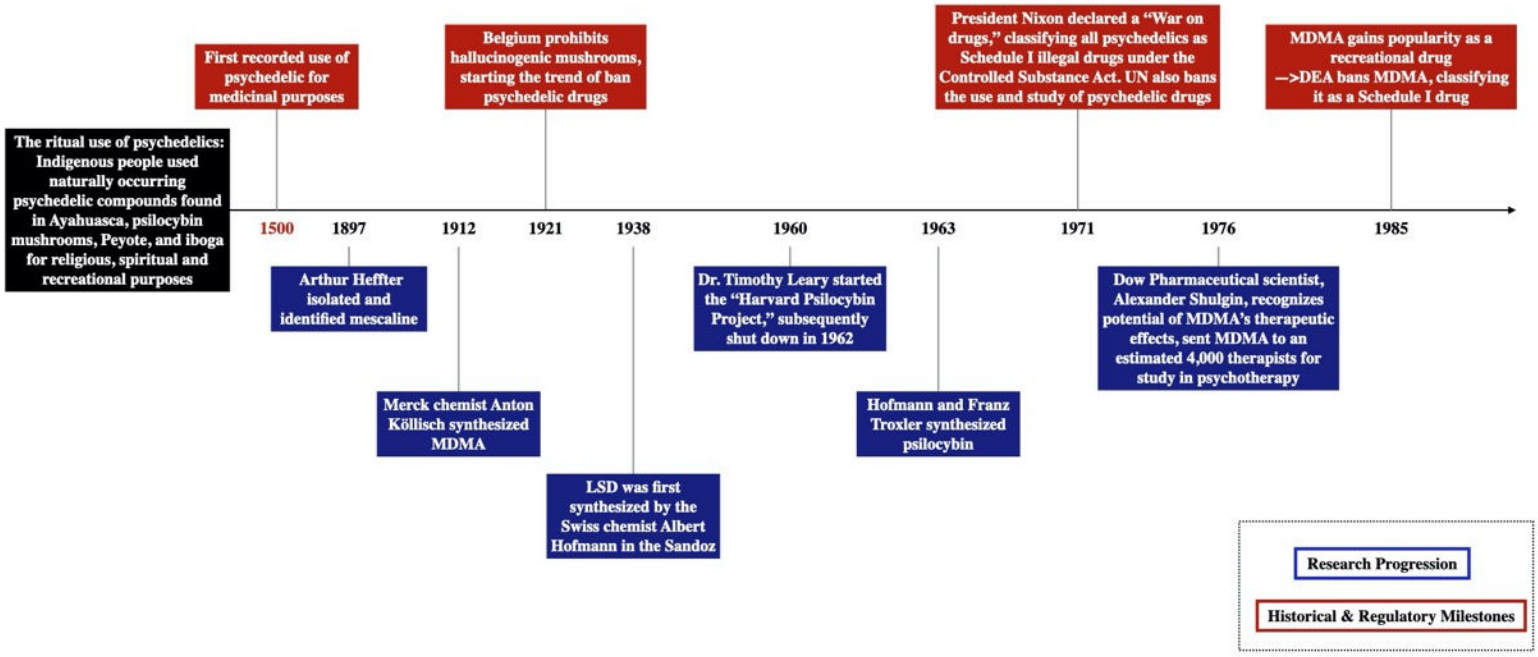

*Source: WHO, IHME, ATAI and ROTH Capital Partners*

## PSYCHEDELICS: FROM PAST TO FUTURE

- **Past: History of Psychedelic Compounds**
  - What is Classified as a Psychedelic?
    - In medical terms, psychedelics are a subcategory of hallucinogens that are able to induce states of altered perception, thought and mood, affecting numerous cognitive processes. These "mind-expanding" drugs heighten awareness of sensory input while diminishing control over what is being experienced[80].
    - Popular culture has grouped prominent psychedelic drugs like LSD and psilocybin with empathogens such as MDMA and dissociatives like ketamine and esketamine. For the purposes of this report, we will use the term "psychedelics" to refer to ayahuasca, DMT, ibogaine, ketamine, LSD, MDMA, psilocybin and all of their respective derivatives.
  - Why We Need Psychedelics?
    - Mental Illness rates in the United States as well as globally are increasing at unprecedented rates. Depression has increased significantly among persons in the U.S. from 2005 to 2015, from 6.6% to 7.3% and especially among ages 12 to 17 increased 8.7% to 12.7% according to a study done by Columbia University[81]. The world and in particular the U.S. is in the midst of what psychologists and other experts are calling a mental health epidemic. Due to side effects of current medications for mental illnesses, only 44.8% receive treatment[82].
    - In hopes of finding a treatment for most people suffering mental illness, the medical community has turned its attention to medicinal psychedelics. The use of psychedelics in healing practices and religious rituals predates recorded history (Figure 3).
      - Psychedelics have been studied since the birth of psychology in the late 19th century and early 20th century as a tool for therapy.
      - However, in 1970 all psychedelics were categorized as a Schedule I drug in the U.S. and then in the UN, ceasing all medical studies. Due to these restrictions, a powerful subset of drugs remains woefully understudied for medicinal purposes.
      - Recently, the FDA has approved breakthrough therapy designations for ketamine, MDMA, and psilocybin with new research institutions turning their focus on the potentials of psychedelics. Psychedelics, ayahuasca, DMT, ibogaine, ketamine, LSD, MDMA, psilocybin and all their respective derivatives demonstrate potential to treat a wide array of mental illnesses.

[80] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4813425/
[81] https://pubmed.ncbi.nlm.nih.gov/29021005/
[82] https://www.nimh.nih.gov/health/statistics/mental-illness.shtml

**Figure 3: Timeline Summary for Psychedelic History**

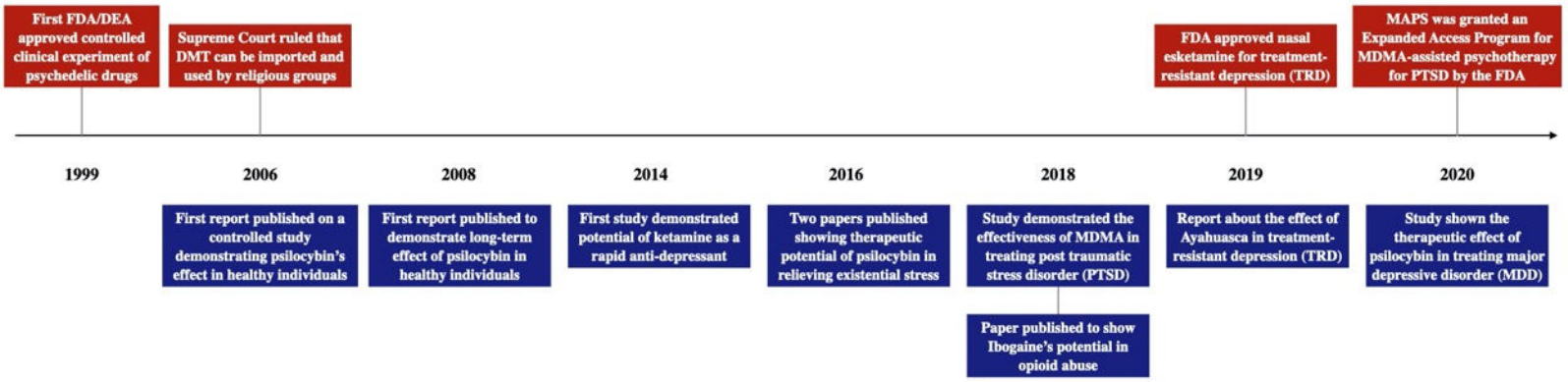



*Source: MAPS "Brief History of Psychedelic Psychiatry[83]", Nichols et al. "Psychedelics[84]", NIMH "MDMA[85]", The Beckley Foundation "Psychedelic Research Timeline[86]", and ROTH Capital Partners*

[83] https://maps.org/news/media/5289-a-brief-history-of-psychedelic-psychiatry
[84] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4813425/
[85] https://www.drugabuse.gov/publications/research-reports/mdma-ecstasy-abuse/what-is-the-history-of-mdma
[86] https://www.beckleyfoundation.org/psychedelic-research-timeline-2/

- **Current: Contemporary Clinical Studies and Regulatory Milestones**
  - From the first regulatory approved, controlled study in 1999, to the recent promising clinical data, researchers have made significant progress towards realizing the therapeutic potential for treating CNS disease with psychedelic drugs.
    - FDA has eased some restrictions on the usage for medical and religious purposes (red brackets in Figure 4)
    - Many psychedelic compounds, including psilocybin, MDMA, ayahuasca and ibogaine, have demonstrated efficacy in treating various psychiatric disorders, including depression, posttraumatic stress disorder (PTSD) and substance abuse (blue brackets in Figure 3).

**Figure 4: Contemporary Clinical Studies and Regulatory Milestones**




*Source: ROTH Capital Partners Research*

- **Future: 2nd Generation Compounds**
  - Issues with Using 1st Generation Compounds
    - **Side effects:** Despite having shown therapeutic potential as a breakthrough therapy, there are certain risks and side-effects associated with using 1st generation compounds. By re-engineering the structure, derivatives could have different pharmacological profiles, mitigating some adverse effects such as hallucinogenic effects, hyperthermia and neurotoxicity.
    - **IP protection:** Psychedelic mushrooms are not appropriate for pharmaceutical use, since their compounds vary wildly across species and within individual mushrooms. Thus, most of the psychedelic drugs are synthesized under good manufacturing practices (GMP). Patents on most psychedelic compounds have expired. In addition, many of them are Schedule 1 controlled substances, creating potential regulatory hurdles. On the other hand, 2nd generation compounds could have long IP protection, and avoid being labelled as controlled.

## PSYCHEDELICS: ACTIVE INGREDIENTS & SAFETY PROFILE

While early in the development of psychedelic molecules, seven common active ingredients are of interest to become useful in benefits of potential use in various medical and wellness therapies. There are a number of paths of use with a focus on developing second generation psychedelic drugs to be used in a psychedelic assisted psychotherapy to treat mental health conditions, while functional plant-based nutraceutical solutions are being developed effectively by removing the psychoactive component of a psychedelic to treat various health disorders.

- **Entheogenic versus Synthetic Drugs**
  - Entheogenic plants are defined as those yielding one or more chemical substances that, when ingested by humans, produces a "non ordinary state of consciousness for religious or spiritual purposes[87]". For compounds and active ingredients, the entheogenic plants include ayahuasca, DMT, ibogaine, and psilocybin.
  - Synthetic psychedelic drugs are those that are construed in a laboratory setting that achieve the same results as their entheogenic cousins. The synthetic psychedelic drugs include ketamine, lysergic acid diethylamide (LSD), and methylenedioxymethamphetamine (MDMA). DMT can be obtained via extraction from a plant or synthesized in a lab.
- **Focused Active Ingredients & Target Markets**

  Psychedelics include a group of serotonergic agonists that can be effective in treating headache, substance use disorder, end-of-life anxiety, depression and obsessive-compulsive disorder (OCD).
  - **Lysergic acid diethylamide (LSD)** acts primarily as a serotonergic agonist, while it also binds dopaminergic and adrenergic receptor sites, effects lasts up to 12 hours[88]
    - Implications: It is most widely used for treating **alcoholism**. It can also significantly reduce anxiety in patients with **anxiety associated with life-threatening illnesses**[89].
    - Side effects: Disorientation, anxiety and fear of insanity ("Bad trip"); hallucinogen persisting perceptual disorder (HPPD) ("Flashback")[90];
  - **Psilocybin:** 5-HT 2A, 1A and 2C receptor agonists, effects lasting 4-12 hours[91].
    - Implications: It may have potential for rehabilitation programs to reduce **recidivism**. It can also induce **mystical experiences** and increase openness, eliciting significant changes in personality. Pilot studies also showed its effectiveness in treating **anxiety** secondary to a cancer diagnosis, **obsessive-compulsive disorder (OCD)**, treatment-resistant **depression** and **smoking cessation**[92]

[87] https://maps.org/news/bulletin/articles/385-bulletin-spring-2014/5575-entheogenic-education-psychedelics-as-tools-of-wonder-and-awe
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- Side effects: Moderate to severe disorientation, anxiety, or fear responses under the influence[93].

- **Mescaline** is a naturally occurring psychedelic found in peyote and San Pedro cactus, whose effects last up to 12 hours[94]

  - Implications: Long-term users demonstrated significantly greater psychological well-being and general positive affect while no cognitive deficits compared to non-drug controls. Possible therapeutic effects include treating alcoholism[95].

  - Side effects: Disorientation, anxiety, fear responses under the influence and nausea[96].

- **N,N-Dimethyltryptamine (DMT):** 5-HT 2A, 2C, and 1A receptors agonist; Sigma-1 and trace amine associated receptors agonist. It is naturally present in healthy adults[97]

  - Implications: Possible therapeutic effect in modulating immune function and reducing inflammation[98]. Currently data on DMT as a clinical aid are still lacking.

  - Side effects: DMT was better tolerated than other 5-HT 2AR agonists[99]

- **Ayahuasca:** Combination of DMT and the β-carboline alkaloids harmine, tetrahydroharmine, and harmaline, preventing the first-pass oxidative deamination of DMT[100].

  - Indications: Pilot studies suggest its potential for enhancing psychological well-being, decreasing problematic **substance abuse**[101] and treating **depression**[102].

  - Side effects: Similar to DMT

Entactogens: refer to a group monoamine releasers and reuptake inhibitors, which may evoke a sense of emotional openness and connection that have shown benefits in posttraumatic stress disorder (PTSD) and anxiety.

- **3,4-Methyl-enedioxy-methamphetamine (MDMA)** acts both as a potent releaser of catecholamine neurotransmitters and as a potent releaser of presynaptic serotonin[103].

  - Indications: MDMA has shown potential therapeutic benefits in **PTSD** and is being evaluated as a treatment for **social anxiety** in adults and **end-of-life anxiety**[104]**.**

[93] Bienemann, B., Ruschel, N. S., Campos, M. L., Negreiros, M. A., & Mograbi, D. C. (2020). Self-reported negative outcomes of psilocybin users: A quantitative textual analysis. PloS one, 15(2), e0229067. https://doi.org/10.1371/journal.pone.0229067
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[103] Karch SB. A historical review of MDMA. Open Forensic Science Journal. 2011;4:20–24
[104] Sessa, B., Higbed, L., & Nutt, D. (2019). A Review of 3,4-methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy. Frontiers in psychiatry, 10, 138. https://doi.org/10.3389/fpsyt.2019.00138

- Side effects: Hyperthermia; Neurotoxicity associated with chronic recreational usage[105].

Dissociatives refer to a group of glutamatergic N-methyl-D-aspartate (NMDA) antagonists. Their therapeutic uses are being explored in depression and substance use disorders

- **Ketamine**: NMDA receptor antagonist with dissociative, anesthetic and hallucinogenic properties last between ten minutes and four hours[106].
  - Indications: **Addiction**[107] and **treatment-resistant depression**[108].
  - Side effects: Chronic abuse would cause serious toxicity to gastrointestinal & kidney, along with persisting cognitive deficits and severe withdrawal symptoms[109].
- **Dextromethorphan (DXM):** Non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptor with effects upon the serotonin transporter (SERT), sigma-1 receptors and α3β4 nicotinic acetylcholine receptors[110]
  - Indications: It has shown potential as an aid in **pain management** [111]and **opioid withdrawal**[112], as a rapid-acting **antidepressant**[113]**.**
  - Side effects: High doses would elicit acute cognitive impairment in attention and memory[114].

Atypical hallucinogens refer to a group of unrelated substances with some hallucinogenic properties Their therapeutic applications range broadly, from treating substance abuse to pain management

- **Ibogaine:** 5-HT 2A agonist, μ-opioid receptors (MOR) agonist, κ-opioid receptor (KOR) antagonist, & N-methyl-D-aspartate (NMDA) antagonist[115]
  - Indications: It has demonstrated effectiveness in treating **substance abuse**, including alcohol, cannabis, cocaine and opioid[116].
  - Side effects: At dosages of >100 mg / kg, it could induce neurotoxicity and cardiac toxicity[117] [118]

[105] Dumont GJ, Verkes RJ. A review of acute effects of 3,4-methylenedioxymethamphetamine in healthy volunteers. J Psychopharmacol. 2006 Mar;20(2):176-87. doi: 10.1177/0269881106063271. PMID: 16510476.
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[113] Lauterbach EC. Dextromethorphan as a potential rapid-acting antidepressant. Med Hypotheses. 2011 May;76(5):717-9. doi: 10.1016/j.mehy.2011.02.003. Epub 2011 Mar 1. PMID: 21367535.
[114] https://www.mayoclinic.org/
[115] Mash DC, Kovera CA, Buck BE, Norenberg MD, Shapshak P, Hearn WL, Sanchez-Ramos J. Medication development of ibogaine as a pharmacotherapy for drug dependence. Ann N Y Acad Sci. 1998 May 30;844:274-92. PMID: 9668685.
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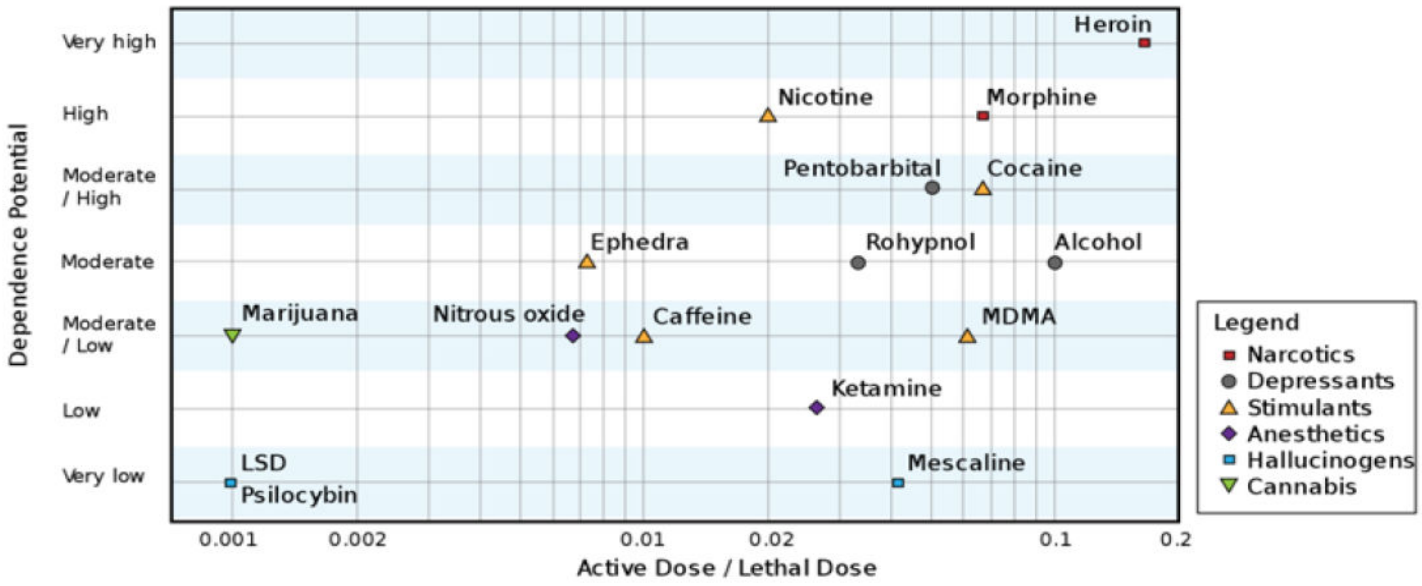
[117] Hoelen DW, Spiering W, Valk GD. Long-QT syndrome induced by the antiaddiction drug ibogaine. N Engl J Med. 2009 Jan 15;360(3):308-9. doi: 10.1056/NEJMc0804248. PMID: 19144953.
[118] O'Hearn E, Molliver ME. Degeneration of Purkinje cells in parasagittal zones of the cerebellar vermis after treatment with ibogaine or harmaline. Neuroscience. 1993 Jul;55(2):303-10. doi: 10.1016/0306-4522(93)90500-f. PMID: 8377927.

