

*Breakthrough?:
Psychedelic
psychotherapies,
interventional
psychiatry, and
other new and
prospective
treatments for
mental health
challenges*

Kurt L. White, LICSW, LADC

December 4, 2023

Agenda

Background/innovation timeline


TMS

Esketamine

Psilocybin

MDMA

The future....



Innovation in psychiatry: some notable developments...

MEDICATIONS

- Great hope of the development of so-called second generation antipsychotic medications, from clozapine and forward...
- Great hope of SSRI medications, as a safer and equally effective antidepressant treatment...
- Anti-seizure and second gen antipsychotic agents to treat bipolar mania...
- Benzodiazepines and "z-drugs" as improvements on barbiturates...

ALTHOUGH...

- And in some cases, these treatments did indeed prove to have advantages on the older treatments — and I was witness to some people, early in my career especially — that had remarkable results from making a shift from something old to something new. But... these medications were all, in their own ways, incremental improvements on treatments that has been around for some time.
- In some cases, the improvements were also more elusive that we would have wished for... or had their own, new and very serious side effect issues. Or sometimes showed new versions of older problems.

In psychotherapy (my field)

SOME NEW AND PROMISING TREATMENTS OF PAST FEW DECADES

- Motivational interviewing
- DBT, ACT, and other 3rd wave CBT
- EMDR, IFS, and embodied psychotherapy methods
- Increased mainstream attention to context and culture
- Increased attention to the intersubjective nature of psychotherapy as an enterprise – often a lesson learned slowly, and from people with lived experience educating “the experts”
- Increased attention to stigma and discrimination has led to more people feeling comfortable seeking help, and doing so at an earlier point of distress

BUT ON THE DOWNSIDE

- The period of managed care but before State and Federal parity restricted care for many;
- Many new treatments are actually no more effective than older ones, in head to head trials; differences between models may have more to do with other effects in the therapy (not the model per se)
- Access to care remains a challenge for many, as the system continued to fight with uncertainty about what the system should “look like”;
- While inpatient care is shorter, with many positives resulting from this, more is demanded of outpatient treatment than it can always bear

And also...

STRESSORS IN THE WORLD

- Many issues seem to be heading in the wrong direction, making it so that the effect of some innovation in the field has been erased by worsening conditions on the ground: the complex and multifaceted opioid epidemic; deaths of despair; gradual and not-so-gradual increases in suicide rates
- And the overall state of the world – the change in political tone, conflict and wars that feel never so far from home, the climate crisis (which is affecting us all, but is a central stressor for many young people) continues to be quite challenging

AND MORE SPECIFICALLY

- The good news has always been that we really can and do help people – probably far more than most therapists even believe! *But we don't help everyone equally.*
- For me, this has led to some specific preoccupations of my career: *how do we reach the people who aren't calling us (not the subject of today's talk); and how do we help people who aren't so easily helped by the interventions that we do have?*

What's new and what is happening NOW, and under what oversight?

FDA APPROVED AND BEING STUDIED

- TMS for Treatment Resistant Depression (available now)
- Esketamine for Treatment Resistant Depression/Acute Suicidality (available now)
- MDMA for PTSD – under investigation/data available from studies
- Psilocybin for Depression, other conditions – under investigation/data available from studies

OFF-LABEL AND “OTHER”

- IV Ketamine (off label)
- IM Ketamine (off label)
- Ketamine Lozenges (off label)
- “Off-label” TMS protocols for conditions other than TRD
- Patient self-administering other substances (mushrooms, LSD, etc.) - currently illegal under state/federal laws

TRD and PTSD

TREATMENT RESISTANT DEPRESSION

- "The estimated 12-month prevalence of medication-treated MDD in the United States was 8.9 million adults, and 2.8 million (30.9%) had TRD. The total annual burden of medication-treated MDD among the US population was \$92.7 billion, with \$43.8 billion (47.2%) attributable to TRD. The share of TRD was \$6.6% (\$25.9 billion) of the health care burden, 47.7% (\$8.7 billion) of the unemployment burden, and 32.2% (\$9.3 billion) of the productivity burden of medication-treated MDD."

