

Statistical Analysis Plan for Social Anxiety MDMA-Assisted Therapy
Investigation (SAMATI)

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Statistical Analysis Plan

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Study Design

This is a randomized, open-label delayed treatment study to assess the safety and effect of MDMA-assisted therapy in treating 20 participants diagnosed with moderate-to-severe social anxiety disorder (SAD) of the generalized subtype. Half of the enrolled participants (N = 10) will proceed immediately into treatment once enrolled (immediate treatment group), and half (N =10) will receive the experimental treatment after an initial 16 week wait (Delayed treatment group).

The primary outcome assessment will occur at two weeks post final integration session. There will also be a 6-month follow up assessment (28 weeks after final integration session). The study is preregistered at clinicaltrials.gov.

Randomization Plan

We will use permuted block randomization with random blocks of 2 and 4 to minimize the possibility of guessing. This randomization will be conducted by a PhD level scientist who is not involved in the trial so the study team can remain blinded.

Primary Outcome Measures

Leibowitz Social Anxiety Scale (LSAS)

The primary outcome assessed in the study is social anxiety symptom severity measured LSAS (Heimberg et al., 1999). The LSAS is a 24-item, semi-structured interview on the severity of social anxiety disorder, which assesses fear (0 to 3 = none, mild, moderate, severe) and avoidance (0 to 3 = never, occasionally, often, usually) of 24 social situations over the previous week, providing an overall social anxiety severity rating and subscale scores for performance fear, performance avoidance, social fear, and social avoidance. Scores range from a minimum of 0 to maximum of 144 with higher scores indicating a worse outcome.

Secondary Outcome Measures

Sheehan Disability Scale (SDS)

The SDS is a clinician-rated assessment of functional impairment (Sheehan, 1986). The items indicate degree of impairment in the domains of work/school, social life, and home life, with response options based on an eleven-point scale (0=not at all to 10=extremely), and five verbal tags (not at all, mildly, moderately, markedly, extremely) and has been validated for use in clinical trials (K. H. Sheehan & Sheehan, 2008) and psychiatric impairment (Leon, Olfson, Portera, Farber, & Sheehan, 1997). The SDS takes 1 to 2 minutes to complete.

Internalized Shame Scale (ISS)

The ISS is a 24-item self-report questionnaire measuring internalized shame that has been used in numerous studies of trait shame and has been demonstrated to have good construct validity and reliability in both clinical and nonclinical populations (del Rosario & White, 2006). This measure is included to assess changes in shame, which is thought to be important to SAD, and in relation to MDMA, which has been hypothesized to facilitate self-acceptance.

Acceptance of Shame and Embarrassment Scale (ASES)

The ASES is a 17 item self-report measure (Sedighimornani, Rimes, Verplanken, & Gauntlett-Gilbert, 2019) intended to assess avoidance of shame and embarrassment, two emotions hypothesized to be central to the experience of SAD. The measure shows good internal reliability, factor structure, and correlation with theoretically meaningful constructs (Sedighimornani et al., 2019). This measure is being included because MDMA has been theorized to reduce avoidance.

Interpersonal Needs Questionnaire – Thwarted Belongingness Subscale (INQ)

The 9-item Thwarted Belongingness subscale from the INQ (Freedenthal, Lamis, Osman, Kahlo, & Gutierrez, 2011) will be used to assess the degree to which participants feel a sense of belonging, connection, and closeness with others. A recent comprehensive review of measures of social connectedness concluded the INQ was the most psychometrically sound measure (Hare Duke, Denning, de Oliveira, Milner, & Slade, 2019).

Hidden Self Scale (HSS)

The HSS (Levinson, Rodebaugh, Lim, & Fernandez, 2015) is a 4-item subscale of the Core Extrusion Schema–Revised and is thought to measure attempts to hide one's “true self” from others so as to avoid potential ostracism and rejection. This measure was created for use in SAD populations. The measure has demonstrated good psychometrics and the HSS subscale predicts the intensity of social interaction

anxiety. This measure is included based on the idea that MDMA may increase participants' sense of authenticity and reduce fear of revealing vulnerable parts of oneself.

Self-Compassion Scale – Short Form (SCS)

The SCS short form (Raes, Pommier, Neff, & Van Gucht, 2010) is a 12-item self-report measure of self-compassion, or responding to one's own failure, suffering or inadequacies with kindness and compassion and recognizing one's own flaws and suffering as part of common human experience. Because the measure is being administered repeatedly and we wanted it to be sensitive to change, we modified the measure slightly from to refer only to experiences in the last week. It is estimated to take about 3 minutes to complete. This brief measure has been shown to correlate highly with the well-validated longer version of this scale and to have excellent psychometric characteristics itself (Raes et al., 2010).

Analytic plan

Primary Analyses

Primary outcome analyses are intent-to-treat comparing mean scores on the LSAS at primary outcome assessment in the immediate treatment condition ($n = 10$) compared to the 16-week re-assessment in the delayed treatment condition ($n = 10$). A participant is considered eligible for the ITT analysis if they have completed at least one Experimental Session and at least one LSAS assessment beyond baseline. We will use an independent samples t-test to compare means across groups. Hedges' G will be reported as measure of effect size with confidence intervals calculated at 95%.

Secondary Analyses

Descriptive statistics for all primary and secondary outcome variables will be calculated.

To examine the change in social anxiety severity for all participants who received MDMA-assisted therapy, we will also collapse participants in the immediate and delayed treatment groups ($N = 20$) and use a paired samples t-test to compare mean change in LSAS scores from baseline to primary outcome.

To examine sustained treatment effects over time for the entire sample ($N=20$), we use a paired sample t-test to compare LSAS mean scores at baseline with LSAS mean scores at 6-month follow up. Hedges' G will be used to estimate the effect size and confidence intervals will be calculated at 95%. If there is significant heterogeneity in variance across time points, Glass' Delta will be used to estimate the effect.

Secondary outcome analyses are intent-to-treat comparing mean scores on the measure (SDS, ASES, ISS, INQ, SCS, and HSS) at primary outcome assessment in the immediate treatment condition ($n = 10$) compared to the 16-week re-assessment in the delayed treatment condition ($n = 10$). We will use an independent samples t-test to compare means across groups. Hedges' G will be reported as measure of effect size with confidence interval calculated at 95%.

Change in secondary measures will be analyzed using the full sample by collapsing immediate and delayed treatment groups ($N = 20$) and conducting a series of paired samples t-tests comparing all secondary outcome measures (SDS, ASES, ISS, INQ, SCS, and HSS) at baseline, primary outcome and 6 month follow up.

We will report correlations between the primary outcome measure (LSAS) and secondary outcome measures. We will estimate the strength of the relation between change in social anxiety symptom

severity as measured by the LSAS and change in secondary outcome measures from baseline assessment to post-treatment. Specifically, we will subtract baseline scores from primary outcome scores for each measure and calculate bivariate correlations between this change score for the LSAS and change in each secondary outcome measure.

Other Pre-registered Data Analyses

Additional exploratory analyses not described here will be outlined in subsequent pre-registrations and posted to publicly available online repositories prior to data analysis.