- **Safety Profile of Psychedelics**
  - The prohibition of psychedelic drugs as a Scheduled I has led to misinformed public perception that psychedelics are dangerous mind tripping drugs. The DEA has limited both cannabis and psychedelics in allowing meaningful clinical studies to prove the potential efficacy and safety to remove the substances from a Schedule I listing.
  - Follow-up studies of LSD and psilocybin have been shown to be non-addictive and among the least harmful and safest drugs from the safety standpoint (Figure 5).

**Figure 5: Physiological Safety of Psychedelics**




*Source: Gable RS (2006) Acute toxicity of drugs versus regulatory status. Drugs and Society: U.S. Public Policy pp149-158.*

## CLINICAL DEVELOPMENT OF PSYCHEDELICS

- **Contemporary Clinical Studies - 1st Generation Compounds**

  - 1999: First FDA/DEA-approved controlled experiment of psilocybin, Griffiiths *et al.*,[119] , published in 2006, demonstrated that in healthy volunteers, psilocybin can induce mystical-type experiences.

    We will be quoting directly from the abstracts of the publications of this study and others to follow on subsequent pages.

    "*Rationale* Although psilocybin has been used for centuries for religious purposes, little is known scientifically about its acute and persisting effects.

    *Objectives* This double-blind study evaluated the acute and longer-term psychological effects of a high dose of psilocybin relative to a comparison compound administered under comfortable, supportive conditions.

    *Materials and methods.* Participants were hallucinogen-naïve adults reporting regular participation in religious or spiritual activities. Two or three sessions were conducted at two-month intervals. Thirty volunteers received orally administered psilocybin (30mg/70kg) and methylphenidate hydrochloride (40mg/70kg) in counterbalanced order. To obscure the study design, six additional volunteers received methylphenidate in the first two sessions and unblinded psilocybin in a third session. The 8-h sessions were conducted individually. Volunteers were encouraged to close their eyes and direct their attention inward. Study monitors rated volunteers' behavior during sessions. Volunteers completed questionnaires assessing drug effects and mystical experience immediately after and two months after sessions. Community observers rated changes in the volunteer's attitudes and behavior.

    *Results* **Psilocybin produced a range of acute perceptual changes, subjective experiences, and labile moods including anxiety**. Psilocybin also increased measures of mystical experience. At two 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.

    *Conclusions* When administered under supportive conditions, **psilocybin occasioned experiences similar to spontaneously occurring mystical experiences**. The ability to occasion such experiences prospectively will allow rigorous scientific investigations of their causes and consequences."

  - 2008: 14-month follow-up report on psilocybin. During the 14-month follow-up of the original controlled study, Griffiths *et al.*,[120] showed that mystical-type experiences occasioned by psilocybin among subjects mediate the attribution of their personal meaning and spiritual significance.

    "Psilocybin has been used for centuries for religious purposes; however, little is known scientifically about its long-term effects. We previously reported the effects of a double-blind study evaluating the psychological effects of a high psilocybin dose. This report presents the 14-month follow-up and examines the relationship of the follow-up results to data obtained at screening and on drug session days. Participants were 36 hallucinogen-naïve adults reporting regular participation in religious/spiritual activities. Oral psilocybin (30mg/70kg) was administered on one of

[119] Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl). 2006 Aug;187(3):268-83; discussion 284-92. doi: 10.1007/s00213-006-0457-5. Epub 2006 Jul 7. PMID: 16826400.
[120] Griffiths, R., Richards, W., Johnson, M., McCann, U., & Jesse, R. (2008). Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. Journal of psychopharmacology (Oxford, England), 22(6), 621–632. https://doi.org/10.1177/0269881108094300

two or three sessions, with methylphenidate (40mg/70kg) administered on the other session(s). During sessions, volunteers were encouraged to close their eyes and direct their attention inward. At the 14-month follow-up, 58% and 67%, respectively, of volunteers rated the psilocybin-occasioned experience as being among the five most personally meaningful and among the five most spiritually significant experiences of their lives; 64% indicated the experience increased well-being or life satisfaction; 58% met criteria for having had a "complete" mystical experience. Correlation and regression analyses indicated a central role of the mystical experience assessed on the session day in the high ratings of personal meaning and spiritual significance at follow-up. Of the measures of personality, affect, quality of life, and spirituality assessed across the study, only a scale measuring mystical experience showed a difference from screening. When administered under supportive conditions, **psilocybin occasioned experiences similar to spontaneously occurring mystical experiences that, at 14-month follow-up, were considered by volunteers to be among the most personally meaningful and spiritually significant of their lives."**

- 2014: Ketamine in major depressive disorder by Lapidus *et al*.,[121] provides evidence supporting the rapid antidepressant effects of intranasal ketamine without serious adverse effects.

  "*Background*. The N-methyl-D-aspartate glutamate receptor antagonist ketamine, delivered via an intravenous route, has shown rapid antidepressant effects in patients with treatment-resistant depression. The current study was designed to test the safety, tolerability, and efficacy of intranasal ketamine in patients with depression who had failed at least one prior antidepressant trial.

  *Methods*. In a randomized, double-blind, crossover study, 20 patients with major depression were randomly assigned, and 18 completed two treatment days with intranasal ketamine hydrochloride (50 mg) or saline solution. The primary efficacy outcome measure was change in depression severity 24 hours after ketamine or placebo, measured using the Montgomery-Åsberg Depression Rating Scale. Secondary outcomes included persistence of benefit, changes in self-reports of depression, changes in anxiety, and proportion of responders. Potential psychotomimetic, dissociative, hemodynamic, and general adverse effects associated with ketamine were also measured.

  *Results*. Patients showed significant improvement in depressive symptoms at 24 hours after ketamine compared to placebo ($t = 4.39$, $p < .001$; estimated mean Montgomery-Åsberg Depression Rating Scale score difference of 7.6 ± 3.7; 95% confidence interval, 3.9–11.3). Response criteria were met by 8 of 18 patients (44%) 24 hours after ketamine administration compared with 1 of 18 (6%) after placebo ($p = .033$). Intranasal ketamine was well tolerated with minimal psychotomimetic or dissociative effects and was not associated with clinically significant changes in hemodynamic parameters.

  *Conclusions*. This study provides the **first controlled evidence for the rapid antidepressant effects of intranasal ketamine.** Treatment was associated with minimal adverse effects. If replicated, these findings may lead to novel approaches to the pharmacologic treatment of patients with major depression."

[121] Lapidus KA, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, Feder A, Iosifescu DV, Charney DS, Murrough JW. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry. 2014 Dec 15;76(12):970-6. doi: 10.1016/j.biopsych.2014.03.026. Epub 2014 Apr 3. PMID: 24821196; PMCID: PMC4185009.

- 2016: Psilocybin in anxiety and depression. Both Griffiths *et al*.,[122] and Ross *et al*.,[123] has demonstrated the efficacy of psilocybin in alleviating anxiety and depression in patients with life-threatening cancers

  - Griffiths *et al*.,

  "Cancer patients often develop chronic, clinically significant symptoms of depression and anxiety. Previous studies suggest that psilocybin may decrease depression and anxiety in cancer patients. The effects of psilocybin were studied in 51 cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety. This randomized, double-blind, cross-over trial investigated the effects of a very low (placebo-like) dose (1 or 3mg/70kg) vs. a high dose (22 or 30mg/70kg) of psilocybin administered in counterbalanced sequence with 5 weeks between sessions and a six-month follow-up. Instructions to participants and staff minimized expectancy effects. Participants, staff, and community observers rated participant moods, attitudes, and behaviors throughout the study. **High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism, and decreases in death anxiety**. At six-month follow-up, these changes were sustained, with about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety. Participants attributed improvements in attitudes about life/self, mood, relationships, and spirituality to the high-dose experience, with >80% endorsing moderately or greater increased well-being/life satisfaction. Community observer ratings showed corresponding changes. Mystical-type psilocybin experience on session day mediated the effect of psilocybin dose on therapeutic outcomes."

  - Ross *et al*.,

  "*Background*: Clinically significant anxiety and depression are common in patients with cancer, and are associated with poor psychiatric and medical outcomes. Historical and recent research suggests a role for psilocybin to treat cancer-related anxiety and depression.

  *Methods*: In this double-blind, placebo-controlled, crossover trial, 29 patients with cancer-related anxiety and depression were randomly assigned and received treatment with single-dose psilocybin (0.3 mg/kg) or niacin, both in conjunction with psychotherapy. The primary outcomes were anxiety and depression assessed between groups prior to the crossover at 7 weeks.

  *Results*: Prior to the crossover, psilocybin produced immediate, substantial, and sustained improvements in anxiety and depression and led to decreases in cancer-related demoralization and hopelessness, improved spiritual wellbeing, and increased quality of life. **At the 6.5-month follow-up, psilocybin was associated with enduring anxiolytic and anti-depressant effects (approximately 60–80% of participants continued with clinically significant reductions in depression or anxiety), sustained benefits in existential distress and quality of life, as well as improved attitudes towards death.** The psilocybin-induced mystical experience mediated the therapeutic effect of psilocybin on anxiety and depression.

[122] Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. Journal of psychopharmacology (Oxford, England), 30(12), 1181–1197. https://doi.org/10.1177/0269881116675513

[123] Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S. E., Belser, A., Kalliontzi, K., Babb, J., Su, Z., Corby, P., & Schmidt, B. L. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. Journal of psychopharmacology (Oxford, England), 30(12), 1165–1180. https://doi.org/10.1177/0269881116675512

*Conclusions*: In conjunction with psychotherapy, single moderate-dose psilocybin produced rapid, robust and enduring anxiolytic and anti-depressant effects in patients with cancer-related psychological distress."

- 2018: MDMA in posttraumatic stress disorder (PTSD) by Mithoefer *et al.*,[124] indicated that MDMA-assisted psychotherapy can be effective in treating posttraumatic stress disorder patients without evidence of severe adversive event.

  "Twenty patients with chronic posttraumatic stress disorder, refractory to both psychotherapy and psychopharmacology, were randomly assigned to psychotherapy with concomitant active drug (n=12) or inactive placebo (n=8) administered during two 8-h experimental psychotherapy sessions. Both groups received preparatory and follow-up non-drug psychotherapy. The primary outcome measure was the Clinician Administered PTSD Scale, administered at baseline, four days after each experimental session, and two months after the second session. Neurocognitive testing, blood pressure, and temperature monitoring were performed. After two-month follow-up, placebo subjects were offered the option to re-enroll in the experimental procedure with open-label MDMA. Decrease in Clinician-Administered PTSD Scale scores from baseline was significantly greater for the group that received MDMA than for the placebo group at all three time points after baseline. **The rate of clinical response was 10/12 (83%) in the active treatment group versus 2/8 (25%) in the placebo group**. There were no drug-related serious adverse events, adverse neurocognitive effects or clinically significant blood pressure increases. MDMA-assisted psychotherapy can be administered to posttraumatic stress disorder patients without evidence of harm, and it may be useful in patients' refractory to other treatments."

- 2018: Ibogaine in opioid abuse by Mash *et al.*,[125] showed that ibogaine can alleviate drug craving and opioid withdrawal in opioid dependent individuals

  "Ibogaine may be effective for transitioning opioid and cocaine dependent individuals to sobriety. American and European self-help groups provided public testimonials that ibogaine alleviated drug craving and opioid withdrawal symptoms after only a single dose administration. Preclinical studies in animal models of addiction have provided proof-of-concept evidence in support of these claims. However, the purported therapeutic benefits of ibogaine are based on anecdotal reports from a small series of case reports that used retrospective recruitment procedures. We reviewed clinical results from an open label case series (N = 191) of human volunteers seeking to detoxify from opioids or cocaine with medical monitoring during inpatient treatment. Whole blood was assayed to obtain pharmacokinetic measures to determine the metabolism and clearance of ibogaine. Clinical safety data and adverse events (AEs) were studied in male and female subjects. There were no significant adverse events following administration of ibogaine in a dose range that was shown to be effective for blocking opioid withdrawal symptoms in this study. We used multi-dimensional craving questionnaires during inpatient detoxification to test if ibogaine was effective in diminishing heroin and cocaine cravings. Participants also completed standardized questionnaires about their health and mood before and after ibogaine treatment, and at program discharge. One-month follow-up data were reviewed where available to determine if ibogaine's effects on drug craving would persist outside of an inpatient setting. We report here that ibogaine therapy administered in a safe dose range diminishes opioid withdrawal symptoms and reduces drug cravings. Pharmacological treatments for opioid dependence include

[124] Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, Wymer J, Holland J, Hamilton S, Yazar-Klosinski B, Emerson A, Doblin R. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. Lancet Psychiatry. 2018 Jun;5(6):486-497. doi: 10.1016/S2215-0366(18)30135-4. Epub 2018 May 1. PMID: 29728331.

[125] Mash, D. C., Duque, L., Page, B., & Allen-Ferdinand, K. (2018). Ibogaine Detoxification Transitions Opioid and Cocaine Abusers Between Dependence and Abstinence: Clinical Observations and Treatment Outcomes. Frontiers in pharmacology, 9, 529. https://doi.org/10.3389/fphar.2018.00529

detoxification, narcotic antagonists and long-term opioid maintenance therapy. **Our results support product development of single oral dose administration of ibogaine for the treatment of opioid withdrawal during medically supervised detoxification to transition drug dependent individuals to abstinence."**

- 2019: Ayahuasca in treatment-resistant depression (TRD) by Palhano-Fontes *et al.*,[126] provides evidences to support the safety and therapeutic value of ayahuasca in clinical setting, to treat depression.

  "*Background*. Recent open-label trials show that psychedelics, such as ayahuasca, hold promise as fast-onset antidepressants in treatment-resistant depression.

  *Methods.* To test the antidepressant effects of ayahuasca, we conducted a parallel-arm, double-blind randomized placebo-controlled trial in 29 patients with treatment-resistant depression. Patients received a single dose of either ayahuasca or placebo. We assessed changes in depression severity with the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating scale at baseline, and at 1 (D1), 2 (D2), and 7 (D7) days after dosing.

  *Results.* We observed significant antidepressant effects of ayahuasca when compared with placebo at all-time points. MADRS scores were significantly lower in the ayahuasca group compared with placebo at D1 and D2 ($p = 0.04$), and at D7 ($p < 0.0001$). Between-group effect sizes increased from D1 to D7 (D1: Cohen's $d = 0.84$; D2: Cohen's $d = 0.84$; D7: Cohen's $d = 1.49$). Response rates were high for both groups at D1 and D2, and significantly higher in the ayahuasca group at D7 (64% v. 27%; $p = 0.04$). Remission rate showed a trend toward significance at D7 (36% v. 7%, $p = 0.054$).

  *Conclusions.* To our knowledge, this is the first controlled trial to test a psychedelic substance in treatment-resistant depression. **Overall, this study brings new evidence supporting the safety and therapeutic value of ayahuasca, dosed within an appropriate setting, to help treat depression.** This study is registered at http://clinicaltrials.gov (NCT02914769)."

- 2020: Psilocybin in major depressive disorder (MDD) by Davis *et al.*,[127] showed that psilocybin with therapy is effective in treating MDD among patients with cancer.

  "*Importance*. Major depressive disorder (MDD) is a substantial public health burden, but current treatments have limited effectiveness and adherence. Recent evidence suggests that one or two administrations of psilocybin with psychological support produces antidepressant effects in patients with cancer and in those with treatment-resistant depression.

  *Objective*. To investigate the effect of psilocybin therapy in patients with MDD.

  *Design, setting, and participants*. This randomized, waiting list-controlled clinical trial was conducted at the Center for Psychedelic and Consciousness Research at Johns Hopkins Bayview Medical Center in Baltimore, Maryland. Adults aged 21 to 75 years with an MDD diagnosis, not currently using antidepressant medications, and without histories of psychotic disorder, serious suicide attempt, or hospitalization were eligible to participate. Enrollment occurred between August 2017 and April 2019, and the four-week primary outcome assessments were completed in July 2019. A total of 27 participants were randomized to an immediate treatment condition group (n = 15)

[126] Palhano-Fontes, F., Barreto, D., Onias, H., Andrade, K. C., Novaes, M. M., Pessoa, J. A., Mota-Rolim, S. A., Osório, F. L., Sanches, R., Dos Santos, R. G., Tófoli, L. F., de Oliveira Silveira, G., Yonamine, M., Riba, J., Santos, F. R., Silva-Junior, A. A., Alchieri, J. C., Galvão-Coelho, N. L., Lobão-Soares, B., Hallak, J., … Araújo, D. B. (2019). Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychological medicine, 49(4), 655–663. https://doi.org/10.1017/S0033291718001356

[127] Davis AK, Barrett FS, May DG, et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2020 Nov. DOI: 10.1001/jamapsychiatry.2020.3285.

or delayed treatment condition group (waiting list control condition; n = 12). Data analysis was conducted from July 1, 2019, to July 31, 2020, and included participants who completed the intervention (evaluable population).