Zhdanova M, Pilon D, Orlowski I, Chow W, Joshi K, Lafudre B, Sheehan JJ. The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. *J Clin Psychiatry*. 2021 Mar 16;82(2):20m13699. doi: 10.4088/JCP20m13699. PMID: 33989464.

POSTTRAUMATIC STRESS AND TRAUMA

- PTSD is a common problem in psychotherapy practices and clinics; with hospitals and CMHCs seeing a very large subgroup of people who are often experiencing significant disability from PTSD.
- It's one of only a few major "DSM disorders" around which there has been substantial controversy around even the definition and inclusion criteria— which were created with only a specific subset of trauma-affected individuals in mind.
- Some treatments which have been proven effective involve exposure as a core method, and some of these have very high dropout rates.
- We may not even know how many people's lives are significantly affected by trauma every day, or have a clear idea of who who aren't helping.

Transcranial Magnetic Stimulation for TRD

ONE VARIETY OF TMS MACHINE



SOME BASICS

- TMS (transcranial magnetic stimulation) is an FDA approved treatment for people with major depressive disorder (MDD) that have not had lasting relief with first-line treatments like antidepressants and psychotherapy. TMS is a type of noninvasive brain stimulation that applies electrical pulses to the brain using a magnetic coil placed over the head. When electromagnetic pulses are targeted at a specific region of the brain that is either underactive or overactive in those with MDD, new neural pathways are stimulated. When done repetitively over a 6 week period, TMS can strengthen these newly formed connections between brain cells. Increased connectivity between brain cells helps to improve overall brain function and mood.
- A notable feature of TMS is how few side effects it has...

TMS for TRD

SOME COMPLEXITIES

- Many machines exist, and many protocols; this can get very technical; so far, TRD is the primary indication "on label" use of TMS. It is also being studied (and used, off-label in most instances) for many other problems including especially OCD, smoking cessation, negative symptoms of schizophrenia, etc.

INSURANCE COVERAGE AND ACCESS

- Medicare, some State medicaid products, and many private insurances do cover TMS for TRD; usually with prior authorization and demonstration that prior treatments have not worked
- Diagnoses are often restricted to MDD, severe (not BPAD or other depression), which can be limiting
- The treatment is *not well known* to the public

TMS for TRD

REMISSION AND RECURRENCE

- Like other interventional treatments for depression, it may be better at helping people out of depressive episodes than keeping them out of said episodes
- Most payment protocols do not allow for "maintenance" TMS, as is sometimes done with ECT, for example; though a person can sometimes be "re-treated"

THE FUTURE?

- Clinicaltrials.gov now lists over 1400 current studies involving TMS – for mental health and other conditions;
- Notably, it is being studied for depression and other conditions in young people, which may be ideal given the low side effect profile



10

Esketamine (Spravato) for TRD

WHAT IS ESKETAMINE?

- Esketamine is s-ketamine: the left/sinister mirror image stereoisomer of racemic ketamine
- Classified as a dissociative anesthetic agent, ketamine (often as an IV preparation) has been used for long-periods of time in emergency rooms as an effective and low-risk anesthetic agent

WHAT ARE PEOPLE INTERESTED IN THIS?

- Ketamine gained interest in the world of psychiatry for a new – and notably rapid – way of lifting people out of severely depressed (and suicidal) states, with few side effects, and without interfering with most medications that people were taking



11

Esketamine

FDA APPROVAL

- Approved for TRD and Depressive Symptoms with acute suicidality in 2019, under specific rules called "REMS" – risk evaluation and mitigation strategy – which restricts to whom and how it can be administered;
- This formulation is a self-administered nasal spray preparation done in a medical office setting, with a two-hour period of monitoring following dosing

IMMEDIATE EFFECTS

- The medication causes a person to become sedated, and somewhat disoriented, and there can be a risk of high blood pressure.
- They are monitored by staff during this process, but when the medications wears off, they are relatively few lingering effects



