

# MDMA-Assisted Psychotherapy for PTSD: Social Connectedness as a Moderator

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## Presentation Outline

Despite recent critiques of MDMA-assisted therapy and questions regarding its validity in treating PTSD, I propose that we can understand its effectiveness through the concept of social connectedness. I contend **MDMA-assisted psychotherapy for PTSD is effective because it promotes a sense of connectedness in participants and social connectedness moderates PTSD symptom severity.**

## Presentation Outline

Continued...

**Rationale:**

- PTSD Prevalence
- Current treatment options low success rates and high dropout rates

Introduction to the **main concepts** and variables:

- **Post-traumatic stress disorder (PTSD)**
  - o Current diagnostic criteria
  - o History
- **MDMA-assisted psychotherapy**
  - o History
  - o Description (protocol and dosing)
- **Social connectedness**
  - o Definition

## Presentation Outline

Continued...

Working hypotheses:

## MDMA-assisted psychotherapy is effective in treating PTSD

- Research evidence

## MDMA increases participants' sense of social connectedness

- Research evidence

## Social connectedness moderates PTSD symptom severity

- Research evidence

Discussion:

- Future research to address FDA panels concerns
- Potential other applications for MDMA-assisted psychotherapy
- Watts connectedness scale
- Maladies of disconnection
- Conclusion
- Q&A
- References

### PTSD Prevalence:

- According to The Daily, which is Statistics Canada (2024) official release bulletin, 8% of Canadians reported moderate to severe PTSD symptoms in 2023
- In the United States, according to Goldstein et al. (2016), 6% of the population will have PTSD at some point in their life.

## Rationale cont...

## PTSD Impact

- Economic
  - The economic cost of PTSD in the US from a societal perspective was estimated to be \$232.2 billion in 2018 alone (Davis, et al., 2022).

## Persona

- nightmares, flashbacks, hyperarousal, avoidance behaviors, negative thoughts and feelings, disruptions to their interpersonal relationships and overall distress (Bryant, 2019).
- 47% increased risk of mortality (Nilaweera et al. 2023)

## Rationale cont...

## Current Treatments

- Selective serotonin reuptake inhibitors (**SSRI's**), which are estimated to have a **20-30%** success rate (Alexander, 2012).
- Therapeutic modalities, such as prolonged exposure therapy, have had more success than medication alone, but have very high dropout rates (Najavits, 2015).

### PTSD Diagnostic criteria:

### DSM-5 Criteria for PTSD

Full copyrighted criteria are available from the American Psychiatric Association (2). All of the criteria are required for the diagnosis of PTSD. The following text summarizes the diagnostic criteria:

**Criterion A (1 required):** The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, in the following way(s):

- Direct exposure
- Witnessing the trauma
- Learning that the trauma happened to a close relative or close friend
- Indirect exposure to aversive details of the trauma, usually in the course of professional duties (e.g., first responders, medics)

## Diagnostic criteria cont...

**Criterion B (1 required):** The traumatic event is persistently re-experienced, in the following way(s):

- Unwanted upsetting memories
- Nightmares
- Flashbacks
- Emotional distress after exposure to traumatic reminders
- Physical reactivity after exposure to traumatic reminders

## PTSD

## Diagnostic criteria cont...

**Criterion C (1 required):** Avoidance of trauma-related stimuli after the trauma, in the following way(s):

- Trauma-related thoughts or feelings
- Trauma-related reminders

# PTSD

## Diagnostic criteria cont...

**Criterion D (2 required):** Negative thoughts or feelings that began or worsened after the trauma, in the following way(s):

- Inability to recall key features of the trauma
- Overly negative thoughts and assumptions about oneself or the world
- Exaggerated blame of self or others for causing the trauma
- Negative affect
- Decreased interest in activities
- Feeling isolated
- Difficulty experiencing positive affect

# PTSD

## Diagnostic criteria cont...

**Criterion E (2 required):** Trauma-related arousal and reactivity that began or worsened after the trauma, in the following way(s):

- Irritability or aggression
- Risky or destructive behavior
- Hypervigilance
- Heightened startle reaction
- Difficulty concentrating
- Difficulty sleeping

# PTSD

## Diagnostic criteria cont...

**Criterion F (required):** Symptoms last for more than 1 month

**Criterion G (required):** Symptoms create distress or functional impairment (e.g., social, occupational)

**Criterion H (required):** Symptoms are not due to medication, substance use or other illness.

Two specifications:

1. **Dissociative Specification.** In addition to meeting criteria for diagnosis, an individual experiences high levels of either of the following in reaction to trauma-related stimuli:
  - Depersonalization. Experience of being an outside observer of or detached from oneself (e.g., feeling as if "this is not happening to me" or one were in a dream).
  - Derealization. Experience of unreality, distance, or distortion (e.g., "things are not real").
2. **Delayed Specification.** Full diagnostic criteria are not met until at least 6 months after the trauma(s), although onset of symptoms may occur immediately.