*Interventions.* Two psilocybin sessions (session 1: 20 mg/70 kg; session 2: 30 mg/70 kg) were given (administered in opaque gelatin capsules with approximately 100 mL of water) in the context of supportive psychotherapy (approximately 11 hours). Participants were randomized to begin treatment immediately or after an eight-week delay.

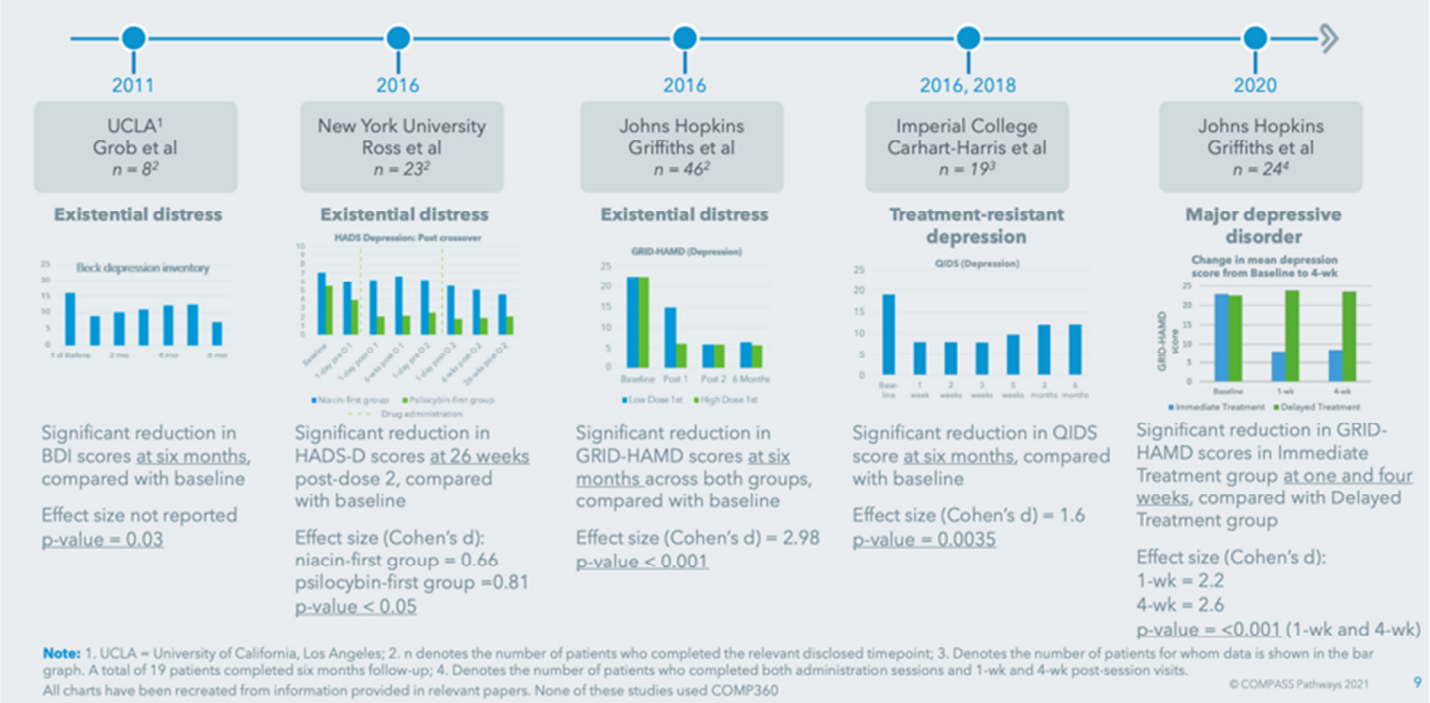
*Main outcomes and measures.* The primary outcome, depression severity was assessed with the GRID-Hamilton Depression Rating Scale (GRID-HAMD) scores at baseline (score of ≥17 required for enrollment) and weeks 5 and 8 after enrollment for the delayed treatment group, which corresponded to weeks 1 and 4 after the intervention for the immediate treatment group. Secondary outcomes included the Quick Inventory of Depressive Symptomatology-Self Rated (QIDS-SR).

*Results.* Of the randomized participants, 24 of 27 (89%) completed the intervention and the week 1 and week 4 post-session assessments. This population had a mean (SD) age of 39.8 (12.2) years, was composed of 16 women (67%), and had a mean (SD) baseline GRID-HAMD score of 22.8 (3.9). The mean (SD) GRID-HAMD scores at weeks 1 and 4 (8.0 [7.1] and 8.5 [5.7]) in the immediate treatment group were statistically significantly lower than the scores at the comparable time points of weeks 5 and 8 (23.8 [5.4] and 23.5 [6.0]) in the delayed treatment group. The effect sizes were large at week 5 (Cohen $d = 2.2$; 95% CI, 1.4-3.0; $P < .001$) and week 8 (Cohen $d = 2.6$; 95% CI, 1.7-3.6; $P < .001$). The QIDS-SR documented a rapid decrease in mean (SD) depression score from baseline to day 1 after session 1 (16.7 [3.5] vs 6.3 [4.4]; Cohen $d = 3.0$; 95% CI, 1.9-4.0; $P < .001$), which remained statistically significantly reduced through the week 4 follow-up (6.0 [5.7]; Cohen $d = 3.1$; 95% CI, 1.9-4.2; $P < .001$). In the overall sample, 16 participants (67%) at week 1 and 17 (71%) at week 4 had a clinically significant response to the intervention (≥50% reduction in GRID-HAMD score), and 14 participants (58%) at week 1 and 13 participants (54%) at week 4 were in remission (≤7 GRID-HAMD score)."

*Conclusions and relevance.* **Findings suggest that psilocybin with therapy is efficacious in treating MDD, thus extending the results of previous studies of this intervention in patients with cancer and depression and of a nonrandomized study in patients with treatment-resistant depression."**

The figure on the next page depicts the summary of some of the academic trials in TRD and other mental health conditions (Figure 6).

**Figure 6: Data Summary of Some of the Academic Studies in TRD and Other Mental Health Conditions**

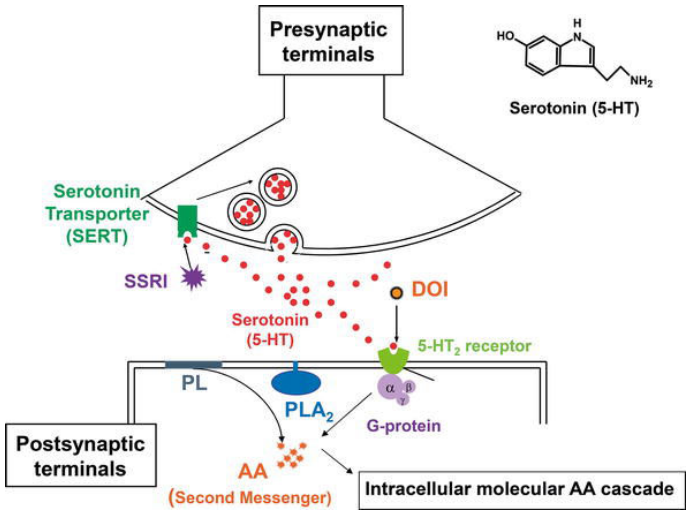



*Source: COMPASS Pathways Presentation, March 2021*

## PSILOCYBIN & ITS THERAPEUTIC POTENTIAL IN MENTAL HEALTH

- **Serotonin and Mental Health**[128]
  - Overview
    - 5-Hydroxytryptamine (5-HT) receptors are activated by the serotonin neurotransmitter, while the 5-HT transporter is responsible for reuptake of serotonin from the synaptic cleft back to presynaptic vesicles[129] (Figure 7).
      - The binding of serotonin to its receptors coupled via a G-protein to PLA2 hydrolyzes arachidonic acid (AA) from membrane phospholipids.
      - Different drugs activate PLA through different routes.
        - 5-HT2A/2C agonist, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) directly binds to 5-HT2 receptors.
        - Selective serotonin reuptake inhibitor (SSRI) such as fluoxetine inhibits 5-HT uptake, thus increasing the availability 5-HT in the synaptic cleft.
    - Altered 5-HT signaling, receptor and serotonin transporter (SERT) functioning are associated with mental disorders, including depression, eating disorders and body dysmorphic disorder.

**Figure 7: Serotonin (5-HT) Synaptic Transmission**




*Source:* *https://www.intechopen.com/books/serotonin/introductory-chapter-from-measuring-serotonin-neurotransmission-to-evaluating-serotonin-post-recepto;*

[128] Lin, S. H., Lee, L. T., & Yang, Y. K. (2014). Serotonin and mental disorders: a concise review on molecular neuroimaging evidence. Clinical psychopharmacology and neuroscience : the official scientific journal of the Korean College of Neuropsychopharmacology, 12(3), 196–202. https://doi.org/10.9758/cpn.2014.12.3.196

[129] Ying Qu (January 21st 2019). Introductory Chapter: From Measuring Serotonin Neurotransmission to Evaluating Serotonin Post-Receptor Signaling Transduction, Serotonin, Ying Qu, IntechOpen, DOI: 10.5772/intechopen.84187. Available from: https://www.intechopen.com/books/serotonin/introductory-chapter-from-measuring-serotonin-neurotransmission-to-evaluating-serotonin-post-recepto

- Dysfunctional Serotonin Pathways in Mental Illnesses
  - **Depression Disorders**
    - *Role of Serotonin Receptors*.
      - Positron emission tomography (PET) imaging studies showed that the binding potential of 5-HT1A receptors in the raphe and mesiotemporal cortex of subjects with MDD was lower than that in controls[130], suggesting that 5-HT receptors are associated with the pathology of MDD.
    - *Role of Serotonin Transporters (SERT)*.
      - Greater availability of SERT was associated with more negative and dysfunctional attitudes among patients with MDD[131].
      - A lower SERT availability binding potential was found in the amygdala of drug-naïve patients with MDD[132], while increased SERT availability in the left frontal cortex, right cingulate cortex and thalamus and striatum among MDD patients[133], suggesting that SERT is associated with MDD.

## Psilocybin as a Serotonin Agonist

- History of Psilocybin
  - Psilocybin is a naturally occurring psychoactive compound found in over 100 species of mushrooms. It can also be synthetically produced. Historically, It is widely used in religious ceremonies, spiritual rituals and recreation predates[134].
  - In the 1960s, it was first studied for medicinal purposes in the Harvard Psilocybin Project, conducted by Harvard Professors Timothy Leary and Richard Alpert.
    - Due to safety and ethical concerns the study was stopped in 1963[135].
  - During the counterculture movement of the 1960s, psilocybin mushrooms became popular.
  - Psilocybin was banned in the 1970s under the Controlled Substances Act.
  - Through the late 1990s and early 2000s. Research on psilocybin was slow due to the restriction imposed by government regulation

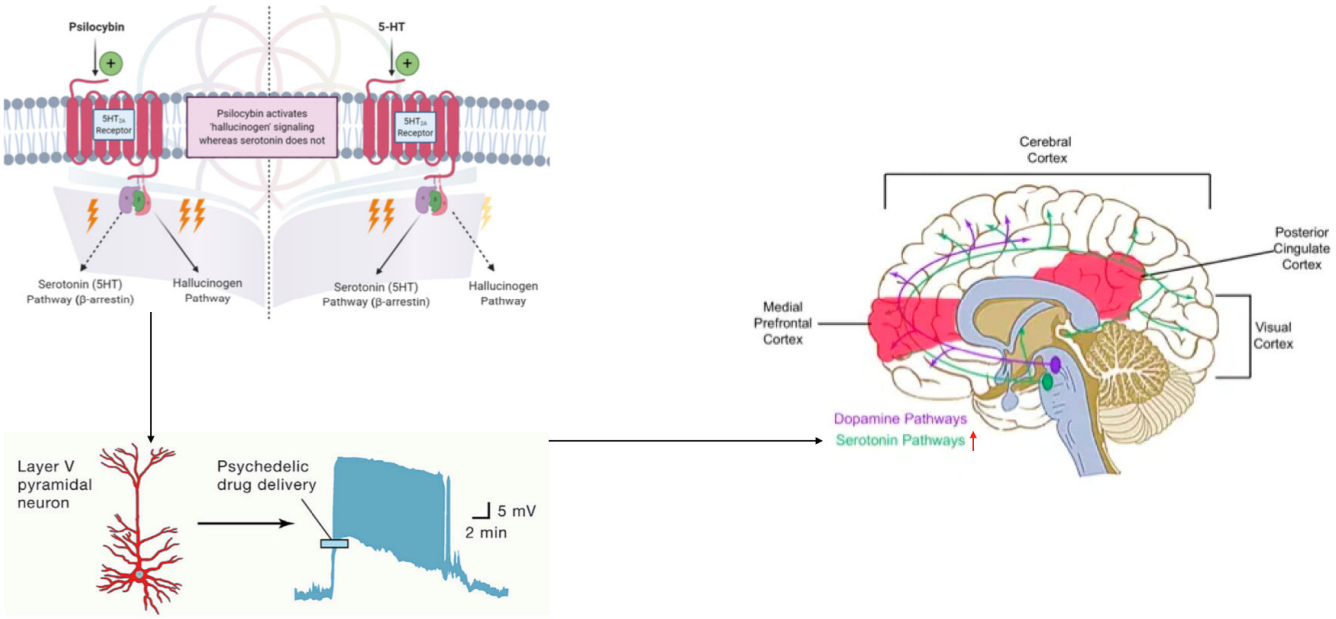
[130] Sargent PA, Kjaer KH, Bench CJ, Rabiner EA, Messa C, Meyer J, Gunn RN, Grasby PM, Cowen PJ. Brain serotonin1A receptor binding measured by positron emission tomography with [11C]WAY-100635: effects of depression and antidepressant treatment. Arch Gen Psychiatry. 2000 Feb;57(2):174-80. doi: 10.1001/archpsyc.57.2.174. PMID: 10665620.
[131] Meyer JH, Houle S, Sagrati S, Carella A, Hussey DF, Ginovart N, Goulding V, Kennedy J, Wilson AA. Brain serotonin transporter binding potential measured with carbon 11-labeled DASB positron emission tomography: effects of major depressive episodes and severity of dysfunctional attitudes. Arch Gen Psychiatry. 2004 Dec;61(12):1271-9. doi: 10.1001/archpsyc.61.12.1271. PMID: 15583118.
[132] Parsey RV, Hastings RS, Oquendo MA, Huang YY, Simpson N, Arcement J, Huang Y, Ogden RT, Van Heertum RL, Arango V, Mann JJ. Lower serotonin transporter binding potential in the human brain during major depressive episodes. Am J Psychiatry. 2006 Jan;163(1):52-8. doi: 10.1176/appi.ajp.163.1.52. PMID: 16390889.
[133] Cannon DM, Ichise M, Rollis D, Klaver JM, Gandhi SK, Charney DS, Manji HK, Drevets WC. Elevated serotonin transporter binding in major depressive disorder assessed using positron emission tomography and [11C]DASB; comparison with bipolar disorder. Biol Psychiatry. 2007 Oct 15;62(8):870-7. doi: 10.1016/j.biopsych.2007.03.016. Epub 2007 Aug 2. PMID: 17678634.
[134] https://www.fieldtriphealth.com/blog/the-history-of-magic-mushrooms
[135] https://www.fieldtriphealth.com/blog/the-history-of-magic-mushrooms

- In 2018, the FDA approved psilocybin as a breakthrough therapy for COMPASS Pathways (CMPS – Buy) to treat depression. Later the FDA designated it as a breakthrough therapy for Usona Institute to treat major depressive orders.
- In addition to COMPASS, Johns Hopkins Center for Psychedelic and Consciousness Research, along with University of Toronto, Beckley Foundation, Usona Institute are conducting clinical research on psilocybin.

- Legal Status of Psilocybin
  - Schedule I drug in the U.S. and UN
  - Schedule III drug in Canada
  - FDA breakthrough therapy designations for COMPASS Pathways and Usona Institute.
- Clinical Progress: 40 total studies completed, Usona Institute, Johns Hopkins, Imperial College and COMPASS Pathways are all engaged in Phase 2 trials with psilocybin for either major depressive disorder or treatment-resistant depression.
- Mechanism of action:
  - **Synaptic Level**: Upon ingestion, psilocybin is rapidly converted to psilocin, which acts as a partial agonist for 5-HT2A, 1A and 2C receptors, whose effects lasting 4-8 hours, leads to activation of both serotonin pathway and hallucinogen pathway[136] (Figure 9, upper left).
  - **Neuronal Level**: The activation of 5-HT receptors in the cortex leads to depolarization of layer V pyramidal cells, which causes rapid repeated neuronal firing. These neurons are responsible for organizing cross-cortical integration. Their activation results in a profound alteration of cortical signaling[137] (Figure 9, lower left).
    - Under normal circumstances, these layer V neurons regulate perceptual and cognitive predictions that form the basis of normal brain processing.
    - Under the influence of psychedelics the brain deviates from its usual predictable ways of signaling, thus allowing new insights into past behavior, memories, actions, feelings, and beliefs.
  - **Brain Network Level**: On the systematic level, psilocybin leads to decreased activity in several brain regions, with some of the largest decreases in default-mode areas including the medial prefrontal cortex and posterior cingulate cortex[138] (Figure 9, right panel).
    - The downregulation of the default mode network was evaluated by imaging studies. There is a profound alteration of brain network connectivity while exposed to psilocybin (vs. placebo; Figure 10)[139].

[136] Nichols D. E. (2016). Psychedelics. Pharmacological reviews, 68(2), 264–355. https://doi.org/10.1124/pr.115.011478
[137] Nutt D, Erritzoe D, Carhart-Harris R. Psychedelic Psychiatry's Brave New World. Cell. 2020 Apr 2;181(1):24-28. doi: 10.1016/j.cell.2020.03.020. PMID: 32243793.
[138] https://sitn.hms.harvard.edu/flash/2015/worth-the-trip-psychedelics-as-an-emerging-tool-for-psychotherapy/
[139] Petri G, Expert P, Turkheimer F, Carhart-Harris R, Nutt D, Hellyer PJ, Vaccarino F. Homological scaffolds of brain functional networks. J R Soc Interface. 2014 Dec 6;11(101):20140873. doi: 10.1098/rsif.2014.0873. PMID: 25401177; PMCID: PMC4223908.

