



Incannex - New Frontiers in Treatment

Canary in the Coal Mine - December 2021

INCANNEX HEALTHCARE LIMITED (ASX:IHL) (NASDAQ:IHXL (upcoming listing))

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“Psychedelics, used responsibly and with proper caution, would be for psychiatry what the microscope is for biology and medicine, or the telescope is for astronomy.” - *Stanislav Grof*

Czech-born psychiatrist - founder and chief theoretician of transpersonal psychology

COVID has thrust health into the spotlight. There has been increased interest in health-related activities, from eating sustainable food to riding your Peloton bike. COVID has increased public awareness of the scale of mental health issues worldwide, and the scarcity of available treatments. Over 700m people globally are affected by mental illness, addiction or eating disorders. It is the current \$70bn market for mental health which creates an opportunity for psychedelic based treatments. The psychedelics industry was valued at US\$2bn in 2019 and is forecast to be US\$7bn by 2027.

Incannex (ASX: IHL, NASDAQ: IXHL(upcoming listing)), in conjunction with Dr Paul Liknaitzky and Professor Terence O'Brien, are developing world-class programmes of R&D which concentrate on synergistic medicines and treatments in the global wellness market. Incannex is conducting a world-first Phase 2a clinical trial combining psilocybin with psychotherapy to treat Generalised Anxiety Disorder (GAD). GAD's treatment options are currently very limited, with fewer than half of those suffering the condition achieving remission following treatment. This exposes a significant unmet need for patients. In addition, there are high rates of relapse and substantial side effects from existing treatment.

Psilocybin assisted therapy has USFDA "Breakthrough Therapy" designation in treating major depressive disorder and treatment-resistant depression. The Phase 2a clinical trial will be conducted at BrainPark, a state-of-the-art research platform and collaboration between the Monash School of Psychological Sciences and the Department of Psychiatry.

Cannabinoids and psychedelics are emerging as a possible solution for pain management, sleep apnoea, traumatic brain injury and generalised anxiety disorder. The pain management market turns over \$52 billion annually, the antidepressant market is around \$14 billion, and the global wellness market is approaching \$4.5 trillion annually. Incannex has combined scientific trials, artificial intelligence, and drug development to solve some of the most significant medical challenges of our time. Early predictions suggest the market could be worth \$100 billion.^[1]

Psychedelics are substances that alter perception and mood by affecting several cognitive processes. When used in conjunction with therapists, there is an opportunity to 're-shape the way parts of the brain speak to each other', said Jennifer Mitchell, University of California, San Francisco.

Psychedelics bind to serotonin receptors in the brain, which alters the structure and changes the brain. This effectively may mean that psychedelics have an opportunity to rewire and repair circuits in the brain, outlining their potential application to mental health treatment. Psychedelics fall into either entheogens or synthetic drug categories. Entheogenic psychedelics are derived from plants. Synthetic psychedelics are created in a laboratory.

