



PSYCHEDELIC THERAPY IN SOCIETY: EXPLORING THE MECHANISMS OF ACTION AND DELIVERY OF CARE

The latest research in psychedelic therapy suggests the potential for a transformation in how we approach treatment of depression, anxiety and certain forms of mental anguish. Early results show that a single dose in combination with preparation and follow-up could have an impact long after the substance has left the body. As research is taken into broader clinical trials, questions remain around what exactly happens that facilitates such a transformation and its impact.

PRESENTERS

Heidi L. Allen, Ph.D., Associate Professor, School of Social Work, Columbia University, New York, NY

Robin L. Carhart-Harris, Ph.D., Head of Psychedelic Research, Centre for Neuropsychopharmacology, Division of Brain Sciences, Faulty of Medicine, Imperial College London, London, United Kingdom

Tania de Jong, AM, Singer, Speaker, Social Entrepreneur; Founder Mind Medicine Australia, Creative Universe, Creative Innovation Global and Creativity Australia, South Melbourne, Victoria, Australia

Adam Halberstadt, Ph.D., Assistant Adjunct Professor, Department of Psychiatry, University of California San Diego, La Jolla, CA

Jack Henningfield, Ph.D., Vice President, Research, Health Policy and Abuse Liability, Pinney Associates, Bethesda, MD & Professor, Adjunct, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD

John D. McCorvy, Ph.D., Assistant Professor, Cell Biology, Neurobiology & Anatomy, Medical College of Wisconsin, Milwaukee, WI

Bill Miller, Mohican Tribe from northern Wisconsin, award winning Native American recording artist, performer, songwriter, painter, flutist, speaker and three-time Grammy Award Winner

Stevens Rehen, Ph.D., Chief of Scientific Programs and Outreach, D’Or Research and Education Institute (IDOR); Full Professor, Biomedical Sciences Institute, Universidad e Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Louie Schwartzberg, Cinematographer, Director and Producer, BlackLight Films and Moving Art™, Los Angeles, CA

Art Shegonee, Menominee and Potawatomi Tribes of Wisconsin, Ambassador to Wisconsin’s Indian Summer and Co-founder of Call For Peace Drum & Dance Company

Will Siu, M.D., DPhil, Psychiatrist, New York, NY

Craig A. Vercruysse, MBA, Partner, Moss Adams, San Francisco Bay Area, CA

Bennet A. Zelner, Ph.D., Associate Professor, Robert H. Smith School of Business. University of Maryland, College Park, MD

MODERATORS

William Linton, President & CEO, Promega Corporation, Madison, WI (Welcome & Closing Remarks)

Penny Patterson, Vice President, Communications, Promega Corporation, Madison, WI (Presentations Moderator)

Steve Paulson, Executive Producer, To The Best Of Our Knowledge, Wisconsin Public Radio and PRX, Madison, WI (Panel Moderator)

MUSICIANS AND IMMERSION ARTISTS

Tony Castañeda Latin Jazz Band, Tom Ross and Josh Pultorak, Becca McKnight, Lisa O’Connor, Malynn Utzinger

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Psychedelics: Therapeutic Mechanisms Robin L. Carhart-Harris, Ph.D.

This talk will present a model on the brain action of psychedelics that addresses the receptor level pharmacology, function of serotonin 2A receptor agonism, acute global brain effects and post-acute brain changes. Special reference will be given to hierarchical predictive processing and the action of psychedelics on brain and mind organization within this particular scheme.

Use of Behavioral Models to Investigate the Mechanism of Action of Psychedelic Drugs Adam L. Halberstadt, Ph.D.