**Figure 9: Psilocybin Mechanism of Action**

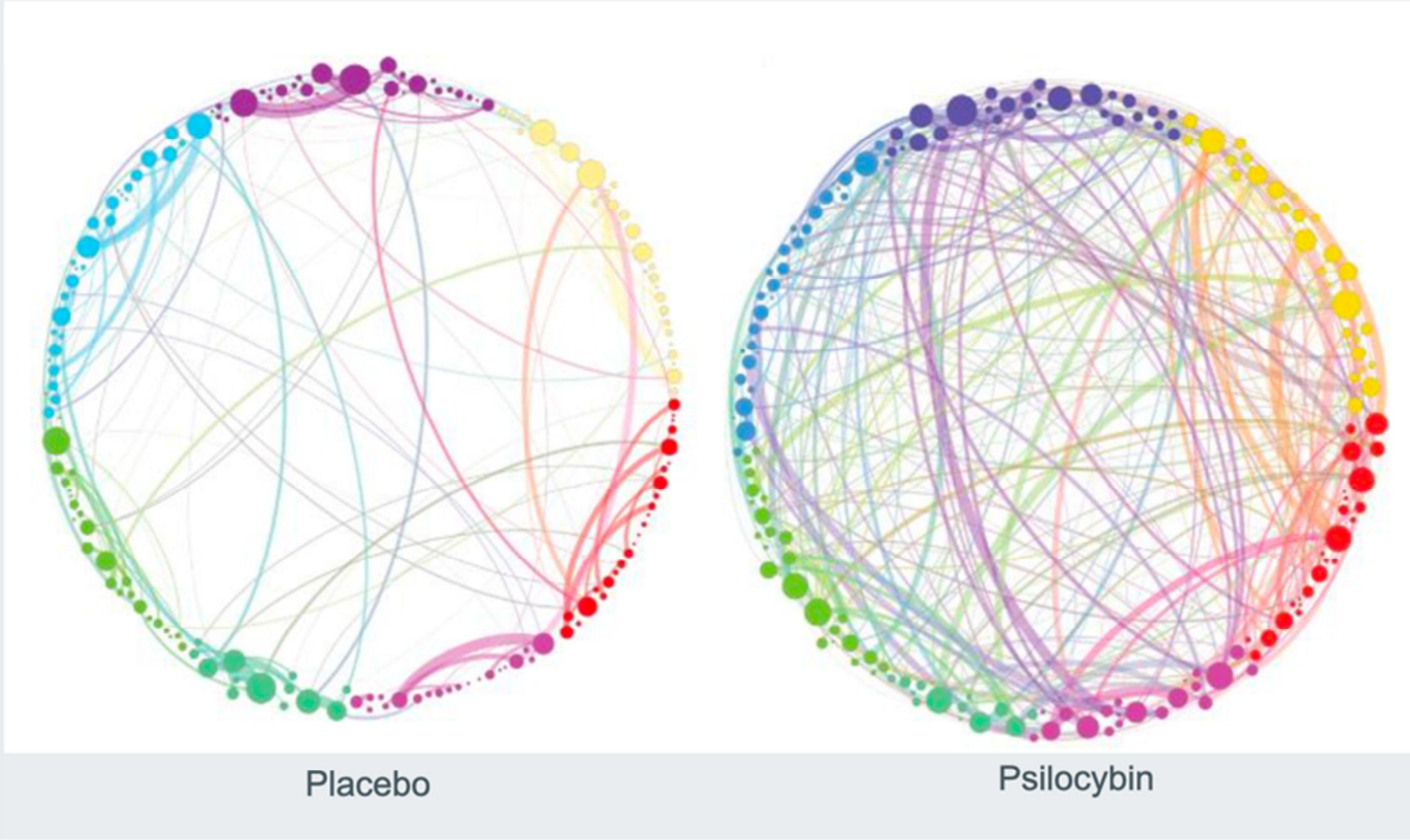



*Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4813425/*

*https://sitn.hms.harvard.edu/flash/2015/worth-the-trip-psychedelics-as-an-emerging-tool-for-psychotherapy/*

*https://www.cell.com/cell/pdf/S0092-8674(20)30282-8.pdf;*

**Figure 10: Alteration of Brain Network Activity Following the Administration of Psilocybin**




*Source: Petri et al, 2014* [140]

- Therapeutic potential: Psilocybin fits in two distinct treatment approaches: macro-dosing or micro-dosing.
  - **Macro-dosing**, a single high-dose session of psilocybin, is linked with mystical experiences and increased openness, which has demonstrated its potential in psychotherapy for treatment-resistant depression and substance abuse[141].
  - **Micro-dosing**, a low dose of psilocybin that could be taken daily or multiple times weekly to enhance mental clarity, creativity and energy, can be used for treating anxiety and mood disorders[142].

[140] Petri G, Expert P, Turkheimer F, Carhart-Harris R, Nutt D, Hellyer PJ, Vaccarino F. Homological scaffolds of brain functional networks. J R Soc Interface. 2014 Dec 6;11(101):20140873. doi: 10.1098/rsif.2014.0873. PMID: 25401177; PMCID: PMC4223908.
[141] Barrett, F.S., Doss, M.K., Sepeda, N.D. et al. Emotions and brain function are altered up to one month after a single high dose of psilocybin. Sci Rep 10, 2214 (2020). https://doi.org/10.1038/s41598-020-59282-y
[142] Anderson, T., Petranker, R., Christopher, A. et al. Psychedelic microdosing benefits and challenges: an empirical codebook. Harm Reduct J 16, 43 (2019). https://doi.org/10.1186/s12954-019-0308-4

## CYBIN INNOVATION

**Sublingual Psylocybin: Innovative Psychedelic Delivery**

- **Metabolism of Psilocybin**
  - Following oral administration, psilocybin is rapidly dephosphorylated under acidic environment of the stomach or by alkaline phosphatase in intestine, kidney and blood to generate the **psilocin**, which easily crosses the blood-brain barrier (BBB) and reaches to the nervous system[143].
    - The hallucinogenic effects of psilocybin usually occur within 30 minutes of ingestion and last between four and six hours[144].
  - **Psilocin** shares similar structure as serotonin. It can be further metabolized by a demethylation and oxidative deamination, catalyzed by liver **monoamine oxidase (MAO)** or aldehyde[145].
  - **Monoamine oxidase (MAO)** is an enzyme that oxidatively deaminates tryptamines and other neuroactive amines in the liver, gut and brain[146].
    - Co-consumption of MAO inhibitors intensifies the hallucinogenic effects of psilocybin[147].
    - The presence of MAO reduces the duration of psilocybin's effect[148].
- **Sublingual Drug Delivery**
  - Definition
    - Sublingual drug delivery is a promising route for fast and direct absorption of compounds into systemic circulation[149].
    - Sublingual area is permeable for drug absorption, bypassing the hepatic first-pass metabolism and leading to greater bioavailability compared with oral ingestion[150].
    - Through passive diffusion mechanism, compounds are rapidly absorbed into the reticulated veins and transported through the facial veins to reach the systemic circulation[151].
  - Benefits
    - The absorption through the sublingual route is 3 to 10 times greater than oral ingestion. Generally, it is mostly rapid in action, while shorter acting in duration[152].

[143] Dinis-Oliveira, R. (2017). Metabolism of psilocybin and psilocin: clinical and forensic toxicological relevance. Drug Metabolism Reviews, 49, 84 - 91.
[144] https://www.medicalnewstoday.com/articles/308850#what-is-psilocybin
[145] Dinis-Oliveira, R. (2017). Metabolism of psilocybin and psilocin: clinical and forensic toxicological relevance. Drug Metabolism Reviews, 49, 84 - 91.
[146] https://www.mdpi.com/1422-0067/21/23/9279/pdf
[147] Halpern JH. (2004). Hallucinogens and dissociative agents naturally growing in the United States. Pharmacol Ther 102:131–138.
[148] https://www.mdpi.com/1422-0067/21/23/9279/pdf
[149] Nayak, Bhabani & Sourajit, Subham & Palo, Manaswini & Behera, Subhasmita. (2017). SUBLINGUAL DRUG DELIVERY SYSTEM: A NOVEL APPROACH. INTERNATIONAL JOURNAL OF PHARMACEUTICS & DRUG ANALYSIS. 5.
[150] Nayak, Bhabani & Sourajit, Subham & Palo, Manaswini & Behera, Subhasmita. (2017). SUBLINGUAL DRUG DELIVERY SYSTEM: A NOVEL APPROACH. INTERNATIONAL JOURNAL OF PHARMACEUTICS & DRUG ANALYSIS. 5.
[151] Ghosh TK, Chatterjee DJ, Pfister WR. Quick dissolving oral dosage forms: Scientific and regulatory considerations from a clinical Pharmacology and Biopharmaceutical perspective, In: Ghosh TK, Pfister WR, editors, Drug Delivery to the Oral Cavity Molecules to Market, NY, USA; CRC Press: 3537-3567 (2005)
[152] Thosar M M. Intra oral sprays -An overview. Int J Pharm Life Sci. 2011; 2(11):1235-1246.

- The sublingual route is an attractive alternative drug delivery method for pediatric, geriatric, and psychiatric patients with dysphagia[153].

- Limitations

  - This delivery system is not well suited to sustained delivery systems[154].

  - Certain criterias for the drugs have to be met, including lipophilic, no bitter taste, doses lower than 20-25 mg, small to moderate molecular weight, good stability in saliva[155] [156].

- **Sublingual Psilocybin: Rationale**

  - There are **potential benefits** of sublingual psilocybin.

    - **Faster onset of action with a lower dose.** Sublingual orally-dissolvable film allows psilocybin to bypass gastrointestinal (GI) and liver metabolism, which can potentially offer rapid delivery of psilocybin with increased rate of absorption & bioavailability and faster onset of action with a lower dose. One milligram of IV administered psylocibin leads to similar plasma levels of psilocin when compared to a 10-20mg oral dose in healthy volunteers.[157]

    - **Increased rate of absorption and bioavailability.** Orally ingested psilocybin capsules have less than 50% of psilocybin reach systemic blood circulation, whereas from oral film the absorption yield could be much higher.

    - **Reduced side effects.** Lower doses of psilocybin and bypassing the GI system may also help reduce certain adverse events, such as nausea.

    - **Reduced pill burden.** Challenges with swallowing are a constant concern in the elderly and certain neurological and psychiatric patients. Therefore, orally dissolvable formulations and zero pill burden are advantageous features for those patients.

[153] [153] Nayak, Bhabani & Sourajit, Subham & Palo, Manaswini & Behera, Subhasmita. (2017). SUBLINGUAL DRUG DELIVERY SYSTEM: A NOVEL APPROACH. INTERNATIONAL JOURNAL OF PHARMACEUTICS & DRUG ANALYSIS. 5.
[154] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Del Rev. 1997; 23: 3-25.
[155] Shojaie AH. Buccal mucosa as a route for systemic drug delivery: A review. J Pharm Pharm Sci. 1998; 1(1): 15-30.
[156] Richman MD, Fox D, Shangraw RF. Preparation and stability of glyceryl trinitrate sublingual tablets prepared by direct compression. J Pharm Sci. 1965; 54(3): 447-451
[157] https://pubmed.ncbi.nlm.nih.gov/9204776/

**Deuterated Tryptamines: Second Generation Psychedelics**

- **Tryptamine: Definition, Classification, Mechanism of Action & Metabolism**
  - Definition: **Tryptamines** are naturally occurring compounds derived from tryptophan. The structure is a combination of a benzene ring and a pyrrole ring, with a two-carbon side chain[158].
  - Classifications of Tryptamines[159]
    - **Simple Tryptamines**
      - Without modification of the indole ring, including dimethyltryptamine (DMT)
      - Modification on the 4-position on the indole ring, including psilocybin
      - Modification on the 5-position on the indole ring, including bufotenine.
    - **Ergolines**
      - Include lysergic acid diethylamide (LSD) and lysergic acid amide (LSA)
  - Mechanism of Action: Generally, tryptamines are agonists at 5HT2a-1a-2c serotonin receptors, leading hallucinogenic properties[160].
    - Certain tryptamine structures facilitate crossing the blood brain barrier (BBB), leading a rapid onset and high potency
    - Certain structures prevent rapid metabolic degradation by monoamine oxidase (MAO), thus increasing the duration of action
  - Metabolism of Tryptamine
    - **Monoamine oxidase (MAO)** is an enzyme that oxidatively deaminated tryptamines and other neuroactive amines in the liver, gut and brain.
    - Some orally-ingested tryptamines may need MAO inhibitors to prevent their peripheral degradation[161].

[158] Tittarelli, R., Mannocchi, G., Pantano, F., & Romolo, F. S. (2015). Recreational use, analysis and toxicity of tryptamines. Current neuropharmacology, 13(1), 26–46. https://doi.org/10.2174/1570159X13666141210222409
[159] Tittarelli, R., Mannocchi, G., Pantano, F., & Romolo, F. S. (2015). Recreational use, analysis and toxicity of tryptamines. Current neuropharmacology, 13(1), 26–46. https://doi.org/10.2174/1570159X13666141210222409
[160] https://www.mdpi.com/1422-0067/21/23/9279/pdf
[161] https://www.mdpi.com/1422-0067/21/23/9279/pdf

- **Deuterated Drugs: Definition, Benefits, Challenges and Examples**

  - Definition of deuterium: Naturally occurring, non-radioactive, stable isotope of hydrogen that contains one proton, one electron, and a neutron instead of one proton and one electron in hydrogen. It effectively doubles the mass of the deuterium isotope without changing its properties significantly, leading to the **kinetic isotope effect -** change in the reaction rate when one of the atoms in the reactants is replaced by one of its heavier isotopes[162].

  - Benefits of Deuterium Strategy[163]

    - Lower costs of preclinical development due to existing preclinical results for non-deuterated compounds

    - Significant body of clinical knowledge have already been derived from non-deuterated compounds, which are useful to guide clinical development and lower clinical costs.

    - Benefit from patent protections of deuterated versions

    - Improved therapies by increasing the half-lives for active metabolites, lower peak-to-trough fluctuations and reduction of the dose

  - Potential Challenges of Patenting Deuterated Drugs[164]

    - The field of deuterium has increasingly been questioned when this approach will become seen as 'obvious' under 35 U.S.C. §103 by patenting authorities, which may change the nature of research and commercialization in this area**.**

    - However, exact metabolic outcomes in clinical trials from deuteration would not be anticipated from the prior art, which has enabled allowance. Therefore, development of deuterated drugs are likely to remain commercially attractive for some time in the future

  - Approved Drug: Deutetrabenazine

    - Austedo (deutetrabenazine) is a deuterated version of tetrabenazine. It was developed by Teva and approved by the FDA in 2017 as a treatment for Huntington's disease

    - It has a longer half-life than the non-deuterated form of tetrabenazine, which had been approved earlier for the same use[165].

      - Deutetrabenazine has a longer half-life for active metabolites and lower peak-to-trough fluctuations for the sum of the metabolites compared with tetrabenazine in steady-state conditions.

      - Deutetrabenazine doses estimated to provide total exposure comparable to tetrabenazine 25 mg are 11.4-13.2 mg.

[162] Shao L, Hewitt MC. The kinetic isotope effect in the search for deuterated drugs. Drug News & Perspectives. 2010 Jul-Aug;23(6):398-404. DOI: 10.1358/dnp.2010.23.6.1426638.
[163] Timmins G. S. (2014). Deuterated drugs: where are we now?. Expert opinion on therapeutic patents, 24(10), 1067–1075. https://doi.org/10.1517/13543776.2014.943184
[164] Timmins G. S. (2014). Deuterated drugs: where are we now?. Expert opinion on therapeutic patents, 24(10), 1067–1075. https://doi.org/10.1517/13543776.2014.943184
[165] DeWitt SH, Maryanoff BE. Deuterated Drug Molecules: Focus on FDA-Approved DeutetrabenazinePublished as part of the Biochemistry series "Biochemistry to Bedside". Biochemistry. 2018 Feb 6;57(5):472-473. doi: 10.1021/acs.biochem.7b00765. Epub 2017 Nov 21. PMID: 29160059.

- **Clinical Development of Deuterated Drugs**

  - C20-D3-Retinyl Acetate

    - **Rationale:** Accumulation of lipofuscin (granular deposits) in the retinal pigment epithelium is a hallmark of major degenerative eye diseases including Stargardt disease. The intrinsic dimerization of vitamin A plays a key role in the formation of ocular lipofuscin. Vitamin A enriched with the stable isotope deuterium at carbon twenty (C20-D(3)-vitamin A) can slow the dimerization process and pathogenesis *in vitro*.

      - Ma *et al.,* showed that C20-D3-vitamin A slows lipofuscin accumulation and electrophysiological retinal degeneration in a mouse model of Stargardt disease[166].

      - Kaufman *et al.,* showed that C20-D(3)-vitamin A slows the formation of vitamin A dimers in wild-type rodents[167].

    - **Clinical Progress:** Open-label Phase 2 study by Alkeus Pharmaceutical (NCT04239625)

      **12-month Interim Result**

      "*Purpose*: Stargardt disease (STGD1) is the most prevalent inherited macular dystrophy. In the absence of an approved treatment, there is a growing interest and need for well-designed and controlled clinical trials. We present the design, baseline data, and one-year interim safety and pharmacokinetics of the prospective "TEASE" clinical trial.

      *Methods*: TEASE is a two-year Phase 2 double-masked placebo-controlled study enrolling 50 subjects with ABCA4-related STGD1 and a well-delineated area of atrophy. The study drug ALK-001, is a selectively deuterated vitamin A used as vitamin A replacement and taken orally once-a-day. Deuterium slows vitamin A dimerization 4-5 fold without inhibiting the visual cycle. Subjects are randomized 2:1 ALK-001:placebo. After one year of treatment, 50% of placebo subjects crossover to ALK-001 in a masked and randomized fashion to compare atrophy progression before and after crossover. The primary endpoint is safety of two dose levels of ALK-001, while efficacy outcomes include atrophy lesion size by fundus autofluorescence (FAF), best-corrected visual acuity (BCVA), reading speed, dark adaptation and retinal sensitivity (microperimetry).