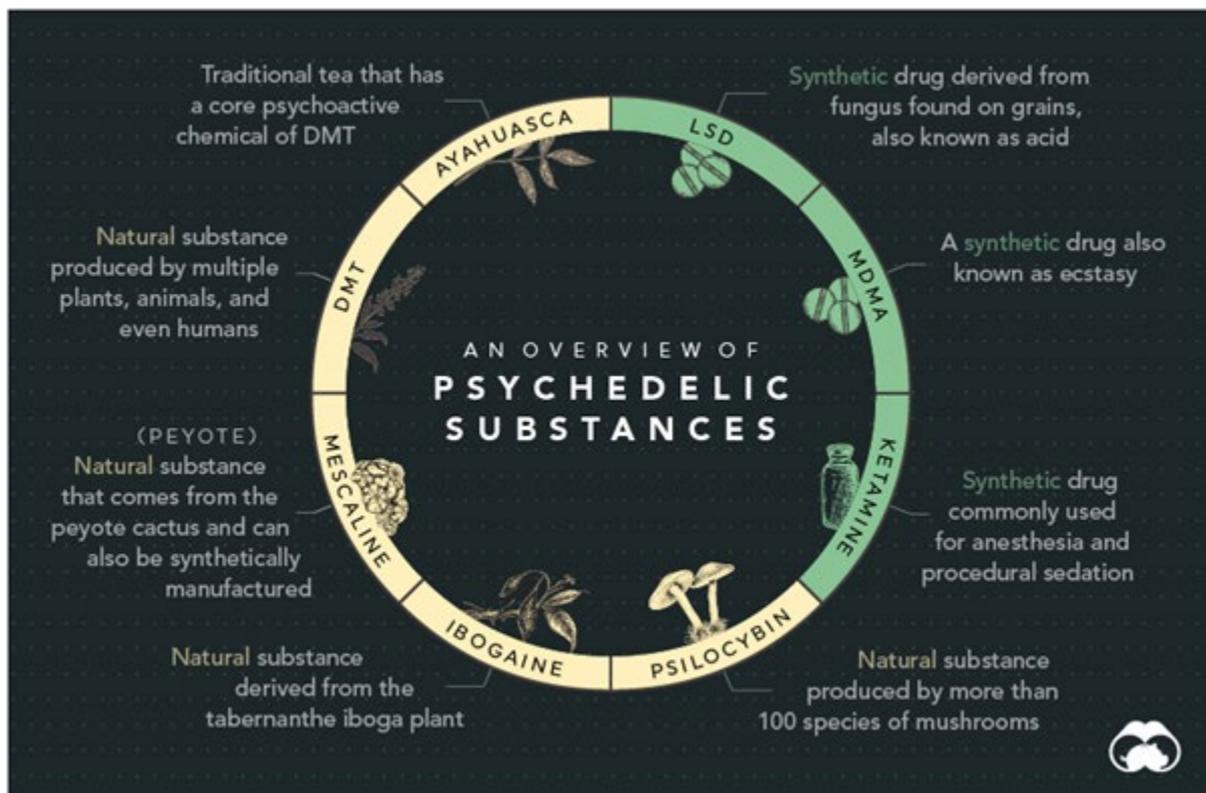
Types of Psychedelic Substances

- Ayahuasca: traditional tea that has a core psychoactive chemical of DMT.
- N-dimethyltryptamine (DMT): natural substances produced by multiple plants, animals, and humans.
- Mescaline is a natural substance that comes from the peyote cactus and can also be synthetically manufactured.
- Ibogaine: natural substance derived from the tabernanthe iboga plant.
- Psilocybin: a natural substance produced by more than 100 species of mushrooms.
- Ketamine: synthetic drug commonly used for anaesthesia and procedural sedation.
- MDMA: synthetic drug also known as ecstasy.
- LSD is a synthetic drug derived from a fungus found on grains, also known as acid.

Cannabinoids are compounds found in cannabis. The most notable cannabinoid is the phytocannabinoid tetrahydrocannabinol (THC), the primary psychoactive compound found in cannabis. Cannabinoids interact with specific cannabinoid receptors present on the surface of cells. These receptors are found in different parts of the central nervous system, and the two main types of cannabinoid receptors in the body are CB1 and CB2. The most abundant of the cannabinoids is Cannabidiol (CBD), which is thought to have anti-anxiety effects, possibly counteracting the psychoactive effects of THC.

^[1] <https://www.prnewswire.com/news-releases/global-52-1bn-pain-management-drugs-market-outlook-2019-2024--300877857>

In 1992, a naturally occurring substance in the brain that binds to CB1 was discovered, called anandamide. This cannabinoid-like chemical and others that were later found are referred to as endocannabinoids. The effects of cannabinoids depend on the brain area involved. Effects on the limbic system, a complex system of nerves and networks in the brain involving several areas near the edge of the cortex, may alter memory, cognition, and psychomotor performance. Effects on the mesolimbic pathway, a dopaminergic pathway in the brain, may affect the reward and pleasure responses, and pain perception may also be altered.



