The Effect of Healthcare Practitioner–Participant Interactions on Participant Heart Rate During Esketamine Treatment

Authors: *Alexander Deschamps[1]; Adam Kolar[1]; Georgios Lampadariou[1]; Miguel A Pinheiro[1]; Ezekiel Powdar[1]; Jamileh Jemison[1]; Todd M Solomon[1]

[1]Mind Medicine Inc, New York, NY

Introduction

Change in hemodynamic function is a side effect of esketamine and may impact determinants of the safety of treatment for individual participants. As a result of these effects, monitoring of vital signs is a central component of the Risk Evaluation and Mitigation Strategy (REMS) protocol that is required for administration of esketamine (marketed as SPRAVATO) for treatment-resistant depression and depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.[1]

As the REMS protocol for esketamine requires frequent monitoring by healthcare practitioners (HCPs), risk exists for additional vital sign changes during an interaction with an HCP based on what is termed the "white coat effect". This may manifest as changes in a participant's heart rate (HR) while executing the monitoring required to fulfill the REMS protocol for esketamine.

Esketamine's expected C_{max} is between 20 to 40 minutes, with a rapid biphasic decline for 2 to 4 hours.[1] In addition to possible cardiac effects after esketamine administration, the present work examines whether participants undergoing depression-related esketamine treatment experience "white coat effects" such as additional heart rate elevation during vital sign measurement interactions with HCPs. These effects may impact determinants of the safety of esketamine treatment continuation for individual participants.

Methods

The MindMed Session Monitoring System (MSMS) is a passive monitoring system comprised of a smartphone, smartwatch, instructions for use, and a provider-facing mobile application that continuously collects movement and physiological data from participants undergoing treatment with a consciousness-altering drug. Specifically, MSMS is designed to collect heart rate, accelerometer, gyroscope, compass, motion, audio, distance, steps, activity, and pedometer data.[2]

Data collected by MSMS was examined to determine how potentially vital sign–altering interventions may impact a participant's biometrics during an interaction with an HCP. Vital signs were routinely monitored 40 and 120 minutes post-esketamine administration. HR was collected passively by the MSMS from 24 participants who completed 129 esketamine sessions. HR data collected was comprised of hundreds of individual samples per 2-hour session (1 sample approximately every 10 seconds).

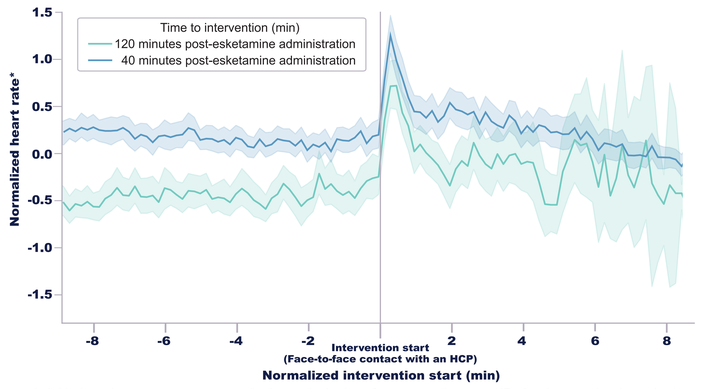
The start of a potentially vital sign–altering intervention was defined as an initiation of face-to-face contact with the participant by an HCP prior to vital sign measurement. MSMS HR data were annotated with time stamps marking the start of an intervention based on audio-recorded initiation of contact. Times are reported as time post-administration. The participant's average HR before and after each intervention start was stratified by time windows ranging from 1 to 6 minutes, and the variances of the windows were compared using a paired *t*-test, a nonparametric Wilcoxon signed-rank test, and an F test.

Results

Study Population Demographics and Health Characteristics

- Participants were predominantly male (58%) and did not specify their race/ethnicity (60%). The mean participant age was 40 ± 15.5 years[2]
- Participants generally exhibited mild to severe levels of depressive symptoms at the beginning of the study with an initial mean Beck Depression Inventory (BDI) score of 43.0 ± 10.44 (maximum score: 63) and an initial mean Patient Health Questionnaire-9 (PHQ-9) score of 13.9 ± 6.2 (maximum score: 27)[2]

Figure 1: Normalized Heart Rate Aligned to Initiation of Face-to-Face Contact With an HCP

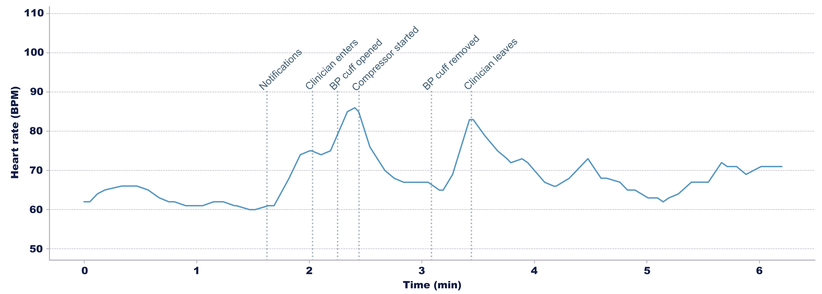


*z-scores per individual session were used as a normalization method, where 0 represents the mean HR of a given session. Intervals above and below zero represent the standard deviation from the mean HR

