Brief Report

Pilot Data on Salivary Oxytocin as a Biomarker of LSD Response in Patients with Major Depressive Disorder

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Pilot Data on Salivary Oxytocin as a Biomarker of LSD Response in Patients with Major Depressive Disorder

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Abstract: Despite growing evidence supporting the efficacy of LSD-assisted psychotherapy in treating major depressive disorder (MDD), identifying reliable psychopharmacological biomarkers remains necessary. Oxytocin, a neuropeptide implicated in social bonding and flexibility, is a promising candidate due to its release following serotonergic psychedelic administration in healthy individuals; however, its dynamics in psychiatric populations are currently unexplored. This observational pilot study aimed to characterize salivary oxytocin dynamics during a single LSD-assisted psychotherapy session in our patients with treatment-resistant MDD. Participants received 100 or 150 µg LSD and salivary oxytocin was measured at baseline, 60, 90, and 180 minutes post-LSD. Concurrently, participants rated subjective drug intensity (0-10 scale) at 60, 90, and 180 minutes. A linear mixed model revealed significant variation of oxytocin levels over time. Perceived psychedelic intensity also significantly varied over time. This supports oxytocin as a potential biomarker. Larger, controlled trials are warranted to replicate these findings and clarify mechanistic links between oxytocin dynamics and clinical outcomes, including changes in depressive symptoms and mental flexibility.

Keywords: psychedelics; LSD; oxytocin; Major depressive disorder; biomarkers

1. Introduction

Despite growing evidence supporting the efficacy of LSD-assisted psychotherapy in treating major depressive disorder (MDD) [1–3], reliable biomarkers of psychopharmacological or treatment response are not yet fully identified [4]. LSD (lysergic acid diethylamide), a classical serotonergic psychedelic, exerts its acute psychoactive effects primarily through partial agonism at the 5-HT_2A receptor, initiating a cascade of neurotransmitter and neuropeptide release [5–8]. The neuropeptide oxytocin, for instance, is released within this cascade and could be a potential psychopharmacological biomarker for LSD-assisted psychotherapy in MDD due to its implication in social bonding, stress modulation, and most importantly, flexibility [9–11]. Indeed, theoretical models suggest that flexibility is a major mechanism underlying mood improvement following psychedelic treatment [12–14].

In healthy volunteers, plasma oxytocin concentrations consistently rise 90–180 minutes after oral LSD administration, subsequently declining after the peak [5,6,15–18]. Studies in rodents, conducted over two decades ago, demonstrated that the selective 5-HT_2A agonist (±)-2,5-dimethoxy-4-iodoamphetamine (DOI) produces a comparable oxytocin increase, which is blocked by the 5-HT_2A antagonist ritanserin [19,20]. Interestingly, in humans, the antagonist ketanserin attenuates LSD's subjective effects [5]. Despite these convergent findings, oxytocin reactivity during psychedelic

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treatment was not yet characterized in psychiatric populations. Furthermore, salivary oxytocin, a convenient and non-invasive measurement method, was not yet assessed during LSD administration.

Here, we report pilot data on salivary oxytocin dynamics during a single LSD-assisted psychotherapy session in patients with treatment-resistant MDD, conducted under compassionate-use approval from the Swiss Federal Office of Public Health. Our primary objective was to characterize salivary oxytocin reactivity across the acute pharmacodynamic window of a single LSD session. We also explored concurrent ratings of subjective drug intensity.