In recent years, there has been increasing scientific interest in psychedelic drugs (serotonergic hallucinogens) such as psilocybin and LSD. The focus on psychedelic drugs has been driven, in part, by accumulating evidence that these compounds possess therapeutic efficacy in the treatment of certain psychiatric disorders, such as anxiety, depression and substance abuse. The recent renaissance of hallucinogen research has also coincided with a marked increase in the availability and recreational use of novel “designer” psychedelic drugs, a phenomenon facilitated by the increasing globalization of online commerce. Although human studies with psychedelic drugs are becoming more common, much of what is known about the mechanism of action of these agents has been derived from animal behavioral models. My presentation will focus on animal models used to study psychedelic drugs and will discuss the pharmacological mechanisms responsible for hallucinogen effects. Although there is extensive evidence, from both animal and human studies, that the characteristic psychedelic effects produced by hallucinogens are largely mediated by interactions with the 5-HT2A receptor, other serotonin receptors may play an ancillary role in the psychopharmacological and behavioral effects produced by these substances. Finally, I will discuss research strategies that can be used to probe the structure-activity relationships of psychedelic drugs and investigate their interactions with multiple 5-HT receptors, techniques that can facilitate the preclinical screening of new drug candidates and other hallucinogenic substances.

Profiling Psychedelics at the Serotonin Receptors John D. McCorvy, Ph.D.

Psychedelic substances induce profound changes in consciousness in humans, which is why they remain a fascinating frontier in consciousness research. In fact, recent clinical research with psychedelics has shown that psychedelics can have profound and long-lasting anti-depressant effects after just one-time use.

What is known is that psychedelics such as LSD, psilocybin and DMT all engage serotonin receptors located in the brain to manifest their altered conscious state. Specifically, the serotonin 5-HT2A receptor, which is located and highly expressed in prefrontal cortex, appears to be the primary target for the psychedelic experience. I will show recent work that the serotonin receptors engage in unique signaling pathways that are dependent on the drug’s chemical structure, a phenomenon known as biased signaling. These molecular insights suggest that the unique engagement of the psychedelic’s chemical structure with the receptor is what drives a unique profile of signal transduction.

This lecture will explore at the structural and molecular level how psychedelics and non-psychedelic drugs engage the serotonin receptors leading to unique patterns of signaling. Importantly, this lecture will open questions about receptors and biochemical pathways are necessary for anti-depressant effects. Ultimately, these studies will catalyze the development of a new class of serotonin drugs for depression and mental health.

Biological Effects of Psychedelics in Human Neural Stem Cells and Brain Organoids Stevens Rehen, Ph.D.

For more than four decades, restrictions on research with psychedelics have abrogated the comprehension of how such substances impact brain

metabolism. Besides the historical restrictions, studies have also been compromised by limitations of adequate models. In the last few years, progress has been made regarding the differentiation of human induced pluripotent stem (iPS) cells into neural stem cells and brain organoids. These approaches recreate features of the cerebral cortex development, showing potential for human brain modeling studies. Here, I will present our recent data regarding the effects of the -carboline alkaloid harmine, N,N-dimethyl-tryptamine (NN-DMT) and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in human neural tissues. Harmine increased the pool of neural progenitor cells by inhibiting DYRK1A (dual specificity tyrosine-phosphorylation-regulated kinase). NN-DMT increased the number of neural stem cells, in a dose dependent manner, through the activation of 5HT2A receptor. These results suggest that harmine and NN-DMT may influence neurogenesis, which is probably associated with the antidepressant effects of Ayahuasca described in patients. Moreover, human neurons exposed to NN-DMT showed increased expression of synaptophysin, while analyses of brain organoids exposed to 5-MeO-DMT revealed proteins broadly distributed on functional activities such as cellular protrusion formation, microtubule dynamics and cytoskeletal reorganization. These data contribute to elucidate neuroplasticity signaling pathways influenced by dimethyltryptamines. Human iPS brain cells offer an exciting new range of opportunities to investigate the influence of psychedelics in the central nervous system.

Human Intelligence 2.0 and Mind Medicine Australia— A Collective Future? Tania de Jong, AM

It is no ordinary time in the history of civilization. The world is moving faster than we can think; so, we have to change our thinking! The transformation upon us means at least three things...Fear, Change and Opportunity.