12

Protocol for esketamine

FROM FDA: RECOMMENDED DOSAGE AND TAPER

• Recommended Dosage for SPRAVATO for TRD Adults

- Induction Phase Weeks 1 to 4: Day 1 starting dose: 56 mg. Administer twice per week. Subsequent doses: 56 mg or 84 mg
- Maintenance Phase Weeks 5 to 8: Administer once weekly 56 mg or 84 mg
- Week 9 and after: Administer every 2 weeks or once weekly* 56 mg or 84 mg

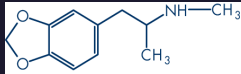
INITIAL PHASE AND MAINTENANCE

- There is a notable difference compared to TMS – that maintenance doses are allowed, and often insurance-supported
- There is some evidence that continued treatment does help to prevent depressive relapse
- There are some different mechanisms of action involving esketamine, and one suggested mechanism is a period of increased neuroplasticity – that may be shared in common with (other) psychedelic agents; this may suggest ways of making the treatment effect more durable, less drug-dependent... (more on this in a bit)

13

Let's move away from Depression for a Minute... (we will be back)

MDMA



WHAT, WHAT???, THAT MDMA!

- Yes, THAT MDMA; ecstasy; "molly", etc.
- As it turns out, this drug has been subject to significant misinformation and moral panic for decades, and also has been the subject of rigorous study as a treatment drug, especially for PTSD, in combination with a specific psychotherapy protocol

14

Club drug or treatment drug? Both or neither?

SET, SETTING, AND SUPPORT



15

Set and setting

CONTEXT MATTERS

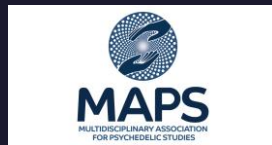
- Following from work of Al Hubbard and Timothy Leary and others, the idea of the "set" - meaning "mindset", broadly encompassing one's intentions, hopes, fears, past experiences, emotional and other context of the person's inner world...
- And "setting" - meaning not just the physical environment, but the context of an experience — who is around, how safe is it, what has the preparation been like, etc.?
- Others have also added the idea of "support systems" - both before, during, and after the experience of a drug.
- It is difficult to underestimate how profoundly different an experience of the same drug is with different set and setting... (some examples)



MDMA and MAPS

PTSD

- Posttraumatic stress disorder, as mentioned, is a highly prevalent, and difficult to treat problem which commonly also involves cross-diagnostic issues of equal severity (depression, anxiety, substance use, suicidality, "personality disorders", "complex" trauma)
- Many effective treatments can be slow to take effect, with patients remaining negatively impacted — and often disabled — in the meantime.



Research on MDMA-AT for PTSD

THE RESEARCH

- MAPS has now completed and published, in major journals, two phase three clinical trials of its research into MDMA-AT for PTSD; they are expected to submit an application for the approval of this as a treatment to the FDA, which would also involve a re-scheduling process with the DEA (as MDMA remains "schedule I")

BREAKTHROUGH STATUS

- The results of the early studies were sufficiently robust that the FDA granted MDMA "breakthrough" status — which accelerates some portions of the study and approval process
- That said, some elements of these processes were not shortcut, due to slow changing perceptions of this investigational product, and concerns about risk and safety



Study results – phase 3 trials

1ST PHASE 3 TRIAL

- Both Studies focused on persons with a focal traumatic event, but did not exclude those who also had complex or other developmental trauma
- "At the primary study endpoint (18 weeks after baseline), 28 of 42 (67%) of the participants in the MDMA group no longer met the diagnostic criteria for PTSD, compared with 12 of 37 (32%) of those in the placebo group after three sessions."
- Mitchell, J.M., Bogenschütz, M., Lilienstein, A. et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med* 27, 1025–1033 (2021). <https://doi.org/10.1038/s41591-021-01336-3>

2ND PHASE 3 TRIAL

- "... 45 of 52 (86.5%) participants treated with MDMA-AT achieved a clinically meaningful benefit, and 37 of 52 (71.2%) participants no longer met criteria for PTSD by study end."
- No deaths or severe treatment emergent adverse events in treatment group.
- Mitchell, J.M., Ot'alora, G., M., van der Kolk, B. et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nat Med* 29, 2473–2480 (2023). <https://doi.org/10.1038/s41591-023-02565-4>