2. Materials and Methods

Design and Setting

This single-center, observational pilot study was integrated into the routine clinical care at the Psychedelic Program of the Division of Addictology, Geneva University Hospitals (HUG), Switzerland. The study protocol was approved by the regional ethics committee (BASEC No.2024-01122) and prospectively registered on ClinicalTrials.gov (NCT06557239). All procedures adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. Patients were invited to participate in this research after they had obtained individual compassionate-use authorization for LSD-assisted psychotherapy from the Swiss Federal Office of Public Health (OFSP). The research protocol, which primarily involved additional salivary sample collection, did not alter the standard clinical routine. All participants provided written informed consent prior to any study procedures. Data collection for this pilot study occurred between September 2024 and February 2025

Participants

Participants were eligible if they met the following inclusion criteria: Major Depressive disorder according to the DSM-5 [21], with criteria of treatment resistance (two or more failed antidepressant treatments of different classes),aged between 18 and 55 years, old, were receiving their first or second LSD treatment with a dose between 100 ug or 150 ug. There were nt restriction related to ongoing antidepressant medication, menstrual cycle phase or hormonal contraception use, due to the pilot nature of the study. Exclusion criteria which are part of the routine protocol were as follow: current psychotic or bipolar disorder, imminent suicide risk, severe cardiovascular, hepatic or neurological disease, pregnancy or breastfeeding, systemic corticosteroid use.

Twelve participants (5 females, 7 males), aged between 25 and 55 years old (Mean: 43.9, SD: 8.79), signed informed consent and agreed to comply with the protocol. However, we initially had problems with salivary sampling of two participants (1 male and 1 female, for who we did not have enough saliva in more than one time-point, impeding the analysis of reactivity). Our instructions and sampling procedures were adapted and repeated measurements could be analyzed for the 10 other participants. Missing data were considered at random and were treated within the Linear mixed model as described below.

Salivary Oxytocin

Saliva samples were collected using Salivette® synthetic swabs (Sarstedt, Germany) at four distinct time-points on the day of LSD administration: Pre-LSD (−10 min before taking the substance, representing baseline), then 60min, 90min and 180 min post-LSD. Samples were temporarily stored at -20 ^{0}C , then centrifuged and stored at −80 °C. Aliquots were subsequently shipped on dry ice to RIAgnosis (Germany) for oxytocin analysis using a radioimmunoassay (RIA). The specific assay procedures are consistent with those described in previous studies, including a study led by our group [22,23].

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Subjective Measures

At each salivary oxytocin collection time-point after LSD intake (60, 90 and 190 min post-LSD), participants provided momentary ratings of subjective drug intensity ranging between 0 (none) and 10 (maximal intensity).

Statistical Analyses

Analyses were performed in IBM SPSS Statistics 28. A linear mixed model (LMM) was employed to investigate the effect of time on oxytocin levels. Oxytocin levels were designated as the dependent variable. Time, a categorical variable with four levels (Pre-LSD, 60min post-LSD, 90min post-LSD, and 180min post-LSD), was included as a fixed effect. To account for the repeated measures nature of the data and individual variability, participant-specific random intercepts were included in the model, with participant ID as the subject grouping variable. An Autoregressive First-Order (AR1) covariance structure was specified for the within-subject repeated measures of oxytocin. The model was estimated using Restricted Maximum Likelihood (REML). A Friedman ANOVA was employed to assess differences in the perceived intensity of psychedelic effects across three repeated measurements (60min post-LSD, 90min post-LSD, and 190min post-LSD). This non-parametric test was chosen due to the ordinal nature of the perceived intensity scale (0-10) and to account for the repeated measures design

3. Results

A linear mixed model analysis revealed a significant main effect of time on oxytocin levels, $F(3, 19.8) = 14.9$, $p < 0.001$. This indicates that oxytocin levels changed significantly across the four measurement points (Pre-LSD, 60min post-LSD, 90min post-LSD, and 180min post-LSD). The estimated marginal means for oxytocin levels and standard errors at each time point are presented in Figure 1.