<https://www.visualcapitalist.com/the-history-of-psychedelics>

RESEARCH INTO PSYCHEDELICS

Johns Hopkins: Centre for Psychedelic & Consciousness Research

The Centre for Psychedelic & Consciousness Research at John Hopkins is considered one of the top psychedelic research institutions in the U.S. Since obtaining regulatory approval in 2000, has performed extensive research into the medical applications of psychedelics.

The most notable research the institute published is *Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance* in 2006.

https://www.hopkinsmedicine.org/press_releases/2006/griffithspilocybin.pdf

The objective of this study was to understand the longer-term psychological effects of a high dose of psilocybin in comparison with that of a similar compound taken in comfortable, supportive conditions. After 2 months, participants in the study highlighted the positivity of the experience as it invoked greater personal understanding and meaning, which was facilitated by beneficial behaviour and attitude changes. Generally, the study concluded that psilocybin when administered under safe and supportive conditions can evoke positive emotional experiences that alter attitudes and behaviours.

Following the 2006 study mentioned above, the Centre for Psychedelic & Consciousness Research has continued to conduct several trial studies to explore and prove psychedelics' real potential as a medicine. Below are some of the research milestones reached by the institute.

- 2008: Publication of guidelines regarding the safe use of psychedelics are published, which have been adopted across the industry.
- 2014: Magic mushrooms shown to aid long time smokers quitting under controlled parameters.
- 2016: Psilocybin proved to ease anxiety in people with life threatening cancer.
- 2018: Recommendation made to reclassify psilocybin from a schedule I drug to a schedule IV drug, which places it in line with prescription sleep aids and tighter controls.

- 2020: Psilocybin is shown to tamp down the brain's ego centre, which promotes a connected feeling.

The centre has an ongoing study named the Johns Hopkins Psilocybin Research Project which is currently in its 15th year and has had 245 participants over 600 sessions. The results of the study so far are nothing short of impressive with 80% of volunteers, a month after ½ doses of psilocybin, reporting the experience to be in the top 5 most personally meaningful and spiritually significant experiences in their lives. 50% of participants said that it was the top experience. Further details of this study can be founded by clicking the video below where Roland Griffiths, the Principal Investigator at the centre, shares the findings in a TedMED talk.

<https://www.youtube.com/watch?v=81-v8ePXPd4&t=26s>

Multidisciplinary Association for Psychedelic Studies (MAPS)

Founded in 1986, MAPS is a non-for-profit research and educational organisation, which is directly involved in the study of psychedelic medicines on several human illnesses. MAPS has three main areas of study being MDMA-Assisted Psychotherapy, Medical Marijuana and LSD-Assisted Psychotherapy.

- MDMA-Assisted Psychotherapy studies are aimed at understanding whether MDMA-assisted psychotherapy could repair the psychological and emotional damage that victims of sexual assault, war, violent crime, and other traumatic experience. In the U.S, the study is currently in Phase 3 trials seeking FDA approval to engage in clinical

trials. Trials are expected to be completed in 2022, with FDA approval given in as early as 2023. Phase 2 trials have also begun in Europe.

- Medical Marijuana. MAPS has received regulatory approval to conduct trials on individuals who are suffering from PTSD and specifically in those or returned war veterans. Following 48 years of restrictions, in 2016, the DEA finally announced their desire to grant licenses to additional growers for research, which was of great benefit to MAPS.
- LSD-Assisted Psychotherapy. MAPS recently completed a phase 2 pilot study in 12 subjects, which reported positive reductions in anxiety following the sessions. Furthermore, the study promoted the safety and efficacy of the trial for future research.

MARKET OPPORTUNITY FOR PSYCHEDELICS

Mental health issues currently cost the global economy \$1 trillion per year. A recent study estimated this could reach \$16 trillion by 2030.

<https://www.psychiatrytimes.com/view/mental-illness-will-cost-world-16-usd-trillion-2030>

The need for psychedelic based treatments is ever present with numerous mental disorders and illnesses plaguing society. According to the National Institute of Mental Health in the US, over 17 million Americans have at least one depressive episode per year and up to 30% of them receive less than adequate medical treatment. Additionally, treatment of PTSD using Psychedelics has garnered great interest in the US due to the ever-increasing level of returned veteran suicides, which accounts for 22 deaths per day. Initial studies have shown a large improvement in mental state following application of psychedelic treatment.