      *Results*: 50 subjects (38 white; 28 female) have been randomized at seven clinical sites. Median age was 46 years (range, 18-60) and disease duration nine years (0-36). 48 of 50 subjects have completed the one-year follow-up visit. On average, 90% of vitamin A was replaced with deuterated vitamin A, which was maintained over time. ALK-001 was well-tolerated with no unexpected adverse reactions, no report of night blindness or impaired dark adaptation, and no clinically-significant increases in liver function tests or in total vitamin A (natural + deuterated). Atrophic lesions at baseline were bilateral in 74% of cases with a 5.1 mm2 (0.3-31.6) median area. 46% and 52% of subjects had BCVA better than 20/40 or worse than 20/100, respectively. Mean retinal sensitivity was 8.3 dB (SD: 4.8). Deep scotomatous areas covered approximately 32% of a 20-deg disc centered on the fovea (approx. 8 mm2, n=75 eyes).

[166] Ma L, Kaufman Y, Zhang J, Washington I. C20-D3-vitamin A slows lipofuscin accumulation and electrophysiological retinal degeneration in a mouse model of Stargardt disease. J Biol Chem. 2011 Mar 11;286(10):7966-7974. doi: 10.1074/jbc.M110.178657. Epub 2010 Dec 14. PMID: 21156790; PMCID: PMC3048683.
[167] Kaufman, Y., Ma, L., & Washington, I. (2011). Deuterium enrichment of vitamin A at the C20 position slows the formation of detrimental vitamin A dimers in wild-type rodents. The Journal of biological chemistry, 286(10), 7958–7965. https://doi.org/10.1074/jbc.M110.178640.

*Conclusions*: The TEASE study is currently the largest, fully-enrolled clinical effort to slow or prevent the progression of STGD1. This feasible study design opens the avenue to similar studies. An expanded study, TEASE-2, is currently enrolling new participants (≧12 years old) in the USA."

- AVP-786

  - **Rationale:** AVP-786 is the deuterated form of dextromethorphan/quinidine (AVP-923), which is an approved treatment for Pseudo-Bulbar Affect. No phase 2 trial was conducted with AVP-786 for the treatment of agitation in AD; the decision to expedite the development of this drug was based on a successful Phase 2 study with AVP-923[168].

  - **Clinical Progress**

    - **Phase 3 study** for evaluating the efficacy, safety and tolerability of AVP-786 for the treatment of agitation in patients with dementia of the **Alzheimer's type** (NCT02442765).

    Two Phase 3 trials with AVP-786 showed mixed findings probably due to the difference in study design. Early study used the Sequential Parallel Comparison Design (SPCD), which demonstrated a significant improvement on the primary endpoint[169]. However, the later randomized, double-blind, and placebo-controlled study failed to meet its primary and key secondary endpoints. AVP-786 did not improve agitation condition in patients, compared to subjects treated with placebo, as measured by the Cohen-Mansfield Agitation Inventory (CMAI)[170].

    - **Phase 3 study** for evaluating the efficacy, safety and tolerability of AVP-786 for treating **negative symptoms of schizophrenia** (NCT03896945).

      - This study will assess the effect of AVP-786 capsules administered orally twice a day in 370 patients with negative symptoms of schizophrenia.

      - The primary endpoint will be change from baseline to week 15 in the Positive and Negative Syndrome Scale (PANSS) Marder Negative Factors Score.

      - Results are expected in August 2022.

[168] Khoury R, Marx C, Mirgati S, Velury D, Chakkamparambil B, Grossberg GT. AVP-786 as a promising treatment option for Alzheimer's Disease including agitation. Expert Opin Pharmacother. 2021 Feb 26:1-13. doi: 10.1080/14656566.2021.1882995. Epub ahead of print. PMID: 33615952.
[169] [169] Khoury R, Marx C, Mirgati S, Velury D, Chakkamparambil B, Grossberg GT. AVP-786 as a promising treatment option for Alzheimer's Disease including agitation. Expert Opin Pharmacother. 2021 Feb 26:1-13. doi: 10.1080/14656566.2021.1882995. Epub ahead of print. PMID: 33615952.
[170] https://www.avanir.com/press/avanir-pharmaceuticals-inc-reports-data-second-phase-3-study-evaluating-investigational-avp

- SD-1077

  - **Rationale:** Levodopa (L-DOPA) is an amino acid precursor of dopamine. It is a prodrug that is converted to dopamine by DOPA decarboxylase. Once L-DOPA is decarboxylated to dopamine, it can compensate for the depleted supply of dopamine in Parkinson's disease[171]. SD-1077 is a selectively deuterated precursor of dopamine structurally related to L-DOPA.

    - Preclinical animal studies showed that deuteration at α- and β-carbon slowed down the breakdown of deuterated dopamine by monoamine oxidase and dopamine β-hydroxylase[172].

  - **Clinical Progress**

    - **Phase 1 study** for evaluating pharmacokinetics, metabolism and safety of SD-1077 compared to L-DOPA/carbidopa following single oral dose administration in healthy subjects[173].

    "*Aims*: SD-1077, a selectively deuterated precursor of dopamine (DA) structurally related to L-3,4-dihydroxyphenylalanine (L-DOPA), is under development for treatment of motor symptoms of Parkinson's disease. Preclinical models have shown slower metabolism of central deuterated DA. The present study investigated the peripheral pharmacokinetics (PK), metabolism and safety of SD-1077.

    *Methods*: Plasma and urine PK of drug and metabolites and safety after a single oral 150 mg SD-1077 dose were compared to 150 mg L-DOPA, each in combination with 37.5 mg carbidopa (CD) in a double-blind, two-period, crossover study in healthy volunteers (n = 16).

    *Results*: Geometric least squares mean ratios (GMRs) and 90% confidence intervals (90% CI) of SD-1077 vs. L-DOPA for Cmax, AUC0–t, and AUC0–inf were 88.4 (75.9–103.1), 89.5 (84.1–95.3), and 89.6 (84.2–95.4), respectively. Systemic exposure to DA was significantly higher after SD-1077/CD compared to that after L-DOPA/CD, with GMRs (90% CI) of 1.8 (1.45–2.24; P = 0.0005) and 2.06 (1.68–2.52; P < 0.0001) for Cmax and AUC0–t and a concomitant reduction in the ratio of 3,4-dihydroxyphenylacetic acid/DA confirming slower metabolic breakdown of DA by monoamine oxidase (MAO). There were increases in systemic exposures to metabolites of catechol O-methyltransferase (COMT) reaction, 3-methoxytyramine (3-MT) and 3-O-methyldopa (3-OMD) with GMRs (90% CI) for SD-1077/CD to L-DOPA/CD for 3-MT exposure of 1.33 (1.14–1.56; P = 0.0077) and 1.66 (1.42–1.93; P < 0.0001) for Cmax and AUC0–t, respectively and GMRs (90% CI) for 3-OMD of 1.19 (1.15, 1.23; P < 0.0001) and 1.31 (1.27, 1.36; P < 0.0001) for Cmax and AUC0–t. SD-1077/CD exhibited comparable tolerability and safety to L-DOPA/CD.

    *Conclusions*: SD-1077/CD demonstrated the potential to prolong exposure to central DA at comparable peripheral PK and safety to the reference L-DOPA/CD combination. A single dose of SD-1077 is safe for further clinical development in Parkinson's disease patients."

[171] https://pubchem.ncbi.nlm.nih.gov/compound/Levodopa
[172] Malmlöf T, Feltmann K, Konradsson-Geuken A, Schneider F, Alken RG, Svensson TH, et al Deuterium-substituted L-DOPA displays increased behavioral potency and dopamine output in an animal model of Parkinson's disease: comparison with the effects produced by L-DOPA and an MAO-B inhibitor. J Neural Transm 2015; 122: 259–272.
[173] Schneider, F., Erisson, L., Beygi, H., Bradbury, M., Cohen-Barak, O., Grachev, I. D., Guzy, S., Loupe, P. S., Levi, M., McDonald, M., Savola, J. M., Papapetropoulos, S., Tracewell, W. G., Velinova, M., & Spiegelstein, O. (2018). Pharmacokinetics, metabolism and safety of deuterated L-DOPA (SD-1077)/carbidopa compared to L-DOPA/carbidopa following single oral dose administration in healthy subjects. British journal of clinical pharmacology, 84(10), 2422–2432. https://doi.org/10.1111/bcp.13702

- DRX-065

  - **Rationale:** DRX-065 is the R-stereoisomer of pioglitazone, which is a drug approved for treating type 2 diabetes and has demonstrated efficacy in nonalcoholic steatohepatitis (NASH). However, pioglitazone's use is associated with many side effects including weight gain, bone fractures and fluid retention[174].

    - In animal models, PXL065 exhibits the same anti-inflammatory property and NASH efficacy as pioglitazone, while with little or no weight gain or fluid retention side effects associated with peroxisome proliferator-activated receptor gamma (PPAR-γ) activation[175].

  - **Clinical Progress:** DRX was originally developed by DeuteRx. Poxel acquired DRX-065 from DeuteRx in 2018, carrying it forward into clinical phases[176].

    - **Phase 1** open-label study to evaluate the safety, tolerability and pharmacokinetics PXL065 (DRX-065)[177].

    It showed that a single oral dose of 22.5 mg DRX-065 is well-tolerated and anticipated to show a better therapeutic profile than pioglitazone and 15 mg PXL065 predicted similar exposure to R-pio as 45 mg pio (Actos®)[178].

    - **Phase 2** study of PXL065 in patients with nonalcoholic steatohepatitis (NASH) (NCT04321343)[179].

    This study will assess the effect of 3 doses of PXL065 compared with placebo on liver fat content in 120 NASH patients 36 weeks after the treatment.

    The primary endpoint will be the change in the percentage of liver fat content measured by magnetic resonance imaging derived proton density fat fraction (MRI-PDFF).

    The result is expected in 2022.

[174] Waugh J, Keating GM, Plosker GL, Easthope S, Robinson DM. Pioglitazone: a review of its use in type 2 diabetes mellitus. Drugs. 2006;66(1):85-109. doi: 10.2165/00003495-200666010-00005. Erratum in: Drugs. 2006;66(3):340-1. PMID: 16398569.
[175] https://www.businesswire.com/news/home/20200901005908/en/Poxel-Initiates-Phase-2-NASH-Trial-for-PXL065-DESTINY-1-in-Biopsy-Proven-Patients
[176] https://www.businesswire.com/news/home/20180829005794/en/Poxel-Expands-Metabolic-Pipeline-Through-Strategic-Acquisition-Agreement-with-DeuteRx-for-DRX-065-a-Novel-Clinical-Stage-Drug-Candidate-for-NASH-and-Other-Programs
[177] https://adisinsight.springer.com/trials/700276018
[178] https://www.poxelpharma.com/en_us/news-media/press-releases/detail/106/poxel-presents-promising-data-for-pxl770-and-pxl065-for-the.
[179] https://www.businesswire.com/news/home/20200901005908/en/Poxel-Initiates-Phase-2-NASH-Trial-for-PXL065-DESTINY-1-in-Biopsy-Proven-Patients

- VX-561

  - **Rationale:** Cystic fibrosis (CF) is a genetic disorder that affects chloride transport in epithelial cells. Ivacaftor acts at the cystic fibrosis transmembrane conductance regulator (CFTR) channel to moderate its activity. VX-561 (deutivacaftor) is a deuterated form of Ivacaftor designed to keep CFTR proteins at the cell surface open longer than ivacaftor to improve the flow of salt and water across the cell membrane[180].

  - **Clinical Progress:**

    - **Phase 2** study to evaluate efficacy and safety of VX-561 in subjects aged 18 years and older with cystic fibrosis (NCT03911713).

    This study will assess the effect of 4 doses of VX-561 in 77 subjects with cystic fibrosis 12 weeks after the treatment.

    The primary endpoint is the absolute change in percent predicted forced expiratory volume in one second (ppFEV1) within 12 weeks after the treatment.

    Results were expected in August 2020 but delayed due to COVID.

- **Deuterated Tryptamine: Benefits & Preclinical Evidence**

  - Benefits of Deuterated Tryptamines

    - Previous clinical knowledge derived from non-deuterated tryptamine compounds that can be used to guide clinical development.

    - Patent protections of psychedelic drugs

    - Improved therapeutic effects modifying the half-lives for active metabolites, lower peak-to-trough fluctuations and reduce the dose.

    - Allow certain tryptamines to be administered orally without MAO inhibitors.

  - Preclinical Results of Deuterated Tryptamines

    - **Alpha, alpha, beta, beta-tetradeutero-DMT (D4DMT)**

      - Baker *et al.,*[181] and Beaton *et al.,*[182] demonstrated the intraperitoneal injection of α,α,β,β-tetradeutero-N,N-dimethyltryptamine exhibited kinetic isotope effect, compared with non-deuterated form of N,N-dimethyltryptamine.

    "A comparison of the brain levels (microgram/g wet weight of tissue) of the hallucinogen N,N-dimethyltryptamine (DMT) and its deuterated analog alpha, alpha, beta, beta-tetradeutero-DMT (D4DMT) as a function of time and dose is reported. It was observed that the presence of deuterium in the alpha- and beta-positions of the ethylamine side-chain led to a potentiation of the level of DMT in brain. Strikingly different dynamics of uptake and clearance were also noted. We propose that these results are due to

[180] https://www.vrtx.com/research-development/pipeline/
[181] Barker SA, Beaton JM, Christian ST, Monti JA, Morris PE. Comparison of the brain levels of N,N-dimethyltryptamine and alpha, alpha, beta, beta-tetradeutero-N-N-dimethyltryptamine following intraperitoneal injection. The in vivo kinetic isotope effect. Biochem Pharmacol. 1982 Aug 1;31(15):2513-6. doi: 10.1016/0006-2952(82)90062-4. PMID: 6812592.
[182] Beaton JM, Barker SA, Liu WF. A comparison of the behavioral effects of proteo-and deutero-N, N-dimethyltryptamine. Pharmacol Biochem Behav. 1982 May;16(5):811-4. doi: 10.1016/0091-3057(82)90240-4. PMID: 6806829.

primary kinetic isotope effect, illustrating the importance of the alpha-position in the metabolism of DMT."

"The behavioral effects of N,N-dimethyltryptamine (DMT) and α, α, β, β-tetradeutero-N,N-dimethyltryptamine (D4DMT) at dose levels of 2.5 and 5.0 mg/kg were examined in rats on a food reinforced schedule. The D4DMT was observed to produce a significantly greater disruption of behavior, have a longer duration of action and a shorter time to onset than DMT. This potentiation, apparently due to the kinetic isotope effect, suggests that DMT is significantly metabolized and deactivated by deamination at the α-position."

- Halberstadt *et al.,* showed that deuterated derivative of 5-MeO-DMT (α,α,β,β-tetradeutero-5-MeO-DMT) can reproduce the behavioral profile produced by 5-MeO-DMT and an MAO inhibitor[183].

"RATIONALE—Ayahuasca is a psychoactive tea prepared from a combination of plants that contain a hallucinogenic tryptamine and monoamine oxidase inhibitors (MAOIs). Behavioral Pattern Monitor (BPM) experiments demonstrated that the combination of 5-methoxy-N,N dimethyltryptamine (5-MeO-DMT) and a behaviorally inactive dose of an MAO-A inhibitor such as harmaline or clorgyline induces biphasic effects on locomotor activity in rats, initially reducing locomotion and then increasing activity as time progresses.

OBJECTIVES—The present study investigated whether the biphasic locomotor profile induced by the combination of 5-MeO-DMT and an MAOI is a consequence of a reduction in the rate of 5-MeO-DMT metabolism. This hypothesis was tested using a deuterated derivative of 5-MeO-DMT (α,α,β,β-tetradeutero-5-MeO-DMT) that is resistant to metabolism by MAO.

RESULTS—Confirming our previous findings, 1.0 mg/kg 5-MeO-DMT (s.c.) had biphasic effects on locomotor activity in rats pretreated with a behaviorally inactive dose of the non-selective MAOI pargyline (10 mg/kg). Administration of 5-MeO-DMT alone, even at doses greater than 1.0 mg/kg, produced only reductions in locomotor activity. Although low doses of α,α,β,β-tetradeutero-5-MeO-DMT (0.3 and 1.0 mg/kg, s.c.) produced only hypoactivity in the BPM, a dose of 3.0 mg/kg induced a biphasic locomotor profile similar to that produced by the combination of 5-MeO-DMT and an MAOI. Receptor binding studies demonstrated that deuterium substitution had little effect on the affinity of 5-MeO-DMT for a wide variety of neurotransmitter binding sites.

CONCLUSIONS—The finding with α,α,β,β-tetradeutero-5-MeO-DMT indicates that the hyperactivity induced by 5-MeO-DMT after MAO inhibition is a consequence of reduced metabolism of 5-MeO-DMT, leading to prolonged occupation of central serotonin receptors. These results demonstrate that deuterated tryptamines may be useful in behavioral and pharmacological studies to mimic the effects of tryptamine/MAOI combinations."

- **a,a-[2H]tryptamine**

  - Systemic injection of tryptamine stimulates locomotion. The nucleus accumbens have the largest concentrations of binding sites for tryptamine in the brain of the rat. In a study conducted by Marien *et al.*

[183] Halberstadt AL, Nichols DE, Geyer MA. Behavioral effects of α,α,β,β-tetradeutero-5-MeO-DMT in rats: comparison with 5-MeO-DMT administered in combination with a monoamine oxidase inhibitor. Psychopharmacology. 2012 Jun;221(4):709-718. DOI: 10.1007/s00213-011-2616-6.

[184], bilateral injections of deuterated analog of tryptamine, a,a-[2H]tryptamine into the accumbens mimics the effect of tryptamine, which increases movement and vertical activity.

"Previous studies have shown that the systemic injection of tryptamine stimulates locomotion in rats and that the nucleus accumbens, a region involved in locomotion, contains the largest concentrations of binding sites for tryptamine in the brain of the rat. The present study examined the behavioral and neurochemical effects of bilateral injections into the accumbens of a deuterated analog of tryptamine, a,a-[2H]tryptamine. Injections of 25 micrograms a,a-[2H]tryptamine increased movements in rats at 25-70 min after injection and increased vertical (rearing) activity at 25-40 min. Injections of 50 micrograms of a,a-[2H]tryptamine produced a transient suppression of movement and vertical activity at 5-15 min, followed by increases in these activities at 40-65 min after injection that were comparable to the increases elicited by 10 micrograms of d-amphetamine. At 30 min after the injection of 50 micrograms a,a-[2H]tryptamine the concentration of dopamine in the nucleus accumbens was increased by 87%, and was preceded by a transient decrease in the level of the metabolite of dopamine homovanillic acid. The levels of 5-hydroxytryptamine and its major metabolite, 5-hydroxyindoleacetic acid in the nucleus accumbens were not changed. Thus, a,a-[2H]tryptamine may interact with tryptamine receptors in the nucleus accumbens to modulate locomotor behavior through mesolimbic dopamine neurons."