- For interventions 40 minutes post-esketamine administration, participant HRs significantly increased during the minute after face-to-face contact with an HCP compared with the minute before (increase in HR, beats per minute [BPM]: 3.65 ± 5.35, *P*<.01). This effect was consistent for interventions at 120 minutes post-esketamine administration (increase in HR, BPM: 5.54 ± 6.65, *P*<.01)
- In the presence of an HCP, greater increases in HR were observed at interventions 120 minutes post-esketamine administration compared to 40 minutes (increase in HR, BPM: 1.76 ± 7.73, *P*<.05)
- These findings suggest that the start of the intervention, or face-to-face contact with an HCP, is associated with an increase in HR when 40-minute and 120-minute curves are aligned

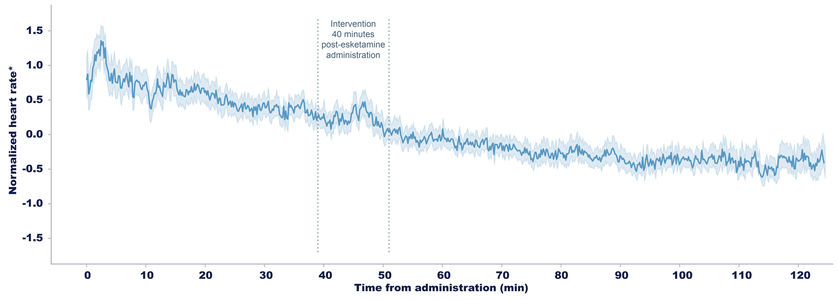
Results (cont)

Figure 2: Participant Heart Rate During HCP Intervention



- Annotations represent monitoring steps executed by an HCP during an intervention to measure vital signs face-to-face, including HR
- Measured HR during the entrance of an HCP and subsequent monitoring steps were associated with a transient increase in HR that returned to baseline when the HCP ended face-to-face contact

Figure 3: Normalized Heart Rate of All Participants Averaged Over All Sessions



*z-scores per individual session were used as a normalization method, where 0 represents the mean HR of a given session. Intervals above and below zero represent the standard deviation from the mean HR

- The first face-to-face HR measurement generally occurred between 40 and 50 minutes post-administration, and corresponded with an average increase in HR during the intervention
- Generally, a participant's HR decreased throughout a session except during face-to-face HR measurement interventions

Results (cont)

Table 1: Phenotypical Analysis of Participants With Higher and Lower HR Increases to Interventions Post-Esketamine Administration

	Higher HR increase (n=12)	Lower HR increase (n=10)	Total* (n=22)
Age (years), mean ± SD	31 ± 5	47 ± 17	39 ± 14
Male participants (%)	17	100	55
Participants with a benzodiazepine prescription (%)	17	80	45
Interventions 40 minutes post-esketamine administration			
Interventions post-esketamine administration, n	49	53	102
HR increase (BPM), mean ± SD	4.46 ± 5.14	2.87 ± 5.37	3.60 ± 5.29
Interventions 120 minutes post-esketamine administration			
Interventions post-esketamine administration, n	37	35	72
HR increase (BPM), mean ± SD	8.69 ± 6.78	2.67 ± 5.40	5.76 ± 6.82
Clinician reported participant sedation, % of sessions	24	26	25

*Two participants had sessions with both higher and lower HR increases and are excluded from this table

- A principal component analysis found 2 groups defined by a higher and lower HR increase. The groups differed from one another across several variables
- 12 participants had sessions with higher HR increases. Participants with higher HR increases showed a mean HR increase of 4.46 ± 5.14 and 2.87 ± 5.37 BPM across interventions at 40 and 120 minutes post-esketamine administration, respectively. 83% of these participants were women with a mean age of 31 ± 4.9 years, and 17% had a benzodiazepine prescription
- 10 participants had sessions with lower HR increases. Participants with lower HR increases showed a mean HR increase of 2.87 ± 5.37 and 2.67 ± 5.40 BPM across interventions both at 40 and 120 minutes post-esketamine administration, respectively. All these participants were men with a mean age of 47 ± 16.8 years, with 80% having a benzodiazepine prescription
- During esketamine sessions, similar sedation scores were observed in both groups

Conclusions

Face-to-face contact of participants with an HCP to measure vital signs during REMS-monitored esketamine sessions at 40 and 120 minute post-administration correlates with statistically significant increases in HR

- HR increase at HCP intervention is greater at 120 minutes post-esketamine administration compared to 40 minutes
- HR increases associated with HCP interaction and monitoring steps are transient during the time of HCP interaction
- Participant demographics including gender, age, and concomitant medication use may play a role in physiological response

HCP interactions with participants during esketamine sessions were associated with increases in HR. HCPs engaging in the REMS process for esketamine should be aware of this potential effect and how it may impact the reliability of physiological measurement central to the fulfillment of the REMS program. Our findings support the use of continuous passive monitoring to remove or reduce white coat effects.

References

1. SPRAVATO [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2019. **2.** Solomon TM, et al. *Frontiers in Digital Health*. 2023;5:1-11.

Abbreviations:

BDI, Beck Depression Inventory; **BPM,** beats per minute; **HCP,** healthcare practitioners; **HR,** heart rate; **MDD,** major depressive disorder, **MSMS,** MindMed Session Monitoring System; **PHQ-9,** Patient Health Questionnaire-9; **REMS,** Risk Evaluation and Mitigation Strategy; **SD,** standard deviation

Disclosures:

AD, AK, GL, MAP, EP, JJ, and TMS are employees of Mind Medicine, Inc.

Acknowledgments:

Technical, editing, and medical writing support, under the direction of the authors, was provided by Amplity, funded by MindMed, Inc.

***Presenting author**

Contact Email: medaffairs@mindmed.co

The study was funded by MindMed, Inc.