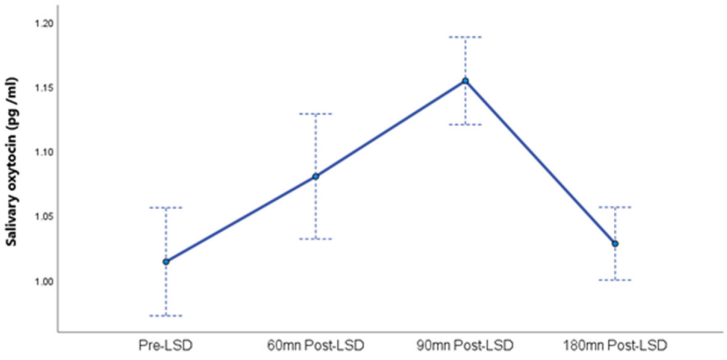

Figure 1. Salivary oxytocin during LSD intake

Figure 1. xxx.

Regarding the random effects, the estimated variance for participant-specific random intercepts was 0.004 (SE = 0.01). The test of this variance component against zero was not significant ($Z = 0.40$, $p = 0.690$), suggesting no detectable significant individual differences in participants' overall oxytocin levels in this pilot study. The 95% confidence interval for the random intercept variance was [~0.000, 0.587], with the lower bound indicating a boundary solution where the estimated variance is effectively zero.

The estimated AR1 parameter for the within-subject covariance structure was 0.009 (SE = 0.011, 95% CI = [0.001, 0.097]). This parameter was also not significantly different from zero ($Z = 0.81$, $p = 0.418$), suggesting no significant autocorrelation between oxytocin levels at adjacent time points within individuals in this sample.

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A Friedman ANOVA indicated a statistically significant effect of time on the perceived intensity of psychedelic effects (Figure 2), χ 2 (2, N = 12) = 21.273, p<.001. This suggests that the perceived intensity of effects varied significantly across the three measurement points (60, 90, and 180 minutes).

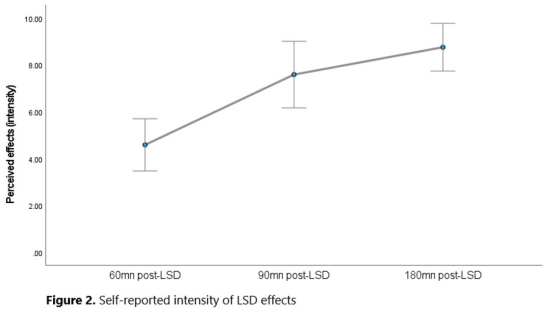

Figure 2. Self-reported intensity of LSD effects

Figure 2. xxx.

4. Discussion

This pilot study presents, to our knowledge, the first characterization of salivary oxytocin dynamics following acute LSD administration in patients with Major Depressive Disorder (MDD). It demonstrates that a non-invasive salivary sampling approach yields temporal information on oxytocin release comparable to that obtained via plasma sampling in earlier investigations. Further, we observed a significant modulation of salivary oxytocin levels over time (with a peak 90 minutes post-LSD intake), paralleling the acute subjective intensity of effects. This finding aligns with previous observations in healthy participants [5,15,24] and is consistent with rodent evidence suggesting 5-HT2A-mediated oxytocin release [19]. While MDMA is more widely recognized for potent oxytocin release and distinct empathogenic properties [16,18], the shared capacity of these compounds to induce oxytocin release, albeit to differing extents, points to potentially convergent neuroendocrine circuits.

Despite encouraging initial findings, it's important to highlight the pilot nature of this study and its obvious limitations. Generalizability, for instance, is further constrained by the open-label design, heterogeneous medication status of participants, and the absence of a control condition. This study also lacked longitudinal oxytocin follow-up and didn't directly assess the relationship between oxytocin release and treatment response (e.g., reduction of depressive symptoms) or mental flexibility. Larger, controlled trials are warranted to replicate these findings and clarify mechanistic links between oxytocin dynamics and clinical outcomes, including changes in depressive symptoms and mental flexibility.

Author Contributions: Conceptualization, TAB; methodology, TAB, LC; formal analysis, TAB; investigation, LC, SA, CA, CM, AB, LF resources, GT, LP, DZ; data curation, TAB, AB; writing—original draft preparation, TAB; project administration, TAB; funding acquisition, TAB. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

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