Globally, the WHO estimates there are 322 million people suffering from depression and 100 million of those suffer from treatment-resistant depression. The increasing relevance of psychedelics as a potential treatment for many of these illnesses has led to the estimation of the global market opportunity for psychedelics at around \$100 billion.

VALUATIONS OF PSYCHEDELIC COMPANIES

With the medicinal potential of psychedelics coming to light, numerous companies have seized the opportunity to enter the industry and, in the process, have amassed sizable valuations in the public markets. Notable examples that recently went public this year include MindMed, a A\$1.12 billion market cap company that focuses on treatment of mental illnesses with substances such as LSD and psilocybin. Another is Atai Life Sciences, a Peter Thiel (venture capitalist/co-founder of PayPal) backed company that is currently valued at A\$1.87

billion. While the size of these companies is indicative of the size of the market opportunity for psychedelics, they have also been instrumental in the validation of pharmaceutical applications of psychedelics.

LEGALISATION OF PSYCHEDELICS

Psychedelics have been labelled as illegal narcotics due to their counterculture connotations and rigid legal status. The industry is now being considered as a viable solution for treating unmet medical needs, in a safe and controlled environment. The U.S. is leading the way in decriminalizing these powerful drugs.

Decriminalisation. With the movement to decriminalise psychedelics in the U.S. starting in late 2010, some progress towards this goal has been attained. In November 2020 Oregon became the first state to legalize psilocybin-assisted therapy, and to decriminalise the personal possession of drugs with the passing of the Oregon Psilocybin Services Act and the Drug Addiction Treatment and Recovery Act. Under the acts, applications related to the manufacture, sale and purchase of psilocybin products and the provision of psilocybin services will be accepted starting on January 2, 2023.

Though Oregon is the state that's furthest along on the path to fully legalise psychedelics, other states have made advancements towards the de-prioritization of psychedelics. De-prioritisation refers to when policing, arrests and prosecutions related to the production, possession and use of psilocybin are considered low priority for law enforcement agencies even though it's still considered illegal. States that have de-prioritised psychedelics are Washington, Colorado, New Jersey, Michigan and Massachusetts.

Research. As the decriminalisation of psychedelics gains traction, legislation to promote the research into the medical applications of psychedelics is being adopted in various states. This includes Texas where a bill was passed in June 2021 calling for a study into the therapeutic use of certain psychedelics. The study, which is led by the Department of State Health Services, is meant to evaluate the therapeutic efficacy of alternative therapies including MDMA, psilocybin, and ketamine for the treatment of specific mental health and medical conditions including depression, anxiety, PTSD, bipolar disorder, chronic pain, and migraines.

More recently in June 2021, a law was passed in Connecticut for the Department of Mental Health and Addiction services to convene a working group to study the benefits of psilocybin and determine if it would be beneficial to the person's physical or mental well-being.

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SIX DRUG DEVELOPMENT PROGRAMS PROVIDING MULTIPLE CHANCES OF SUCCESS

Generalised Anxiety Disorder (GAD) In December 2020, Incannex entered into a partnership agreement with Monash University to conduct a trial to treat Generalised Anxiety Disorder with psilocybin combined with unique psychotherapy. The trial is being led by renowned psychedelic medicine expert Dr Paul Liknaitzky. Dr Liknaitzky is Principal Investigator across several of Australia's first clinical psychedelic trials and is the only full-time psychedelic medicine researcher in Australia.

The phase 2a randomised double-blind active-placebo-controlled trial will recruit at least 72 patients, making it the largest psychedelic R&D project in Australia. The treatment will include psilocybin dosing sessions alongside a program of specialised psychotherapy in the treatment of Generalised Anxiety Disorder. This world-first clinical trial is expected to have a substantial impact on the field globally and puts IHL in the same league as major psychedelic organisations such as Mindmed, Compass Pathways and Cybin Inc – all of which have very large market valuations. A Pre-IND information package and meeting request about a phase 2b trial has been submitted to the FDA.