# PTSD

## History

- The term "post-traumatic stress disorder" came into use in the 1970s, in a large part due to the diagnoses of U.S military veterans of the Vietnam War. It was officially recognized by the American Psychiatric Association in 1980 in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III). PTSD has been known by many names in the past, such as "shell shock" during the years of World War I and "combat fatigue" after World War II, but PTSD does not just happen to combat veterans. PTSD can occur in all people, of any ethnicity, nationality or culture, and at any age.

# Introduction to the main concepts and variables

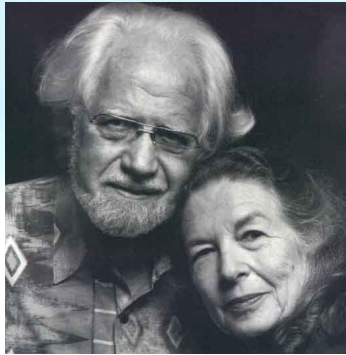
## MDMA-assisted psychotherapy:

- History (Passie, 2018):
  - First synthesized in Germany by Merk in 1912
  - In 1970, 3,4-methylenedioxy-amphetamine (MDA) was made illegal, and the search began for a replacement; another phenylalanine that could assist in psychotherapy
  - Psychiatrist Claudio Naranjo and his associate, chemist Alexander Shulgin, studied derivatives of the essential oils of nutmeg to synthesize MDMA



## The Shulgins

Alexander & Ann



## MDMA-assisted psychotherapy:

### • History continued (Passie, 2018)...

- MDMA an improvement on MDA as it was less toxic
- 1977 Shulgin introduces MDMA to Leo Zeff, a core figure in underground psychedelic therapy
- Zeff went on to administer it to several thousand people and train more than 150 therapists
- Noted early on by therapists using MDMA as an adjunct that it engendered a sense of connection, and was good for treating PTSD



## MDMA-assisted psychotherapy:

- **History continued (Schroder 2007)...**

- 1982 Rick Doblin tried MDMA for the first time as he was connected to the underground psychedelic-psychotherapy movement after dodging the draft because he was a conscientious objector.
- No research was being published for fear of MDMA being made illegal like all the other psychedelics. However, many doctors and psychiatrists were in support and this surprised the DEA when they first designated it as illegal.
- Initially supporters won the judges ruling, but in 1985 DEA overturns judges ruling to make MDMA illegal (Schedule 1)
- 1986 Rick Doblin started up the Multidisciplinary Association of Psychedelic Studies (MAPS, recently renamed Lykos Therapeutics) where the main purpose has been to advocate for psychedelic-assisted psychotherapy, and, in particular, has focused on MDMA-assisted psychotherapy

## MDMA-assisted psychotherapy: History continued...

- MDMA was once believed to be a neurotoxin by some people after some faulty research, but Grob (1998) reported on preliminary investigations in MDMA research with human subjects and stated that, "Comprehensive neuropsychological testing revealed no baseline evidence of deleterious effects on cognition, memory or concentration in individuals with histories of MDMA use, or prospectively in subjects administered the drug" (p.123).
- Since 1985 when MDMA was made illegal, researchers have been trying to provide rationale for utilizing it in psychotherapy (Grinspoon & Bakalar, 1986; Grinspoon & Doblin, 2001). A full review of research is forthcoming.

## MDMA-assisted psychotherapy:

- **Protocol Development**

- Set and setting: *set*, the participants' expectations about the experience, and *setting*, the total social and physical environment (Zinberg & DeLong, 1974).
- Borrowed from protocol for LSD-assisted therapy developed by Stanislav Grof, with music and eye shades for 'inside time'.
- 125mgs at the beginning and then offered an optional supplemental dose of 62.5mgs about 2-2.5 hours later



- Participants had two to three 90-minute preparation sessions before their first experimental session and each of the experimental sessions were followed by three integration sessions.
- Two therapists, typically a male and female dyad, stayed with the participant for the entire day of the experimental session and came back the next morning for the first 90-minute integration session
- The therapeutic approach is non-directive and follows the patients “inner healing intelligence”.
- This is the protocol used for all of the MAPS sponsored research.