We face a host of wicked problems, risks and systemic challenges beyond the reach of existing institutions and traditional authority structures. Over 300 million people globally were estimated to be suffering from depression in 2018 and many more suffer with other mental illnesses, addictions and cognitive disorders.

45% of Australians will suffer from a mental illness in their lifetime. That is why we founded Mind Medicine Australia, a charity that enables the development of regulatory-approved and research-backed psychedelic-assisted psychotherapy for the treatment of mental ill-health in Australia.

Together we will need to raise our collective consciousness and build our Human Intelligence 2.0 skills—creativity, innovation, generosity, inclusivity, resilience and empathy—to manage and prepare for a rapidly changing world and the Fourth Industrial Revolution.

Nature to the Rescue Louie Schwartzberg

Immerse in a magical journey through time and scale and shares how nature’s energy can heal mind, body and soul.

Delivering Psychedelics to Society: Context and Questions Craig A. Vercruysse, MBA

We are at an inflection point in the evolution of humanity as a wide variety of technological advancements converge to create unprecedented transformational change. At the same time, individuals and our society at large, are failing to thrive in facing the complexity of adapting to this transformational change as evidenced by the profound strain on mental health.

Suicide rates have climbed 20% over the last decade and 12.7% of youth aged 12-17 suffer from depression. Furthermore, the delivery system for traditional healthcare, most especially in behavioral health, is strained. As a microcosm of society, healthcare workers themselves are struggling to adapt to the changes required in our antiquated healthcare delivery system. Among the most notable mental health statistics among healthcare workers is the shocking 54% of providers reporting burnout or being colloquially depressed.

This Friday opening session frames the societal context in which the resurgence of psychedelic research and drug development exists. It also frames the practical and philosophical questions that need to be answered

if the wide scale delivery of psychedelics is to live up to its potential as a game-changer in human adaptability.

Delivering Psychedelic Therapy Within and For Community Bennet A. Zelner, Ph.D.

Scientific research has demonstrated psychedelic therapy’s unparalleled ability to treat mental and behavioral disorders such as depression, anxiety, and addiction in a clinical setting. As psychedelic medicines move toward legalization, more attention is being paid to the design of real-world models for delivering care. Traditional clinical approaches to mental healthcare have been focused at the individual level, with community support regarded as an ancillary form of therapeutic intervention. But growing rates of isolation and loneliness in our society have been associated with an increased incidence of the disorders that psychedelic therapy can be used to address, and ample evidence demonstrates the importance of community support in producing better mental health outcomes. For these reasons, delivery-of-care models should leverage psychedelic medicines’ documented ability to foster empathy and connectedness, in order to build community as they provide individual healing. This notion has ample historical precedent: indigenous peoples have used psychoactive plant medicines administered in communal settings to jointly promote individual and community wellness for thousands of years. The ancient collectivist wisdom embodied in these practices has application in our historically individualistic culture. It translates into the community economics concept of pollination, the creation or renewal of local non-financial capital forms to contribute to local production and commerce. A care delivery approach that embodies the mutually reinforcing relationship between individual and community wellness can pollinate local economic activity by restoring depleted human and social capital, providing an economic rationale for the explicit incorporation of community-building into the provision of mental healthcare. Delivering services through locally rooted organizations that reflect a given community’s distinctive cultural attributes will speed acceptance of such an approach, and of psychedelic therapy more generally.

Is There a Way to Revolutionize Mental Health Without Increasing Disparities? Heidi L. Allen, Ph.D.