The MDMA for PTSD Basic Protocol

3 PREP, 3 TREATMENT, 9 INTEGRATION SESSIONS

- Two therapists, who meet with patient for:
- 3 90 min. Preparatory sessions
- Then an 8 hour medication assisted session with both therapists present
- Usually a stay overnight, with a night attendant, and therapists "on call"
- Next morning is the first "Integration" session, also 90 mins.
- 2 more integration sessions over next month
- Then second MDMA session, and cycle repeats through three treatments

The basic premise (from MAPS manual)

- "The basic premise of this treatment approach is that the therapeutic effect is not due simply to the physiological effects of the medicine; rather, it is the result of an interaction between the effects of the medicine and therapeutic setting and the wishes of the participant and the therapists. MDMA produces an experience that appears to temporarily reduce fear, increase the range of positive emotions toward self and others, and increase interpersonal trust without clouding the sensorium or inhibiting access to emotions. MDMA may catalyze therapeutic processing by allowing participants to stay emotionally engaged while revisiting traumatic experiences without being overwhelmed by anxiety or other painful emotions. Frequently, participants are able to experience and express fear, anger, and grief as part of the therapeutic process with less likelihood of either feeling overwhelmed by these emotions or of avoiding them by dissociation or emotional numbing. In addition, MDMA can enable a heightened state of empathic rapport that facilitates the therapeutic process and allows for a corrective experience of secure attachment and collaboration with the therapists. At some point during the MDMA experience, feelings of empathy, love, and deep appreciation often emerge in conjunction with a clearer perspective of the trauma as a past event and a heightened awareness of the support and safety that exist in the present. Research participants have said that being able to successfully process painful emotions during MDMA-assisted psychotherapy has given them a template for feeling and expressing pain that has changed their relationship to their emotions."

What is "happening" in these sessions?

INNER HEALING INTELLIGENCE

- "...it is essential to encourage the patient to trust their inner healing intelligence, which is a person's innate capacity to heal the wounds of trauma. It is important to highlight the fact that the participant is the source of their own healing. The MDMA and the therapists are likely to facilitate access to a deep healing process, but they are not the source of this healing process."

INNER-DIRECTED APPROACH

- "A nondirective approach to therapy based on empathetic rapport and empathetic presence should be used to support the participant's own unfolding experience and the body's own healing process. A non-directive approach emphasizes invitation rather than direction"
- Note: treatment manual can be found on the MAPS website, downloaded for free – it's a good read! - maps.org

32

MDMA – further considerations/thoughts

- Very notable that patient's depressive symptoms also for many participants
- Other protocols and permutations are being studied for this – and other – drugs

WHAT'S NEXT?

- Possible approval in 2024, with actual patient availability hoped for by late 2024
- A hope of treating a million patients in first year, or 10% of known PTSD population in USA
- Workforce and training, scaling up; issues connected to finances and billing, advocacy
- Further "Phase 4" studies planned/requested for adolescents, and possibly younger children – could we help eliminate PTSD before it becomes a lifelong struggle?

33

Psilocybin and TRD, ? Other Conditions

THE PSILOCYBE MUSHROOM



NOT YET APPROVED, STUDIES UNDERWAY

- Is being studied in a number of settings, and for a number of conditions, in the USA and internationally;
- Has been shown to help with anxiety associated with death and dying; smoking cessation (in both US and UK trials), and depression

34

Psilocybin methods and protocols

SET, SETTING, PREPARATION, INTEGRATION

- Similar to MDMA-AT, the specific protocol involves significant attention to set and setting, with both a preparatory and integration element (before and after)
- Different from MDMA, some studies have less emphasis on the specifics of the work done in session – in some cases having a solo but monitored experience followed by integration
- The acute period of psilocybin is also generally shorter than with MDMA, and is considerably shorter than, for example, LSD