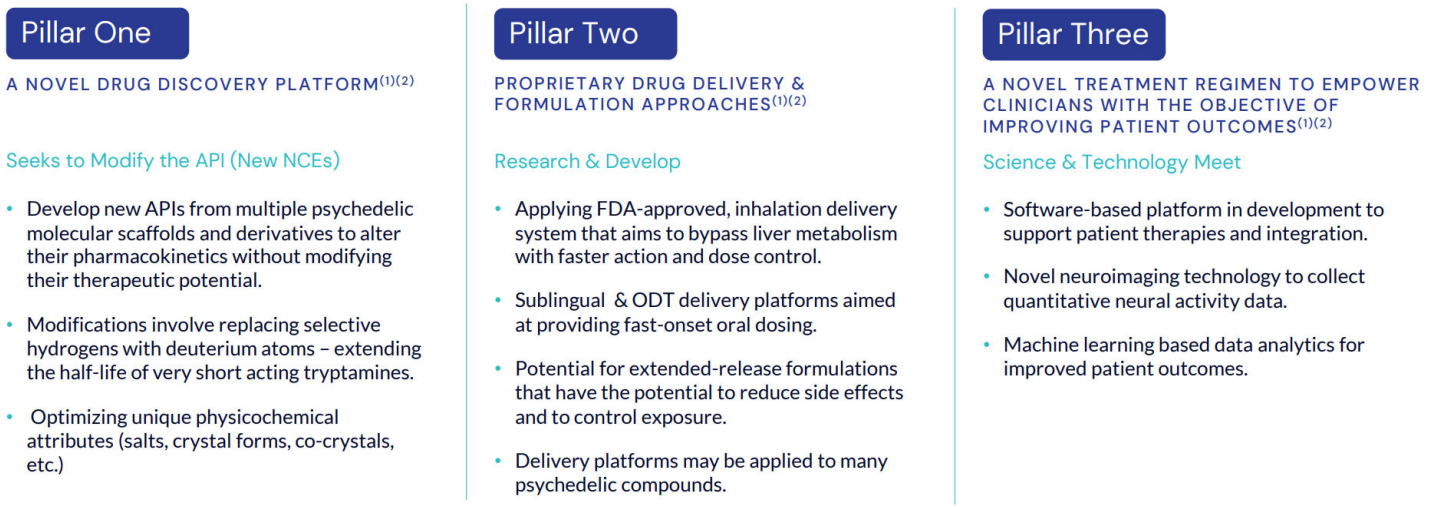
- **Deuterated Tryptamine for Psychiatric Disorders: Rationale**
  - Here are **potential benefits** of novel deuterated tryptamine compounds (CYB003 & CYB004), potential therapies for treatment-resistant psychiatric disorders.
    - **Versatility of tryptamine in treating mental disorders.** Tryptamines are short-acting compounds including psilocybin, dimethyltryptamine (DMT) and lysergic acid diethylamide (LSD), with multiple psychiatric indications.
    - **Patent creation and IP protection** as new compounds. Deuteration strategy would allow the company to develop new active pharmaceutical ingredients (APIs) from multiple psychedelic molecular scaffolds and derivatives to modify their pharmacokinetics without changing their therapeutic potential
    - **Extension of half-life** of very short arting tryptamine through kinetic isotope effect.
    - **Improve the pharmacokinetic profile** by engaging Zydis® orally disintegrating tablet (ODT) technology, which would allow pre-gastric delivery and prevent first pass metabolism.

[184] Marien MR, Gerber R, Boyar WC, Altar CA. Injections of deuterated tryptamine into the nucleus accumbens of the rat: effects on locomotor activity and monoamine metabolism. Neuropharmacology. 1987 Oct;26(10):1481-8. doi: 10.1016/0028-3908(87)90167-5. PMID: 3683763.

## CYBIN: STRATEGY & CLINICAL DEVELOPMENT

- **Overview**
  - Cybin is engaging its proprietary drug discovery platforms, innovative drug delivery systems, novel formulation approaches and treatment regimens (Figure 11) to progress its psychedelic therapeutic pipeline.
    - It is leveraging existing psychedelic molecules that have shown positive early efficacy in certain psychiatric indications, optimizing their pharmacokinetics, bioavailability, and delivery route, and creating second generation and patent-protected psychedelic compounds designed to be scalable and accessible to patients.
    - So far, the company has filed 10 patent applications, covering novel psychedelic compounds, delivery platforms, supportive treatment platforms, drug discovery pipeline of modified and novel tryptamines and phenethylamines.

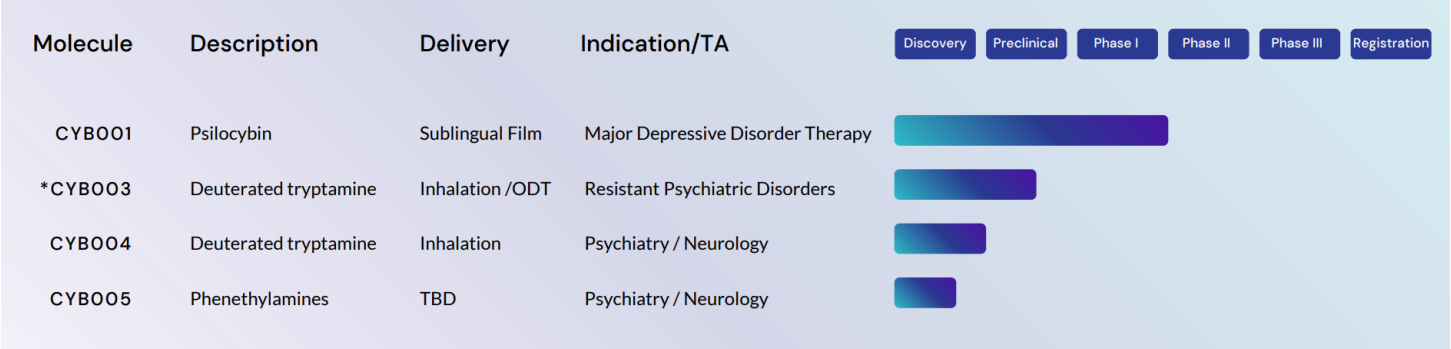
**Figure 11: Three-Pillar Strategy of Cybin**




*Source: Cybin Corporate Presentation, March 2021*

- **Clinical Development for Psychiatric Disorders**
  - Upcoming clinical trials include (Figure 12)**:**
    - **Phase 2a & Phase 2b trials for sublingual psilocybin** in patients with major depressive order (MDD)
    - **Phase 1 clinical trial for deuterated tryptamine CYB003** is planned for 2021
    - **Phase 1 clinical trial for phenethylamines** could be initiated in 2022

**Figure 12: Cybin Pipeline**




*Source: Cybin Corporate Presentation, March 2021*

- **Phase 2a & Phase 2b Trial for Sublingual Psilocybin in Patients with MDD**

The Phase 2a trial will be conducted through the University of the West Indies in Jamaica and Caribbean Institute for Health Research. The study will allow Cybin to use the safety and efficacy date to enter additional markets including the U.S., Canada and Europe. Those clinical trials will be conducted based on International Council on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, aiming to utilize clinical data in jurisdictions such as USA, Canada and Europe[185].

The study is composed of two parts: Phase 2a & Phase 2b (Figure 13).

- Phase 2a
  - **Purpose.** The primary goal is to select the bioequivalence (BE) dose of psilocybin that is administrable with an oral film in subjects with MDD, comparable to an oral 25 mg psilocybin capsule.
  - **Study Design**. Randomised, parallel group, open-label study to evaluate the safety and efficacy of four oral sublingual psilocybin film ascending doses against an oral 25 mg psilocybin capsule.
  - **Participants**. Fifty patients diagnosed with moderate MDD (MADRS Montgomery-Åsberg Depression Rating Scale score 18-34) will be randomised in a 1:1:1:1:1 ratio to 1mg psilocybin film, 3mg psilocybin film, 5mg psilocybin film, 7mg psilocybin film and 25mg psilocybin capsule.
  - **Assessments**. Safety endpoints include adverse events (AEs) & serious AEs (SAEs) and various clinical laboratory tests. Efficacy endpoints include efficacy at 30 days and during four months follow-up, assessed by changes in MADRS scores.
- Phase 2b
  - **Purpose.** The primary goal is to evaluate clinical efficacy by changes in MADRS score after oral psilocybin film, compared to placebo film.
  - **Study Design**. Randomised, double-blind, placebo-controlled study to evaluate the effects of selected dose of psilocybin film compared with placebo in patients with moderate MDD.
  - **Participants**. Additional 120 patients with moderate MDD will be enrolled in a safety and efficacy trial that starts immediately after the Phase 2a study, following the same protocol as Phase 2a. Among those patients, 80 of them will be administered with the selected dose derived from Phase 2a study, while 40 of them will receive placebo film.
  - **Assessments**. Safety endpoints include adverse events (AEs) & serious AEs (SAEs) and various clinical laboratory tests. Efficacy endpoints include efficacy at 30 days and during four-month follow-up compared to placebo film, assessed by changes in MADRS scores.

[185] https://thedalesreport.com/interviews/cybin-comes-to-market-3-weeks-after-closing-the-largest-raise-in-canadian-psychedelics-history/

**Figure 13: Sublingual Psilocybin Clinical Trial Design**

PHASE IIa

| | Psilocybin (PY) | | | | | |
|---|---|---|---|---|---|---|
| | Sublingual Film | | | | Caps | Total Patients |
| Randomized Parallel Group Open Label BE Study | 1 mg | 3 mg | 5 mg | 7 mg | 25 mg | |
| | 8 | 8 | 8 | 8 | 8 | 40 |

PHASE IIb

| | Selected Dose PY Sublingual Film | Placebo | Total Patients |
|---|---|---|---|
| Randomized Double Blind Placebo Controlled Safety & Efficacy Study | 80 | 40 | 120 |

- MDD Patients with moderate depression (MADRS Montgomery-Åsberg Depression Rating Scale score 18 34).
- Primary efficacy at 30 days.
- Patients will be followed for 4 months for safety and efficacy.

| Duration: Approx. 12 Months |
|---|
| Clinical trial will adhere to ICH and GCP guidelines, with the aim to utilize clinical data in jurisdictions such as USA, Canada and Europe.[1][2] |

*Source: Cybin Corporate Presentation, March 2021*

- **Drug Discovery Platform – Deuterated Tryptamine**

The goal of the platform is to create novel second generation psychedelics based on well-known scaffolds, optimizing their pharmacokinetic profiles to provide shorter duration of action and reduced side effects. There are two main approaches to achieve the goal:

- Deuteration. By modifying the compound through replacing selective hydrogens with deuterium atoms, it can extend the half-life of short-acting tryptamines.

- Optimization of Drug Delivery. By inhalation, sublingual or orally dissolving tablet (ODT) delivery, it would allow the compounds to bypass liver metabolism with faster action and dose control and potentially extend the compound release.

  - Cybin has signed a drug development agreement with **Catalent**, to apply Catalent's proprietary Zydis® orally disintegrating tablet (ODT) technology for the delivery of its **deuterated tryptamine (CYB003),** a candidate drug for treatment-resistant psychiatric disorders[186].

  - Catalent is a global provider of delivery technologies and development solutions for drugs, biologics, and consumer health products. It has a variety of oral, injectable, and respiratory delivery technologies to the needs of the pharmaceutical industry[187].

  - With the Zydis technology freeze-dried tablets are created that disperse instantly in the mouth without water. It is prepared in four stages (Figure 14)[188]:

    - **Stage One**: Mixing. The compound is formulated into a liquid solution or suspension.

    - **Stage Two**: Filling and freezing. The liquid is filled into blisters and passed through a cryogenic freezing tunnel in order to control the size of the crystals.

    - **Stage Three**: Lyophilization. The frozen units are then transferred to freeze dryers.

    - **Stage Four**: Sealing. The blisters containing the dried units are sealed to protect the product and ensure long-term stability.

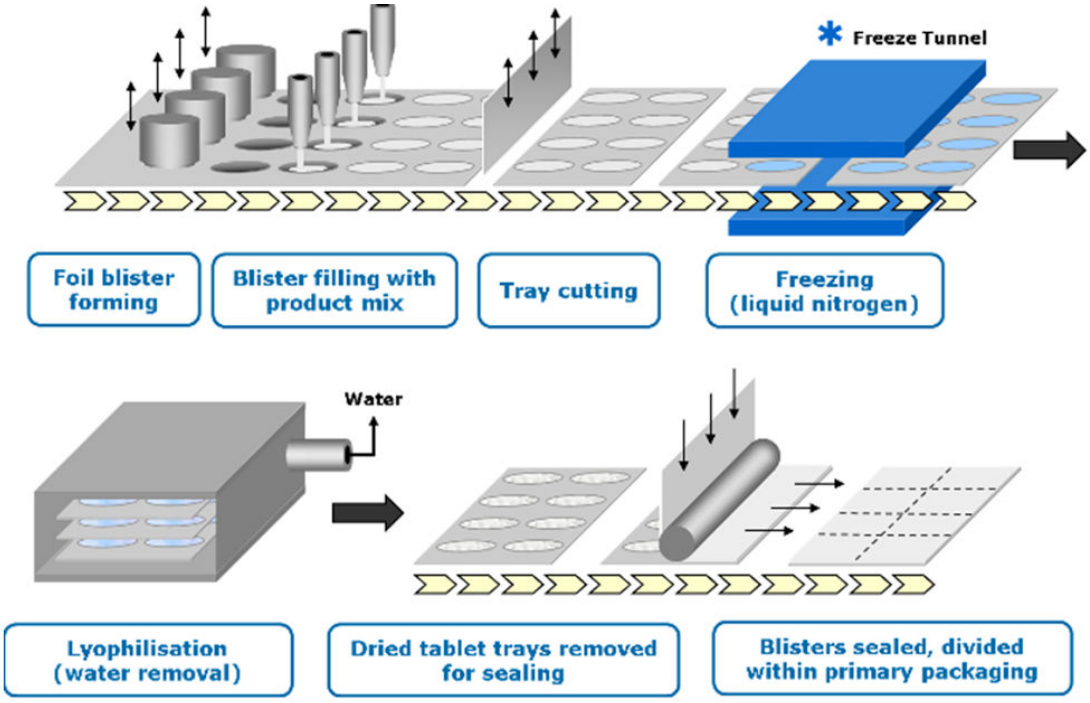
- Candidate Drugs: Deuterated tryptamines in inhalation/ODT formulation (CYB003) and its inhaled formulation of CYB004.

  - Cybin has advanced CYB003 and CYB004 towards pre-clinical studies. These studies are required by FDA enabling trials for investigational new drug applications[189]. The company recently disclosed the achievememt of proof-of-concept utilizing the so-called CEREP 5-HT selectivity panel and the initial target indication in Alcohol Use Disorder for CYB003.

  - Once completed, the results will be submitted to FDA, Health Canada and EMA. Upon regulatory approval these candidates would then advance into Phase 1 human clinical trials for targeting treatment-resistant psychiatric disorders and certain forms of addiction in 2021[190].

[186] https://www.businesswire.com/news/home/20210322005181/en/Cybin-Signs-Drug-Development-Agreement-with-Catalent-for-its-Fast-Dissolve-Formulation-of-Novel-Deuterated-Tryptamine-CYB003
[187] https://www.catalent.com/about-us/overview/
[188] www.catalent.com/index.php/offerings/A-Z-Offerings/zydis
[189] https://finance.yahoo.com/news/cybin-advances-ind-enabling-studies-111500310.html
[190] https://finance.yahoo.com/news/cybin-advances-ind-enabling-studies-111500310.html

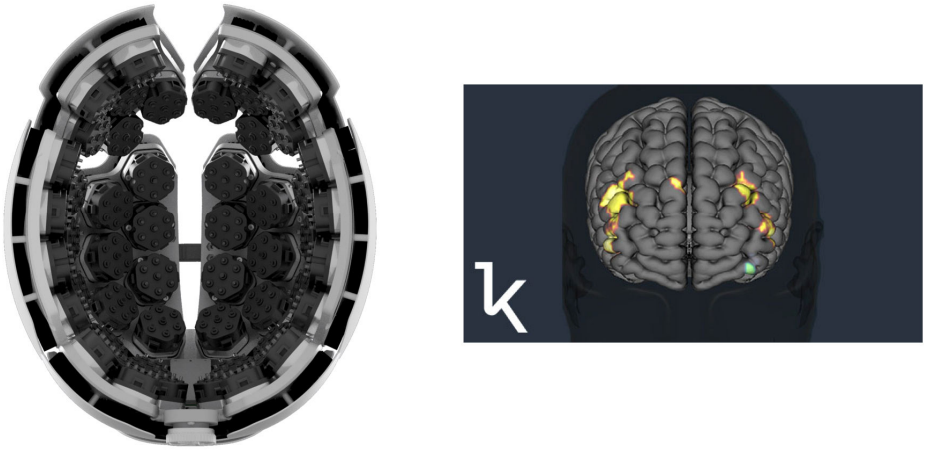
**Figure 14: Zydis® Orally Disintegrating Tablet (ODT) Technology**




*Source: www.catalent.com/index.php/offerings/A-Z-Offerings/zydis;*

- **Technology Partnership Program with Kernel**
  - Cybin has partnered with Kernel to leverage its Flow neuroimaging technology to quantify brain activity in real-time during psychedelic experiences[191].
    - Kernel is a medical device company that specializes in developing brain-recording technologies. Its non-invasive brain interface acquires neural signals with similar quality as functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), electrocorticography (ECoG) and electroencephalography (EEG)[192].
    - Kernel Flow is a non-invasive brain interface that records real-time cortical hemodynamics in order to track brain activity (Figure 15, left panel), which is the first commercially-scalable time-domain near-infrared spectroscopy (TD-fNIRS) system in the world[193].
    - Kernel Flow technology can acquire brain activity in **real time**.
      - Kernel Flow functional data, showing larger (yellow hues) or smaller (blue hues) activations during the impulse control task (Figure 15, right panel).
      - This feature can enable Cybin to quantify psychedelic experience during the human clinical trials.
    - Machine learning can use the data acquired by Kernel's Flow to design personalized treatment for each individual patient in order to improve patient outcomes[194].