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## Social Connectedness

- Townsend and McWhirter (2005) concluded that social connectedness was an “important factor in healthy interpersonal functioning” and leads to resilience for both men and women and “is a protective factor among adolescents” (p. 198).

**My main argument:**

Three main claims:

1. MDMA-assisted psychotherapy is effective in treating PTSD.
2. MDMA increases participants' sense of social connectedness.
3. Social connectedness moderates PTSD symptom severity.

- Mithofer et al. 2010:
  - 20 participants total. n=12 experimental group. n=8 control group, of which 7 crossed over open label after.
  - Good safety profile; no medical complications
  - Statistically significant improvement in the treatment vs placebo group

- Longterm follow up of the previous (2010) study
- 16/19 took part.
- no significant difference between their clinically significant score 2 months following the last experimental session and a score taken an average of 3.5 years later.
- no participants experienced any neurocognitive decline or substance abuse.









## MDMA increases participants' sense of social connectedness

### Research Evidence cont...

- Looking directly at social connectedness, Hysek et al. (2014) investigated if MDMA on its own would enhance emotional empathy and prosocial behavior.
- Utilizing a placebo-controlled, double-blind, random-order, crossover-design in 32 healthy volunteers split evenly between men and women, the effects of MDMA were measured using the Multifaceted Empathy Test, the Social Value Orientation (SVO) test, Facial Affect Recognition, and Visual Analogue Scales (VASs).
- Results indicated MDMA increased mens empathy and pro sociality scores, to the level of women taking the placebo and women did poorly at recognizing fearful, angry, disgusted, and surprised faces

## MDMA increases participants' sense of social connectedness

### Research Evidence cont...

- Looking at the acute effects of MDMA on interpersonal cooperation and trust, Gabay et al. (2019) used a double-blind, placebo-controlled, crossover study with 20 male participants.
- The experiment used the Prisoner's Dilemma and a video game with both trustworthy and untrustworthy opponents.
- Results indicate that "MDMA causes a change in the social tie and appraisal of others' actions, leading to greater recovery of cooperation with trustworthy partners following a breach in trust" (p.319).
- The authors surmised that MDMA increases cooperation and recruitment of social brain areas.







- Using correlations between the measures Solomon et al. (1990) found that social support explained 26% of the loneliness variant and that the social measures accounted for 27% of the PTSD variance (pp. 465-466).
- Most notably of all the perceived social dimensions, only feelings of loneliness were directly related to psychopathology
- authors concluded that perceived social support does not have a "direct protective function but rather promotes mental health via the impact on feelings of loneliness" (p. 468).



## Research Evidence cont...

- Laffaye et al. (2008) examined the relationship between PTSD symptom severity and interpersonal resources versus stressors for veterans with regards to social support from different sources.
- 128 male veterans who had completed a residential program for PTSD treatment were recruited.
- used the PTSD Checklist-Military version and the Interpersonal resources and interpersonal stressors subscales of the Life Stressors and Social Resources Inventory.
- veteran friends provided the most support with the least interpersonal stress as compared to spouses who provided roughly equal support and stress. Non-veteran friends were perceived to provide more support than stress and relatives provided the least support and were perceived to be more stressful than supportive.

## Research Evidence cont...

- To determine whether social connectedness prevents PTSD or social disconnection is a result of suffering from PTSD, Kaniasty and Norris (2008) utilized a longitudinal research design.
- Given this design they were able to illuminate the sequential roles of social causation and social selection with regards to perceived social support and post-traumatic stress symptoms following a natural disaster.
- total of 557 participants were recruited and measured at 6 months, 12 months, 18 months, and 24 months post-disaster. During the phase between 6- and 12-months, social support was seen to decrease PTSD symptoms between 12 and 18 months, both patterns emerged with social selection taking over in the time between 18 and 24 months.
- Kaniasty and Norris (2008) postulated that after that amount of time people still suffering with PTSD symptoms would become burdensome on their social supports who may begin to avoid them, thereby perpetuating the negative sequelae of the PTSD symptoms.



- Sippel et al. (2018) and Sippel et al. (2019) looked at both the social erosion as well as the social causation models of PTSD and social connectedness
- 3789 participants in the first study and 1491 in the second study, all veterans
- Utilized PTSD Checklist–Civilian (PCL-C), and two items from the Brief Addiction Monitor (BAM) in both.
- Both correlational, with the 2019 study looking at 4-month follow-up data
- Findings of the study were consistent with both the social erosion as well as the social causation models of PTSD and social connectedness.