MUSIC

- Music and playlists are also an important part of both MDMA and psilocybin experiences, with music (usually without words) having some relationship to the onset, peak effect, and comedown period of the drug's acute effects



25

Compass Pathways Phase IIb COMP360 psilocybin therapy

- Depression symptoms: patients who received a 25mg dose of COMP360 psilocybin with psychological support experienced a highly statistically significant reduction in symptoms of depression after three weeks: the difference between 25mg group and 1mg group was -6.6 on the MADRS* depression scale at week 3, $p < 0.001$.
- Durability: double the number of patients who received 25mg had a sustained response at week 12, compared to those who received 1mg (20.3% of patients in the 25mg group vs 10.1% in the 1mg group).
- Tolerability: COMP360 psilocybin was generally well-tolerated. On the day of COMP360 administration, headache, nausea, and dizziness were the only adverse events where a dose-related increase in incidence was evident and there were no clinically significant differences between dose group in vital signs or clinical laboratory tests observed during the study.
- Adverse events: In this study suicidal ideation and intentional self-injury were seen in all treatment groups (as is regularly observed in a TMD population), and the majority occurred more than a week after the psilocybin session. There was no mean worsening of suicidal ideation scores in any treatment group. Suicidal behaviors were reported at least 1 month after COMP360 administration for 3 non-responders in the 25mg arm.

26

Psilocybin for smoking cessation

- "In controlled studies, the most effective smoking cessation medications typically demonstrate less than 31% abstinence at 12 months post-treatment... whereas the present study found 60% abstinence more than a year after psilocybin administration"

From: Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. *Am J Drug Alcohol Abuse*. 2017 Jan;43(1):55-60. doi: 10.3109/00952990.2016.1170135. Epub 2016 Jul 21. Erratum in: *Am J Drug Alcohol Abuse*. 2017 Jan;43(1):127. PMID: 27441452; PMCID: PMC5641975.



27

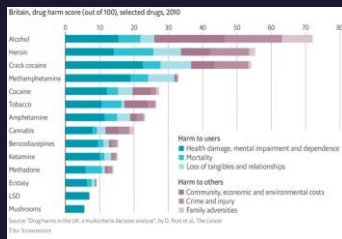
Psychedelic psychotherapies do have risks and potential harms

- Not all experiences are positive, or easily integrated
- Many groups have been excluded from study designs, and some there is much that is not yet known about their experiences
- Caution should be taken around screening, use, set, setting, and potential risks...
- Some conditions may indeed be real contraindications, where risks outweigh benefits
- At the same time, many readily available substances which are legal have similar or greater risk profiles, and so these questions should not be considered in isolation



28

Harm and legal status have little correlation



29

"Great disruptors" of the mental healthcare system? (B. Sessa)

A "MEDICINE" TREATS A SPECIFIC PROBLEM. RIGHT?

WHO CONTROLS "HEALING"?

- Challenge our ideas about diagnostic categories
- Challenge our ideas about what might be possible, what might be long-term and short-term
- Challenge business models to adapt and get ready to implement; space and time and staffing considerations
- Challenge legal structures, and possibly even authority structures in which people use such substances, etc.



30

Critical periods?

- In neurodevelopment, there is a concept of "critical periods", times when the brain is uniquely able to develop certain skills and abilities – some of these have to do with motor function, cognitive development, language acquisition, and visual system development... there's a window, and once it's closed, it's closed – and the brain has to live without, or, in some cases, find another way to do the same tasks (usually slower, harder, less complete)
- It has been an unsettled question as to whether, once closed, a critical period could reopen by means of a drug or treatment (we do know that after a stroke, for example, the motor learning period reopens on its own for 2 weeks, which allows for rehabilitation in that small window of time)



31

Dolen lab, and Dr. Gul Dolen and her team

"The Dolen laboratory has made the groundbreaking discovery that MDMA can reopen a novel critical period of brain plasticity in mice (Nardou et al., Nature, 2019). More recently, we have shown that this property generalizes across psychedelics, including ketamine, psilocybin, LSD, and ibogaine (Nardou et al., Nature 2023). Building on this discovery, we have initiated the PHATHOM project (Psychedelic Healing Adjunct Therapy Harnessing Opened Malleability; www.phathomproject.org), which aims to test the hypothesis that psychedelic drugs are the long-sought 'master keys' for unlocking multiple critical periods across the brain, a property that can be harnessed for therapeutic benefit."