**Figure 15: Kernel Flow**



*Source: https://www.kernel.com/news/sleep-and-impulse-control; https://www.kernel.com/flow;*

[191] https://www.kernel.com/news/kernel-cybin-partner
[192] https://www.crunchbase.com/organization/kernel-co
[193] https://www.kernel.com/flow
[194] Cybin Corporate Presentation, March 2021

## COMPETITION

- **Current and Potential Future Competition**
  - Categories of Compounds and Indications (Figure 16)
    - **First generation compounds (in blue)**: A number of psychedelic drug companies are developing potential therapeutics for various CNS disorders, ranging from depression, anxiey disorders, substance abuse disorders, posttraumatic stress disorder and eating disorder (in black).
    - **Second generation compounds (in red)**: Most companies are still in early stage of development, preparing for IND submission allowing clinical trials.

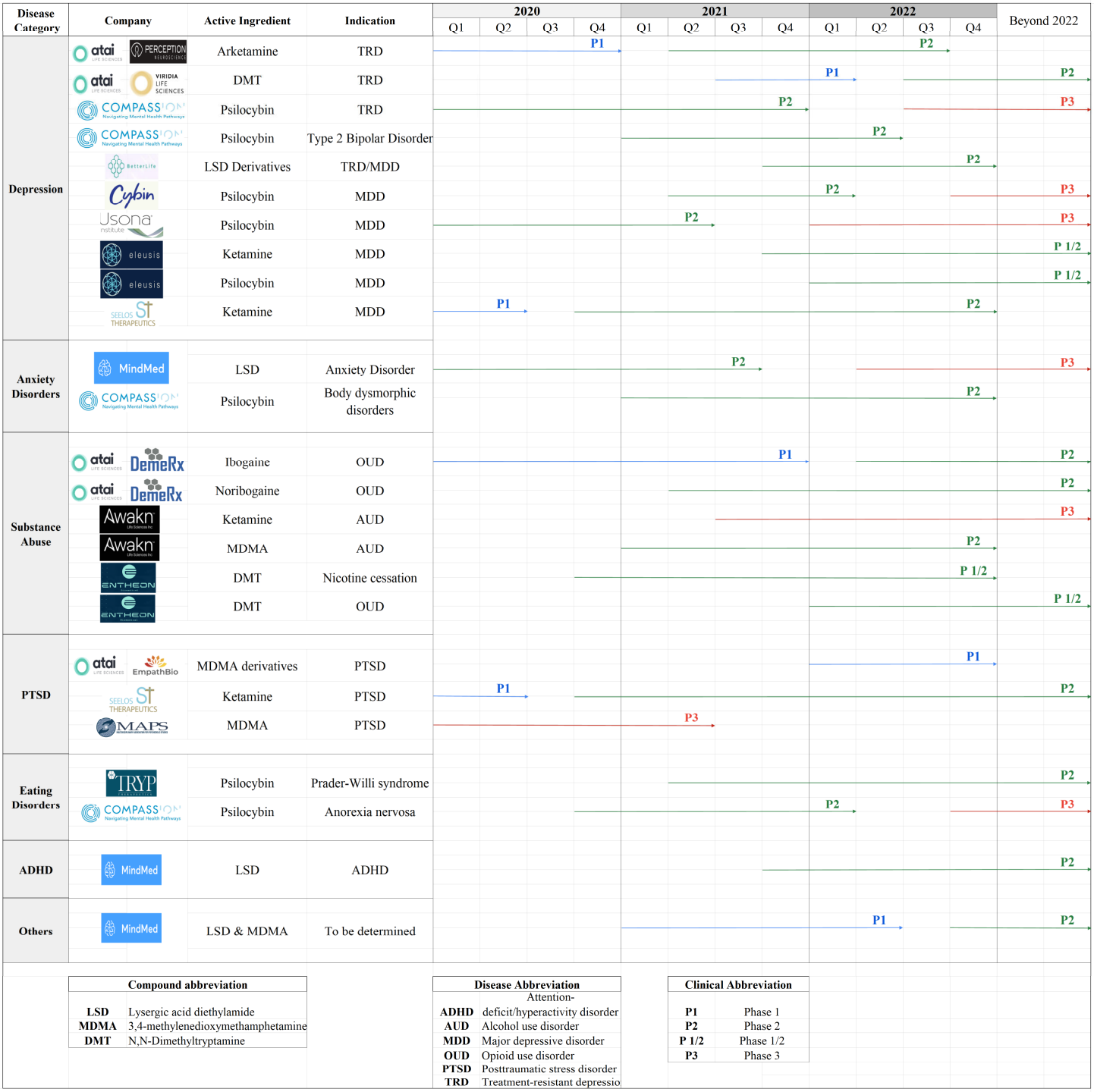
**Figure 16: 1st and 2nd Generation: Drug Discovery Opportunities**


*Source: Company press releases, FDA submissions and ROTH Capital Partners Resesarch*

- Clinical Progression (Figure 17):
  - **Companies**: This year we shall expect clinical result updates from:
    - COMPASS: Psilocybin in TRD program (Phase 2b)
    - Atai & DemeRx: Ibogaine in opioid use disorder program (Phase 1)
    - MindMed: LSD in anxiety disorder program (Phase 2)
    - Cybin: Sublingual film psilocybin in MDD (Phase 2a)
  - **Nonprofit organizations**: Besides pharmaceutical companies, non-profit organizations, including MAPS and Usona Institute, have exciting clinical programs under development. Data from those clinical trials would provide valuable insights to investors to determine which psychedelic companies have the most promising clinical programs. This year we shall expect clinical ressult updates from:
    - MAPS: MDMA in PTSD program (Phase 3)
    - Usona Institute: Psilocybin in MDD (Phase 2)

To help investors track the clinical progress of those programs, we summarized the clinical progress of psychedelic programs for each companies and non-profit organizations in the timeline chart below (Figure 17).

**Figure 17: Timeline of Clinical Trials from the Beginning to the Expected Completion**




*Source: Company Presentations, January-March, 2021;clinicaltrials.gov*

## PRICING, MARKET POTENTIAL & NPV

Cybin plans to pursue major depressive disorder for CYB001 (sublingual film formulation of psilocybin) as a first indication. We believe that initial use of CYB001 will occur in refractory, treatment-resistant depression (TRD) patients.

TRD remains a large unmet need, with over 30% of those who are treated with medications becoming refractory to them in the U.S.[195]. The numbers are staggering: 1.1% of all Americans, or 3.7MM people are no longer responsive to treatment alternatives. The excess annual medical cost is over $20,000 for TRD patients. We believe that CYB001 could offer an ideal, once in a lifetime or very infrequently administered treatment alternative. We estimate that the drug will be priced at par ($20,000 in the U.S. and $13,000 in the EU5) with the excess cost of annual care. We assume that CYB001 could launched in the U.S. and EU5 in 2025 and 2026, respectively.

We assume that five years following launch, in 2030, the drug could achieve ~$5B in sales in the U.S. (5% peak market share; Figure 18) and ~$3B in EU5 (5% peak market share; Figure 19), where the drug would be sold at a price 2/3 of the U.S. list price, in our calculation.
The combined risk-adjusted (25% probability of success) fully taxed (21%) NPV for the CYB001 program in TRD is $2B ($9/share), according to our model (Figure 20).

Considering that other programs are at an earlier stage and at this point it is uncertain which one(s) are going to be fully developed, we opted to ascribe a technology value for these programs totaling $200MM ($1/share).

[195] https://www.psychiatrist.com/read-pdf/29169/

**Figure 18: Market Model - U.S.**

| Treatment-Resistant Depression (TRD) Market - U.S. | | | 2021E | 2022E | 2023E | 2024E | 2025E | 2026E | 2027E | 2028E | 2029E | 2030E | 2031E | 2032E | 2033E | 2034E | 2035E |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ($ (USD) in thousands) | | | | | | | | | | | | | | | | | |
| U.S. Population | | | 333,317 | 335,650 | 338,000 | 340,366 | 342,748 | 345,148 | 347,564 | 349,997 | 352,447 | 354,914 | 357,398 | 359,900 | 362,419 | 364,956 | 367,511 |
| Suffering from major depressive disorder (7.1%)* | | | 23,666 | 23,831 | 23,998 | 24,166 | 24,335 | 24,505 | 24,677 | 24,850 | 25,024 | 25,199 | 25,375 | 25,553 | 25,732 | 25,912 | 26,093 |
| Treated with medication (50%) | | | 11,833 | 11,916 | 11,999 | 12,083 | 12,168 | 12,253 | 12,339 | 12,425 | 12,512 | 12,599 | 12,688 | 12,776 | 12,866 | 12,956 | 13,047 |
| TRD (30.9%) | | | 3,656 | 3,682 | 3,708 | 3,734 | 3,760 | 3,786 | 3,813 | 3,839 | 3,866 | 3,893 | 3,920 | 3,948 | 3,976 | 4,003 | 4,031 |
| Market Penetration | | | | | | | 0.1% | 0.5% | 1% | 2% | 3% | 5% | 5% | 5% | 5% | 5% | 5% |
| Patients treated | | | | | | | 4 | 19 | 38 | 77 | 116 | 195 | 196 | 197 | 199 | 200 | 202 |
| Treatment cost** | | | | | | | $20 | $21 | $22 | $23 | $24 | $26 | $27 | $28 | $30 | $31 | $33 |
| **Total U.S. sales** | | | | | | | **$75,196** | **$397,540** | **$840,678** | **$1,777,782** | **$2,819,607** | **$4,968,852** | **$5,253,815** | **$5,555,122** | **$5,873,708** | **$6,210,565** | **$6,566,741** |
| COGS (5%) | | | | | | | $3,760 | $19,877 | $42,034 | $88,889 | $140,980 | $248,443 | $262,691 | $277,756 | $293,685 | $310,528 | $328,337 |
| R&D | | | $9,600 | $9,600 | $20,000 | $25,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 |
| SG&A | | | $9,600 | $9,600 | $17,000 | $20,000 | $50,000 | $75,000 | $100,000 | $100,000 | $100,000 | $100,000 | $100,000 | $100,000 | $100,000 | $100,000 | $100,000 |
| Total expenses | | | $19,200 | $19,200 | $37,000 | $45,000 | $73,760 | $114,877 | $162,034 | $208,889 | $260,980 | $368,443 | $382,691 | $397,756 | $413,685 | $430,528 | $448,337 |
| **EBT** | | | **($19,200)** | **($19,200)** | **($37,000)** | **($45,000)** | **$1,436** | **$282,663** | **$678,644** | **$1,568,893** | **$2,558,626** | **$4,600,409** | **$4,871,124** | **$5,157,365** | **$5,460,022** | **$5,780,037** | **$6,118,404** |
| Probability of success | 25% | | 25% | 70% | 70% | 90% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |
| **Probability-adjusted EBT** | | | **($19,200)** | **($19,200)** | **($37,000)** | **($45,000)** | **$359** | **$70,666** | **$169,661** | **$392,223** | **$639,657** | **$1,150,102** | **$1,217,781** | **$1,289,341** | **$1,365,006** | **$1,445,009** | **$1,529,601** |
| Discount rate | 15% | | | | | | | | | | | | | | | | |
| **NPV of EBT** | | **$1,724,370** | | | | | | | | | | | | | | | |

*Prevalence: 1.1% of the U.S. population suffers from TRD: https://www.psychiatrist.com/read-pdf/29169/

**The approximate incremental cost of treating TRD patients: https://www.psychiatrist.com/read-pdf/29169/

*Source: ROTH Capital Partners estimates*

**Figure 19: Market Model - EU5**

| Treatment-Resistant Depression (TRD) Market - EU5 | 2021E | 2022E | 2023E | 2024E | 2025E | 2026E | 2027E | 2028E | 2029E | 2030E | 2031E | 2032E | 2033E | 2034E | 2035E |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ($ (USD) in thousands) | | | | | | | | | | | | | | | |
| EU5 Population | 327,275 | 329,566 | 331,873 | 334,196 | 336,535 | 338,891 | 341,263 | 343,652 | 346,058 | 348,480 | 350,920 | 353,376 | 355,850 | 358,341 | 360,849 |
| Suffering from major depressive disorder (7.1%)* | 23,237 | 23,399 | 23,563 | 23,728 | 23,894 | 24,061 | 24,230 | 24,399 | 24,570 | 24,742 | 24,915 | 25,090 | 25,265 | 25,442 | 25,620 |
| Treated with medication (50%) | 11,618 | 11,700 | 11,781 | 11,864 | 11,947 | 12,031 | 12,115 | 12,200 | 12,285 | 12,371 | 12,458 | 12,545 | 12,633 | 12,721 | 12,810 |
| TRD (30.9%) | 3,590 | 3,615 | 3,640 | 3,666 | 3,692 | 3,717 | 3,743 | 3,770 | 3,796 | 3,823 | 3,849 | 3,876 | 3,903 | 3,931 | 3,958 |
| Market Penetration | | | | | | 0.1% | 0.5% | 1% | 2% | 3% | 5% | 5% | 5% | 5% | 5% |
| Patients treated | | | | | | 4 | 19 | 38 | 76 | 115 | 192 | 194 | 195 | 197 | 198 |
| Treatment cost** | | | | | | $13 | $14 | $15 | $15 | $16 | $17 | $18 | $19 | $20 | $20 |
| **Total EU5 sales** | | | | | | **$49,071** | **$259,424** | **$548,603** | **$1,160,132** | **$1,839,998** | **$3,242,536** | **$3,428,495** | **$3,625,120** | **$3,833,020** | **$4,052,844** |
| COGS (5%) | | | | | | $2,454 | $12,971 | $27,430 | $58,007 | $92,000 | $162,127 | $171,425 | $181,256 | $191,651 | $202,642 |
| R&D | $9,600 | $9,600 | $20,000 | $25,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 | $20,000 |
| SG&A | $9,600 | $9,600 | $17,000 | $20,000 | $50,000 | $75,000 | $100,000 | $100,000 | $100,000 | $100,000 | $100,000 | $100,000 | $100,000 | $100,000 | $100,000 |
| Total expenses | $19,200 | $19,200 | $37,000 | $45,000 | $70,000 | $97,454 | $132,971 | $147,430 | $178,007 | $212,000 | $282,127 | $291,425 | $301,256 | $311,651 | $322,642 |
| **EBT** | **($19,200)** | **($19,200)** | **($37,000)** | **($45,000)** | **($70,000)** | **($48,383)** | **$126,453** | **$401,173** | **$982,125** | **$1,627,998** | **$2,960,409** | **$3,137,071** | **$3,323,864** | **$3,521,369** | **$3,730,202** |
| Probability of success 25% | 25% | 70% | 70% | 90% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |
| **Probability-adjusted EBT** | **($19,200)** | **($19,200)** | **($37,000)** | **($45,000)** | **($17,500)** | **($12,096)** | **$31,613** | **$100,293** | **$245,531** | **$406,999** | **$740,102** | **$784,268** | **$830,966** | **$880,342** | **$932,550** |
| Discount rate 15% | | | | | | | | | | | | | | | |
| **NPV of EBT $799,613** | | | | | | | | | | | | | | | |

*We assume a similar prevalence to the U.S. market

**We assume 66% of the treatment cost in the U.S.

*Source: ROTH Capital Partners estimates*

**Figure 20: NPV Model**

| NPV Model (in thousands) | | 2021E | 2022E | 2023E | 2024E | 2025E | 2026E | 2027E | 2028E | 2029E | 2030E | 2031E | 2032E | 2033E | 2034E | 2035E |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Product sales** | | | | | | | | | | | | | | | | |
| TRD - U.S. | | | | | | $75,196 | $397,540 | $840,678 | $1,777,782 | $2,819,607 | $4,968,852 | $5,253,815 | $5,555,122 | $5,873,708 | $6,210,565 | $6,566,741 |
| TRD - EU5 | | | | | | | $49,071 | $259,424 | $548,603 | $1,160,132 | $1,839,998 | $3,242,536 | $3,428,495 | $3,625,120 | $3,833,020 | $4,052,844 |
| **Total product sales** | | | | | | $75,196 | $446,611 | $1,100,102 | $2,326,385 | $3,979,738 | $6,808,849 | $8,496,351 | $8,983,617 | $9,498,827 | $10,043,585 | $10,619,585 |
| **Total EBT*** | | ($38,400) | ($38,400) | ($74,000) | ($90,000) | ($68,564) | $234,280 | $805,097 | $1,970,066 | $3,540,751 | $6,228,407 | $7,831,534 | $8,294,436 | $8,783,886 | $9,301,406 | $9,848,605 |
| **Probability-adjusted EBT** | | ($38,400) | ($38,400) | ($74,000) | ($90,000) | ($17,141) | $58,570 | $201,274 | $492,517 | $885,188 | $1,557,102 | $1,957,883 | $2,073,609 | $2,195,972 | $2,325,351 | $2,462,151 |
| Taxes (21%) | | | | | | | | $42,268 | $103,428 | $185,889 | $326,991 | $411,156 | $435,458 | $461,154 | $488,324 | $517,052 |
| **Probability-adjusted EAT**** | | ($38,400) | ($38,400) | ($74,000) | ($90,000) | ($17,141) | $58,570 | $159,007 | $389,088 | $699,298 | $1,230,110 | $1,546,728 | $1,638,151 | $1,734,817 | $1,837,028 | $1,945,100 |
| Discount rate | 15% | | | | | | | | | | | | | | | |
| **NPV of probability-adjusted EAT** | $1,963,341 | | | | | | | | | | | | | | | |
| Number of fully diluted shares outstandin | 208,719 | | | | | | | | | | | | | | | |
| **NPV of probability-adjusted EAT/sh** | $9 | | | | | | | | | | | | | | | |

*EBT=earnings before taxes

**EAT=earnings after taxes

*Source: ROTH Capital Partners estimates*

## FINANCIALS

As of December 31, 2020, Cybin reported CDN$40MM in cash, cash equivalents, and investments. In February the company raised an additional CDN34MM. The current anticipated 2021 cash burn is ~CDN$30MM, making the cash runway sufficient to cover expenses into 2023.