- Kintzle et al. (2018) explored the role of social connectedness in the development of PTSD
- 722 veterans. PTSD was measured using the PCL-5. Social connectedness was measured using the Social Connectedness Scale.
- Findings indicated a direct effect of social connectedness on PTSD symptoms in that the “extent to which veterans in the study felt socially connected inversely impacted the level of PTSD symptoms” (p. 5).
- Researchers concluded that social connectedness, and its associated sense of belonging, could be targeted as a protective factor in the transition from service to civilian life.

## Evidence From MDMA-Assisted Therapy for PTSD Research

- Van der Kolk et al. (2024) looked at the participants self-experience in MDMA-assisted psychotherapy for PTSD and utilized measures for alexithymia, self-compassion, and altered self-capacities. Self-capacities included affect-regulation, negotiating interpersonal conflicts, abandonment concerns, self-awareness, idealization/dissillusionment, susceptibility to influence, and tension reduction activities.
- They found each one significantly improved with MDMA-assisted therapy as compared to psychotherapy and placebo. In fact, endpoint emotional regulation and self-capacities were critical factors in predicting remission of PTSD.
- Participants with low self-capacity ratings at baseline only saw improvements in their PTSD with the MDMA-assisted therapy and not in the therapy-placebo group. This would indicate that MDMA as an adjunct helped improve participants self-capacities which allowed them to engage in therapy more effectively.

**Sense of social connectedness moderates PTSD symptom severity**  
**Evidence From MDMA-Assisted Therapy for PTSD Research Cont...**

- Van der Kolk et al (2024) point out that the majority of studies looking at mental changes, secondary to administration of MDMA have been conducted in normal populations who are much less likely to suffer from major problems with self-experience. Conversely in this study they examined the effects of MDMA on a group of individuals with major clinical deficits and found that MDMA may be most pertinent for persons with clinically significant impairment in emotional regulation and other self-capacities.
- The vast majority of their participants had been traumatized in early childhood which is known to impair the development of self-capacities and is associated with Alexithymia and a lack of self-compassion. Utilizing MDMA as an adjunct in therapy for this particular population not only appeared to help them improve on these deficits but also simultaneously this allowed for them to engage in therapy better.

**15 MINUTE BREAK**

## Discussion

## Concerns and Limitations

- The field of MDMA-assisted psychotherapy is still in the initial stages. Proponents were hopeful of approval from the FDA for treating PTSD, but on August 9, 2024, the decision to request an additional Phase 3 trial was communicated by the FDA to Lykos Therapeutics (Lykos Therapeutics, 2024)
- Considering this impactful decision, a thorough discussion of the limitations and concerns about the current research is forthcoming.

## Discussion

## Concerns and Limitations

- Low number of clinical trials
- Low number of participants
- Lack of diversity in participants - results generalizable?
- Previous MDMA experience - lower adverse reactions than regular population
- Under-reporting of adverse reactions
- Functional unblinding - participant expectancy could skew results
- Ethical transgressions by therapists
- The therapeutic component is not an approved evidence-based psychotherapy

## ICER Report

- On May 14, 2024, the Institute for Clinical and Economic Review (ICER, 2024) published an evidence report echoing many of the same concerns outlined above (Mustafa et al., 2024).
- ICER report was compiled looking only at evidence from the two Phase 3 trials, Mitchell et al. (2021) and Mitchell et al. (2023).
- This report pointed out that the vast majority of participants correctly identified their treatment group assignment; MDMA versus placebo. This functional unblinding, coupled with accusations that the trial therapists had encouraged favourable reports from participants was assessed as a high risk for bias.

## FDA Advisory Panel

- On June 4, as can be viewed on PBS NewsHour's (2024) YouTube channel, the FDA advisory panel convened and over the course of 9 hours the panel heard from and could ask questions of Lykos representatives, FDA representatives and 33 speakers invited to their open forum.
- Lykos and the FDA talked about a proposed Risk Evaluation and Mediation System (REMS) and they encouraged feedback and suggestions from the panelists and guest speakers.
- Panel deliberated on four discussion questions and two voting questions. In the end, the panel voted against endorsing MDMA-assisted psychotherapy for PTSD with nine out of 11 not seeing enough evidence of its effectiveness and 10 out of 11 not believing the benefits outweigh the risks at this point. Most panelists rationale for their decision included the sentiment that more research needs to be done.