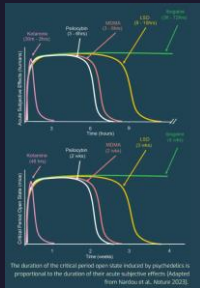
32

Animal models, but with powerful implications

- Octopuses are used for this research because of their significant intelligence, highly developed and centralized nervous systems, and large brains
- Some studies have also been done with mice, with similar effects



33



The period during, and after...

- Dolen's research suggests that much, much more attention needs to be considered about how to make use of the specially neuroplastic state following medication dosing (and after their effects have worn off). It may help to explain some of the extraordinary results that we have already seen from psychedelics with difficult-to-treat conditions that have longstanding neurobiological correlates.

34

How do people experience their integration?

- How might we begin to even categorize peoples' experiences with these substances, and what they mean in their lives?
- Frymann T, Whitney S, Yaden DB, Lipson J. The Psychedelic Integration Scales: Tools for Measuring Psychedelic Integration Behaviors and Experiences. Front Psychol. 2022 May 23;13:863247. doi: 10.3389/fpsyg.2022.863247. PMID: 35677137; PMCID: PMC9168432.

The Psychedelic Integration Scales

Please rate your level of agreement with the following statements, considering the time period since your most recent psychedelic experience. If you have never had a psychedelic experience, indicate your responses only with respect to the time period since you last had a psychedelic experience. Answer as honestly as possible. There are no right or wrong answers. A 5 and 1 are the most extreme, with 3 being the most common score and 2 being middle.

*Some are measured on a 5-point Likert scale: Strongly Disagree, Disagree, Neither agree nor disagree, Agree, and Strongly Agree

Integration Engagement Scale	Experienced Integration Scale
I've given myself mental space to reconnect to the experience.	I feel at peace with my experience.
I've read, viewed, or listened to information content relevant to my experience.	I feel more balanced since my experience.
I've gained insight on my experience through talking with supportive people.	I have a continued sense of open-minded curiosity about my experience.
I've spent time in silent contemplation of my experience.	I feel harmony between the experience and my inner being.
I've spent time in nature to nurture my experience.	I feel harmony between my daily life and my experience.
I've focused up on my experience with focused attention practice (meditation, mindfulness, mantra, journaling, visualization, etc).	I feel a sustained connection to my experience.
I've applied teachings from my experience to my life.	I feel more connection to my life because of my experience.
I've found ways to carry the experience I had for my experience into my daily life.	I have a deep feeling of connection between nature and my experience.
Because of my experience, I've prioritized my mental wellness.	I feel greater self-awareness since my experience.
I've spent time in environments that help me stay attuned to the lessons following from my experience.	I feel the benefit from my experience expressed in my life.
I've been supportive of others as a result of my experience.	I feel the positive effect of the way I interpret my experience.
I've made healthy life choices for myself because of my experience.	I've had the benefit of my experience extending past myself into my community.

35

Not "just the drug" but...

- An interaction between the drug and what we do with it afterward – the so-called integration aspects – whether this is done with peers, professionals, or by one's self.
- Many people who use psychedelic substances will say later on – and sometimes decades later – that these experiences are some of the most powerful and meaningful of their entire lives;
- Surely from that point of view, it's not necessarily a surprise that they might have significant and lasting effects?
- Whether characterized by "deep introspection and insight" or "a mystical" or "transcendental" experience, there would seem to be great potential in these substances, a potential that may transcend psychiatry and the bounds of the helping professions.

36

Thank You

Kurt L. White, LICSW, LADC, CGP, AGPA-F

kwhite@brattlebororetreat.org

(802) 258-4388



37