Incannex Psychedelic Therapies Presentation:

<https://www.asx.com.au/asxpdf/20210811/pdf/44z64h9fkjs2p1.pdf>

Obstructive Sleep Apnoea

IHL-42X is a novel cannabinoid formulated to moderate disordered sleeping and reduce Obstructive Sleep Apnoea (OSA). IHL-42X is currently in Phase 2 clinical trials and is intended to be the first-in-class for treatment of OSA – potentially replacing the cumbersome CPAP machine as the standard of care if clinical trials are successful. IHL_42X has predicted earning capacity of >\$5 billion per annum in sales after approval.

Traumatic Brain Injury

IHL is taking a novel approach in developing a cannabinoid neuroprotective drug to protect the brain against neuronal cell death following a Traumatic Brain Injury (TBI). In December 2020, results from a preclinical study confirmed strong synergistic neuroprotective activity of IHL-216A after TBI. The drug presents potential sales revenue of \$450m per annum in the seven major markets (United States, Japan, France, Germany, Spain, Italy and the United Kingdom). Significantly, this approach meets the standards of the World Anti-Doping Authority for applicability in all sports, which is where many traumatic brain injuries occur. Having a treatment option immediately available on the sidelines of sporting events, at all levels of competition, could lead to drastically improved outcomes for participants following head injuries sustained during sport.

Inflammatory Lung Conditions (ARDS, asthma and bronchitis)

Incannex held a Pre-Investigational New Drug meeting with the US Food & Drug Administration (FDA) in April 2021. FDA agreed that marketing applications for IHL-675A should be made under 505(b)(2) which contains the full safety and effectiveness reports but allows some of the information required for NDA approval. The total addressable market for ARDS is \$675m in the US and extrapolates to a total addressable market of more than \$2 billion in the 7 major markets. Applicability to asthma and other inflammatory lung conditions would markedly increase this potential market.

Rheumatoid Arthritis

In a preclinical study concluded in March 2021, IHL-675A outperformed an existing treatment for arthritis with increased effectiveness ranging from 1.06x to 3.52x. IHL has initiated an additional program to target rheumatoid arthritis exclusively which has a global addressable market of US\$57 billion per annum thus further expanding the revenue generating potential of IHL-675A. Some new treatments for arthritis are highly expensive, representing a major opportunity for IHL in terms of new, effective treatments at a lower price point.

Inflammatory Bowel Disease

In a mouse model of colitis, a form of inflammatory bowel disease, IHL-675A has been shown to outperform cannabidiol (CBD) and Hydroxychloroquine (HCQ) highlighting the synergistic nature between the two. The results indicate that IHL-675A has superior anti-inflammatory activity compared to CBD and HCQ alone. The global market for treatments for IBD is expected to reach US\$22.4B by 2026, growing at a CAGR of 4.4% from 2018 to 2026.

Pharmaceutical Development Plan

IHL is pursuing FDA registration of all new drugs being developed – all preclinical and clinical trials are geared towards this end.

- FDA registration means that all doctors are entitled to prescribe the product and it also entitles the company to marketing exclusivity over its formulations over a period of time (minimum 5 years).
- Once FDA registration is granted, IHL will pursue registration in other regions including Europe and Australia.
- In addition to FDA marketing exclusivity, IHL is generating patent protection over its formulations and therapies. Granted patents provide the company with 20 years of exclusivity over its formulations and facilitates the opportunity to be the sole provider of a therapy, subject to ongoing clinical success.
- Furthermore, as IHL receives more pre-clinical and clinical data on its assets as it pursues registration, the products will be eligible for sale under various global special medicines access schemes, including the Australian special access scheme. This will facilitate sales of its proprietary products even prior to registration, potentially creating a significant market opportunity.

Additional Information Sources:

<https://www.visualcapitalist.com/overview-of-psychedelic-substances-medicine>

<https://blossomanalysis.com/>

<https://reportonpsychedelics.com/>

<https://psychedelicspotlight.com/>

<https://www.prnewswire.com/news-releases/global-52-1bn-pain-management-drugs-market-outlook-2019-2024--300877857.html>