The United States experiences stark disparities in access to efficacious mental health treatments. Such disparities have been observed by race, ethnicity, sexual orientation, insurance status, income, and rurality. Not only are disparities widely prevalent, they have been persistent. Recently, the FDA approved Spravato™ (esketamine) nasal spray, a derivative of ketamine, for serious treatment-resistant depression. This is the first new drug for major depression to come to the U.S. market in decades. Assuming psilocybin and MDMA will soon join ketamine as mainstream evidence-based mental health treatments, how can we avoid replicating and exacerbating existing inequalities in mental health access? Are we prepared to revolutionize mental health without leaving anybody behind? I argue that the only way we can do so is through deliberate and strategic commitment to equity. This commitment begins in conversation and ends in action. Playing by the rules of the “medical model” has resulted in this historic opportunity to level the playing field, but the medical model often fails patients and could undermine the transformational potential of these new treatments if left unchallenged. How can we push for policies, procedures, and practices around these treatments that are inclusive to culture and consider individuals holistically? What are the key decision points that could make or break equity? For example, are minority patients being included in clinical trials, even if they present with higher degrees of social and medical complexity? Are we considering cost-barriers inherent to how we operationalize “set and setting” and in the standards we require of attending practitioners? Are we engaging and educating Medicaid policy-makers, America’s health insurance for the poor? Would it be possible to administer treatments in dyads or group settings? How can we consider issues of equity in our marketing and outreach? My goal for this session is to inform your commitment to equity through a discussion of the U.S. health policy environment and to identify applicable lessons from prior efforts to reduce disparities.

Light & Shadow: Opportunities and Perils in the Clinical Practice of Psychedelic Medicine Will Siu, M.D., DPhil

Psychotherapy was the mainstay of psychiatric study and treatment since Freud, though it eventually gave way to psychopharmacology. Prozac was approved in 1988, and between then and 2002, prescriptions nationally rose from ~2.5 million to ~33 million. And by 2008, Prozac had become the 3rd most-common medication prescribed in the United States. Despite psychopharmacology’s ascent since that time, and of neurochemistry’s parallel rise in the study of mental health, rates of psychiatric illness and suicide have only risen. In 2017 and 2018, the US Food and Drug Administration (FDA) designated MDMA-assisted psychotherapy and psilocybin therapy, respectively, as “Breakthrough Therapies.” The only times these designations have been provided for primary psychiatric diagnoses. The FDA’s acknowledgment of these novel approaches reflected the unparalleled treatment success rates of these novel approaches in clinical research, spearheaded by MAPS beginning in 1986 and later by the Heffter Research Institute. Psychedelics are now shifting the psychiatric profession’s treatment and psychopathology paradigms at the same time that Eastern philosophies, spirituality, and mind-body approaches are becoming increasingly popular in Western culture and scientific investigation. Through the lens of a practicing physician-scientist, I will address the practical ways that psychedelics are impacting treatment approaches and delivery of care for mental illness. I will also address opportunities and perils on the horizon for these exciting areas, depending on how psychedelic science is embraced and implemented in medicine and in culture.

Psychedelics in Mainstream Medicine: How do we get there? Jack E. Henningfield, Ph.D.

The dawn of the 21st century witnessed a dramatic acceleration of psychedelic drug research, paving the way for FDA approval of some psychedelics for therapeutic use. Indeed, the evidence was sufficient with respect to psilocybin and MDMA for FDA to designate applications from two developers as Breakthrough Therapies, meriting expedited development to more rapidly help those with unmet needs. The path to approval is as demanding as for any new drug but is clearly laid out in various FDA guidances including those addressing abuse potential assessment (2017), and developing risk evaluation and mitigation programs (REMS). In the case of psychedelics, the path is even more complicated by the historical social and political baggage, and media reports of apparently rare but sometimes dramatic and disastrous consequences of self-experimentation with illicit psychedelic concoctions that make their approval anathema for many people. Thus, psychedelic researchers and developers will need to develop strong safety programs (REMS), and include active communications efforts to identify and address concerns over the course of development and post approval. Medical practice and third-party payers will also need to adapt to treatment approaches that do not involve daily self-dosing but will likely involve the expense and resources to treat individuals in clinics, with caregiver administered dosing and monitoring in certified clinics and extensive follow-up. Documentation of strong benefits, minimized unintended consequences, healthcare reimbursement will be critical to accelerate assimilation into mainstream medicine.