## VALUATION

We arrive at our 12-month price target of $10/share (USD) by assessing the after-tax, risk-adjusted NPV of potential future cash flows from the TRD indication and including a technology value for earlier programs. The probability-adjusted, fully taxed (21%) NPV (15% discount rate) of potential cash flows through 2035 is $2B or $9/share, in our calculation. Adding $200MM ($1/share) estimated technology value yields $2.2B or $10/share for the company, corresponding to our 12-month price target. Factors that could impede shares from reaching our price target include failure of Cybin's drugs to demonstrate significant efficacy benefit or found to be unsafe, leading to the discontinuation of the programs.

## MANAGEMENT

**Doug Drysdale – Chief Executive Officer**

Mr. Drysdale is an experienced corporate director and CEO. He has chaired the board of directors of a NASDAQ-listed company and acted as a CEO for the past 12 years who has built and turned-around three pharmaceutical companies.

During Mr. Drysdale's 30 years of experience in the healthcare sector, he has formed cohesive management teams, recruited board members, completed 15 corporate acquisitions across three continents and has raised $4 billion of both public and private capital.

Mr. Drysdale led the turnaround of Norwich Pharmaceuticals alongside investors and became the Founding CEO of parent company, Alvogen Group. During his 5.5-year tenure as CEO, Alvogen grew from inception to $450MM in revenues across 35 countries.

In early 2014, Mr. Drysdale led the recapitalization of NASDAQ-listed Pernix Therapeutics, raising $65 million. Within the first year of taking the helm as Chairman and CEO, Mr. Drysdale rebuilt the management team and board of directors, combined several operating locations, and grew the company's enterprise value from $80 million to around $800 million. Under Mr. Drysdale's leadership, Pernix raised $465MM of capital.

From November 2017 to July 2020, Mr. Drysdale was a Director and CEO of Tedor Pharma, a family-owned contract manufacturing business. Mr. Drysdale's efforts to turnaround the business resulted in 60% revenue growth in 2019, leading to Tedor being recognized as one of America's fastest-growing companies, making it to the 2020 Inc 5000 list.

As the former Head of M&A at Actavis Group, Mr. Drysdale led 15 corporate acquisitions across three continents, between 2004 and 2008, including a high-profile public hostile takeover attempt in Central Eastern Europe. Over this period, Mr. Drysdale raised approximately $3B of capital and managed lending syndicates including 25+ banks, to fund the company's growth. Actavis was sold to Watson Pharmaceuticals in 2012 for EUR4.25B.

Mr. Drysdale holds a bachelor's degree in Microbial and Molecular Biology from the University of East Anglia in the U.K. and was recognized as Entrepreneur of the Year by Ernst and Young, in 2012. Mr. Drysdale is an enthusiastic traveler, having traveled to over 45 countries, is an avid reader and enjoys cooking and boating.

**Eric So – Co-Founder, Executive Chairman and President**

Mr. So is the co-founder and managing director of Trinity Venture Partners Inc., a boutique merchant bank. He is a veteran founder, investor, operator and advisor to disruptive companies, he began his career practicing in the areas of corporate commercial, securities, finance and mergers and acquisitions at a leading international law firm.

Mr. So has successfully raised hundreds of millions for various companies and navigated value creation, various exits and liquidity events for investors and shareholders.

Mr. So received his Bachelor of Science Major in Anatomy and Cell Biology and Minor in Psychology from McGill University, Bachelor of Laws from the University of Windsor.

**Alex Nivorozhkin Ph.D. – Chief Scientific Officer**

Dr. Nivorozhkin is the leading NCE inventor of multiple successfully partnered drug discovery and development programs. He is the technology developer of the proprietary formulations for CNS drugs.

Dr. Nivorozhkin is a seasoned medicinal chemist, drug delivery expert and founder of multiple biotech companies.

**Michael Palfreyman Ph.D. – Chief R&D Officer**

Dr. Palfreyman has 30 years of preclinical/clinical development experience: Scriptgen, EnVivo Pharma, Sanofi, GSK, Amorsa Therapeutics, and others.

Dr. Palfreyman has successfully led multiple IND filings and clinical programs and filed significant portfolios of CNS therapeutics patents and commercial products.

**Aaron Bartlone – Chief Operating Officer**

Mr. Bartlone is the former Chief Quality, Patient Safety, HSE & Risk Officer at UCB, Inc leading a team of 1500+ colleagues in 54 countries. He is also the former President at UCB, Inc. leading US commercial

operations through the restructuring into CNS and Immunology Business Units with annualized 27% P&L growth ($2.2B in revenue).
Mr. Bartlone also had various director level research, regulatory and managerial roles at Eli Lilly from 1997 to 2006.

**Alex Belser Ph.D. – Chief Clinical Officer**
Dr. Belser is a licensed psychologist, clinical supervisor, and psychedelic researcher at Yale in psilocybin clinical trials. He has been active in the psychedelic research community for 20 years.
Dr. Belser has conducted clinical research with psilocybin and MDMA for a variety of indications. His research featured on the front page of the NYT, in the Atlantic, the New Yorker, The Guardian, VICE, and in Michael Pollan's book, How to Change Your Mind.

**Joan M. Krakowsky Ph.D. – Senior Program Manager**
Dr. Krakowsky has a unique combination of 25+ years of scientific experience with over a decade of business development and project management experience in the pharmaceutical industry, including Sanofi-Aventis and Sancilio & Company, Inc. She is a research scientist with extensive expertise in GEM (Genetically Engineered Model) development and gene expression profiling studies, leading teams to support research in CNS, Metabolism, Immunology and Oncology.
Dr. Krakowsky has extensive experience as a program manager in the pharmaceutical industry with responsibilities for large-scale global projects.Her project manager role oversees discovery, preclinical, clinical research and chemical manufacturing programs.
Dr. Krakowsky received her Bachelor of Science in Biology and Psychology from Boston College and Doctor of Philosophy in Biomedical Sciences from Wright State University.

**Brett Greene – Chief Innovations Officer**
Mr. Greene is the research administrator for the Center for Drug Discovery (one of the top Cannabinoid and Serotonin research centers in the world) for over a decade. He co-managed $80MM+ in federal funding for cannabinoid and serotonin research.
Mr. Greene is a recognized leader in psychedelics (Co-founder of Psymposia). He also co-managed the NIDA-sponsored Chemistry & Pharmacology of Drug Abuse (CPDA) conference for 5 years.

**Lori Challenger – Chief of Staff**
Ms. Challenger is the former Lead Compliance Program Designer of the non-medical cannabis compliance program at a major Canadian retailer. She is also the ISO 19600 Certified Senior Lead Compliance Manager and PROSCI Certified Change Management Practitioner.
Ms. Challenger has vast experience and knowledge in the design and operation of foundational programs (regulatory compliance, operational) and organizational design & strategy implementation and execution.

**Paul Glavine – Co-Founder and Chief Growth Officer**
Mr. Glavine was the co-founder of Global Canna Brands which was granted the first ever tier 3 cultivation license in Jamaica. He sold his first cannabis startup Truverra to Supreme Cannabis Company Inc. (TSX: FIRE).
Mr. Glavine has advised on M&A and other financings in excess of $50MM. He is also a serial entrepreneur and investor with vast experience in the biotech and cannabis sectors.

**John Kanakis – Co-Founder and Chief Business Officer**
Mr. Kanakis is the co-founder and managing director of Trinity Venture Partners Inc, a Canadian boutique merchant bank. He is also the co-founder of multiple start-ups across various sectors.
Mr. Kanakis has 10+ years of experience in medical device manufacturing and regulatory frameworks. He has also successfully raised over $100MM for various start-ups.

**Greg Cavers – Chief Financial Officer**
Mr. Cavers has 15+ years of experience creating efficient scalable operations financial reporting, IFRS; regulatory reporting OSFI.
Mr. Cavers was the former Ontario Securities Commission contracted Director of Finance and the former Scotiabank senior manager of enterprise functions, the former CFO of Global Maxfin Investments Inc. and the former CIBC small business lending controller who has authority over assets of $31B for external reporting on a monthly and quarterly basis.

**Gabe Fahel – Chief Legal Officer**

Mr. Fahel is a counsel with 20 years of corporate/commercial legal experience, who is responsible for legal, compliance, corporate governance, security and regulatory affairs.

Mr. Fahel previously served as Legal Counsel for the Government of Canada as well as private companies including GrowPacker Inc.

## RISKS

Cybin is a development-stage company, and investment is subject to risk. These risks include but are not limited to:

- **Clinical trial risk:** Cybin is developing CYB001 for treatment-resistant depression (TRD), which is a condition with limited alternative treatment modalities. While in academic work the potential utility of psilocybin was demonstrated before, peer company COMPASS Pathways will be the first to demonstrate the utility of oral psilocybin (COMP360) in a rigorously designed and executed Phase 2b trial in TRD (data are expected by YE21). The risk of variability in response rate, which is a known obstacle in TRD, may make the interpretation of the study difficult. Furthermore, more than one administration of the drug might be necessary to evaluate full benefit. Previously unseen side effects may appear when administered to larger patient populations. All of the above risks may impact Cybin's CYB001, a sublingual formulation of psilocybin. In addition, the sublingual route may not yield sufficient quantities of byproduct psilocin to be effective in the brain.

- **Safety risk:** Sublingual administration of psilocybin may lead to unforeseen adverse events.

- **Regulatory risk:** The FDA and European regulators may require additional clinical trials beyond the ones Cybin currently envisions.

- **Competition risk:** Cybin relies on protection from a number of patents under prosecution worldwide. Those patents may not issue or may not provide sufficient protection from competitors.

- **Financing risk:** The cash position of Cybin was CDN$40MM by the end of December 2020. In February the company raised an additional CDN$34MM. We estimate Cybin to use approximately CDN$30MM over the next 12 months. The company would have to raise additional equity capital, unless licensing deals are forged for its development-stage assets. Financing may not be available under favorable terms, or at all.

## VALUATION

We arrive at our 12-month price target of $10/share (USD) by assessing the after-tax, risk-adjusted NPV of potential future cash flows from the TRD indication and including a technology value for earlier programs. The probability-adjusted, fully taxed (21%) NPV (15% discount rate) of potential cash flows through 2035 is $2B or $9/share, in our calculation. Adding $200MM ($1/share) estimated technology value yields $2.2B or $10/share for the company, corresponding to our 12-month price target. Factors that could impede shares from reaching our price target include failure of Cybin's drugs to demonstrate significant efficacy benefit or found to be unsafe, leading to the discontinuation of the programs.

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## COMPANY DESCRIPTION

Cybin is a leading biotechnology company focused on progressing psychedelic therapeutics by utilizing proprietary drug discovery platforms, innovative drug delivery systems, novel formulation approaches and treatment regimens for psychiatric disorders. Cybin Inc. is headquartered in Toronto, Canada.

### Income Statements

**Cybin Inc** — Elemer Piros, Ph.D. 646-716-3606 epiros@roth.com

| March 31 Fiscal year | 2020E | | | | | 2021E | | | | | 2022E | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *($ (CAD) In thousands, except per share data)* | 1QA | 2QA | 3QA | 4QE | 2020A | 1QE | 2QE | 3QE | 4QE | 2021E | 1QE | 2QE | 3QE | 4QE | 2022E | 2023E |
| **Expenses:** | | | | | | | | | | | | | | | | |
| Share-based compensation | | | 4,213 | | | | | | | | | | | | | |
| Professional fees | | | 1,417 | | | | | | | | | | | | | |
| Salaries and benefits | | | 1,560 | | | | | | | | | | | | | |
| Listing, Transfer agent and regulatory fees | | | 1,711 | | | | | | | | | | | | | |
| Research | | | 644 | | | | | | | | | | | | | |
| Advertising and promotion | | | 1,209 | | | | | | | | | | | | | |
| General and administrative costs | | | 264 | | | | | | | | | | | | | |
| Consulting fees | | | 345 | | | | | | | | | | | | | |
| Foreign exchange loss (gain) | | | 54 | | | | | | | | | | | | | |
| Depreciation | | | 13 | | | | | | | | | | | | | |
| Accretion of convertible debt | | | 0 | | | | | | | | | | | | | |
| Travel | | | 3 | | | | | | | | | | | | | |
| Interest expense | | | (14) | | | | | | | | | | | | | |
| **TOTAL EXPENSES** | | | **11,419** | **12,000** | | **12,000** | **12,000** | **12,000** | **12,000** | **48,000** | **12,000** | **12,000** | **12,000** | **12,000** | **48,000** | **74,000** |
| **NET LOSS AND COMPREHENSIVE LOSS FOR THE PERIOD** | | | **(11,419)** | **(12,000)** | | **(12,000)** | **(12,000)** | **(12,000)** | **(12,000)** | **(48,000)** | **(12,000)** | **(12,000)** | **(12,000)** | **(12,000)** | **(48,000)** | **(74,000)** |
| **Basic loss per share for the period attributable to common shareholders** | | | **(0.10)** | **(0.08)** | | **(0.08)** | **(0.08)** | **(0.08)** | **(0.08)** | **(0.31)** | **(0.07)** | **(0.07)** | **(0.07)** | **(0.07)** | **(0.28)** | **($0.41)** |
| **Weighted average number of common shares outstanding - basic** | | | **110,233** | **147,832** | | **150,000** | **153,000** | **156,060** | **159,181** | **154,560** | **162,365** | **165,612** | **178,924** | **182,503** | **172,351** | **182,503** |

*Source: Cybin Inc. SEDAR filings, ROTH Capital Partners estimates*

Regulation Analyst Certification ("Reg AC"): The research analyst primarily responsible for the content of this report certifies the following under Reg AC: I hereby certify that all views expressed in this report accurately reflect my personal views about the subject company or companies and its or their securities. I also certify that no part of my compensation was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in this report.

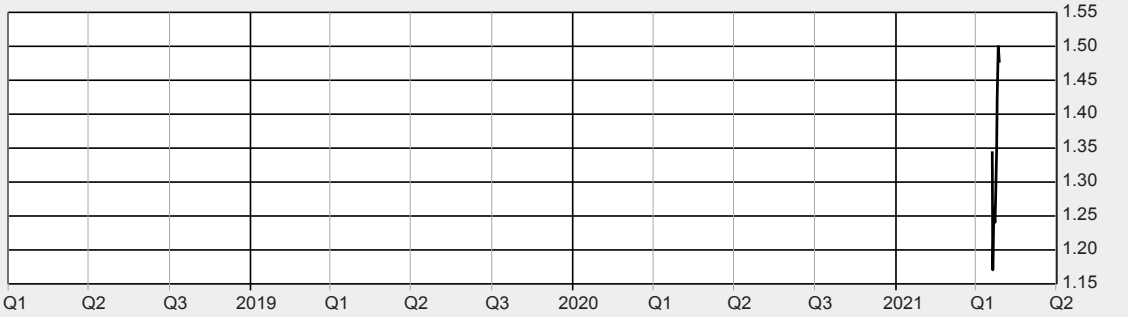
## Disclosures:

Shares of Cybin Inc. may not be eligible for sale in one or more states.

Shares of Cybin Inc. may be subject to the Securities and Exchange Commission's Penny Stock Rules, which may set forth sales practice requirements for certain low-priced securities.

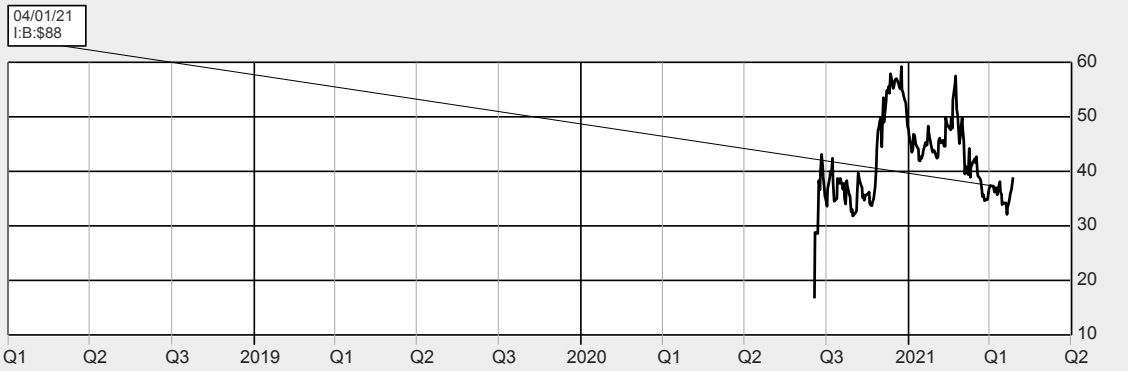
ROTH makes a market in shares of COMPASS Pathways plc and as such, buys and sells from customers on a principal basis.

**Rating and Price Target History for: Cybin Inc. (CLXPF) as of 04-27-2021**




Created by: BlueMatrix

**Rating and Price Target History for: COMPASS Pathways plc (CMPS) as of 04-27-2021**




Created by: BlueMatrix

Each box on the Rating and Price Target History chart above represents a date on which an analyst made a change to a rating or price target, except for the first box, which may only represent the first note written during the past three years. **Distribution Ratings/IB Services** shows the number of companies in each rating category from which Roth or an affiliate received compensation for investment banking services in the past 12 month.

**Distribution of IB Services Firmwide**

| | IB Serv./Past 12 Mos. |
|---|---|

| | | | as of 04/28/21 | |
|---|---|---|---|---|
| **Rating** | **Count** | **Percent** | **Count** | **Percent** |
| **Buy [B]** | **301** | **76.59** | **198** | **65.78** |
| **Neutral [N]** | **52** | **13.23** | **22** | **42.31** |
| **Sell [S]** | **1** | **0.25** | **1** | **100.00** |
| **Under Review [UR]** | **39** | **9.92** | **27** | **69.23** |

Our rating system attempts to incorporate industry, company and/or overall market risk and volatility. Consequently, at any given point in time, our investment rating on a stock and its implied price movement may not correspond to the stated 12-month price target.

Ratings System Definitions - ROTH employs a rating system based on the following:

**Buy:** A rating, which at the time it is instituted and or reiterated, that indicates an expectation of a total return of at least 10% over the next 12 months.

**Neutral:** A rating, which at the time it is instituted and or reiterated, that indicates an expectation of a total return between negative 10% and 10% over the next 12 months.

**Sell:** A rating, which at the time it is instituted and or reiterated, that indicates an expectation that the price will depreciate by more than 10% over the next 12 months.

**Under Review [UR]:** A rating, which at the time it is instituted and or reiterated, indicates the temporary removal of the prior rating, price target and estimates for the security. Prior rating, price target and estimates should no longer be relied upon for UR-rated securities.

**Not Covered [NC]:** ROTH does not publish research or have an opinion about this security.

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