## FDA Decision

- Following the advisory panels advise, on August 9, 2024, the FDA communicated their decision to Lykos that they would not approve MDMA-assisted psychotherapy at this time and requested another Phase 3 trial (Lykos Therapeutics, 2024)
- In their August 9 news release Lykos again reiterated that this decision comes as a great disappointment to many people suffering with PTSD for whom the current treatments are insufficient.

## Looking to the Future

- Future research should look to addressing the FDA advisory panels concerns, some issues will be easier to address than others.
- More clinical trials, more diversity and number of participants, participants who have never tried MDMA, more safety monitoring, pairing MDMA with different types of therapy (more on that in a little bit). All this is time consuming, but doable.
- Ethical transgressions by therapists - more safe guards, more accountability, change in training and culture, (example of touch in MAPS training in 2021)
- Functional unblinding - participant expectancy could skew results - this is very difficult to fix! Any ideas?

## Other Applications for MDMA-assisted therapy

- ## MDMA had been dubbed a 'connectogen'

## Connection to self, others, and the world

- Stocker and Liechti (2024) argue that MDMA is more than an entactogen (connection to self) or an empathogen (connection to others), both names it has been dubbed, and instead they propose calling it a connectogen.
- MDMA can assist psychotherapy by reducing amygdala activity and increasing oxytocin release; in other words, by reducing fear and increasing feelings of love for self and others. There is an inverse relationship between fear and compassion (Hollingsworth, 2008), and MDMA can catalyze this effect when used as an adjunct in therapy. By reducing fear and increasing compassion MDMA can help engender a sense of connectedness to self, others, and the world.
- In agreement, Agin-Liebes et al. (2025) found that **Self-compassion mediates treatment effects** in MDMA-assisted therapy for co-occurring PTSD and depression

# Watts Connectedness Scale

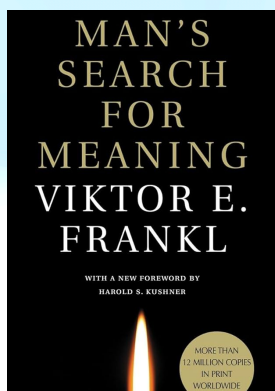
## Maladies of Disconnection

- # Discussion
- ## Maladies of Disconnection
- Addiction (more than just substance use)
  - Depression
  - Anxiety
  - PTSD
  - Interpersonal issues
  - Existential issues
  - Others?



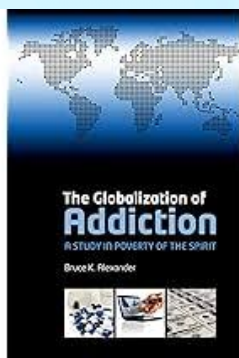
## Maladies of Disconnection

- Viktor Frankl, *Mans Search for Meaning* (1946).
- The Existential Vacuum is when a person lacks a sense of meaning and purpose in their lives
- Meaning and purpose comes from meaningful relationships and meaningful goals, both of which are impossible without self-awareness



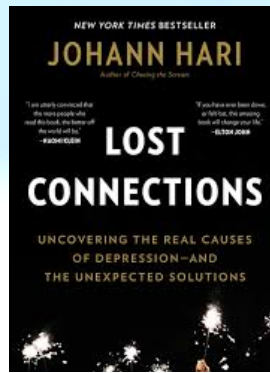
## Maladies of Disconnection

- Bruce Alexander, Psychosocial-dislocation theory of addiction. Globalisation of Addiction (2008)
- Rat Park



## Maladies of Disconnection

- Johann Hari, *Lost Connections: Uncovering the Real Causes of Depression - and the Unexpected Solutions* (2018)



## Discussion

## Future Research Suggestions

- Pair MDMA with Meaning Centred Group Therapy and use the Watt's Connectedness Scale as a standard outcome measure.
- Meaning Therapy (Existential-Humanistic Therapy) focusses directly on connection to self, others, the world. Targeting these as a way to improve participants sense of meaning and purpose.
- Use lower doses to improve interpersonal interaction (Greer & Tolbert 1986; Kirkpatrick & de Wit, 2015) and safety profile.

## Conclusion

## Take home message

- MDMA-assisted therapy could be effective in treating any maladies of disconnection, particularly if the therapeutic aspect aligned theoretically.
- None of the concerns brought forward by the FDA advisory panel negate this conclusion.
- All of the FDA's concerns could be addressed, except for functional unblinding, but as long as the results are durable over time...who cares?!
- Despite the risks, which certainly need to be mitigated, there is ample reason to utilize MDMA as an adjunct in therapy to catalyze healing for the sea of people who are suffering from maladies of disconnection, including PTSD.

# Q&A

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