Linking Adverse Events of Dissociation Reported With Esketamine Dosing by Clinician-Perceived Severity and CADSS Descriptors

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INTRODUCTION

- Dissociation is a term used to describe varying clinical phenomena associated with certain disorders (eg, post-traumatic stress disorder) and with treatments (eg, esketamine nasal spray [ESK])
- The Clinician-Administered Dissociative States Scale (CADSS) is commonly used in research settings to quantify dissociative symptoms, but little is known about how the CADSS corresponds to spontaneous adverse reporting of adverse events (AE) within clinical trials
- The Janssen global development program for ESK in patients with treatment-resistant depression (TRD) includes a large database of contemporaneous CADSS and AE data allowing such analyses. Specific questions of interest were:
  - Which CADSS items are endorsed most frequently? How do these relate to the presence and severity of "dissocation" AE reports?
  - What is the relationship between the severity of the clinician-reported AE of dissociation and the presence of potential positive psychotic symptoms, as quantified by the Brief Psychiatric Rating Scale-Plus (BPRS+)?
  - What is the underlying factor structure of the CADSS?
  - What CADSS score best discriminates those clinically identified as experiencing the AE of dissociation from those not identified as experiencing dissociation?
  - What CADSS total score ranges are associated with the different severity levels of the clinician-reported AE of dissociation?

METHODS

Study Design

- We analyzed data from a previously reported, global, open-label, long-term, multicenter, phase 3 study (SUSTAIN-2, NCT02497287) evaluating the safety and tolerability of intermittently dosed ESK plus a newly initiated oral antidepressant for the treatment of TRD for up to 1 year[1]
- The CADSS, which consists of 23 subjective items (total score range 0-92),[2] was administered on each intranasal dosing day predose and at 40 minutes and 1.5 hours postdose
- Data were analyzed from the 40-minute measurement taken on the first day of dosing, as this provided the greatest range of CADSS total scores
- Study participants received either 28 mg (in those aged ≥65 years) or 56 mg of ESK on the first day of dosing
- Spontaneous reporting of AEs (severity/duration) by the investigator was ongoing throughout the study

Statistical Methods

- A total of 764 patients with TRD were included in this analysis
- Frequency counts of CADSS items and BPRS+ total score were stratified according to clinician-reported severity of dissociation (eg, severity level as captured in the AE report: "not reported," "mild," "moderate," or "severe")
- Confirmatory factor analyses were performed to determine the goodness-of-fit of recently published 1- and 3-factor solutions[3,4]
- An exploratory factor analysis (EFA) was conducted to identify the underlying structure of CADSS items. The number of factors was determined by examining the scree test, eigenvalues, simple structure, and clinical interpretability of the resulting factors
- Logistic regression models along with receiver operator curve (ROC) analysis were used to identify the optimal CADSS cutoff for determining the presence or absence of dissociation, with "presence" being quantified by the clinician coding the presence of an AE of dissociation at any level of severity during the first treatment session
- Equipercentile linking following the method of Leucht[5] was used to determine the range of CADSS scores associated with each clinician-perceived severity level of dissociation

RESULTS

Sample Description

Table 1. Demographics and Clinical Characteristics

	Adverse Events of Dissociation				
	Not Reported n = 655	Mild n = 78	Moderate n = 26	Severe n = 5	Overall N = 764
Age, mean (SD), years	51.9 (13.7)	49.5 (13.6)	48.4 (11.1)	44.6 (10.6)	51.5 (13.6)
Sex, n (%) Men, Women	 236 (36.0) 419 (64.0)	 40 (51.3) 38 (48.7)	 10 (38.5) 16 (61.5)	 1 (20.0) 4 (80.0)	 287 (37.6) 477 (62.4)
Race, n (%) Asian Black or African American White Other/multiple/not reported	 69 (10.5) 14 (2.1) 553 (84.4) 19 (2.9)	 9 (11.5) 1 (1.3) 67 (85.9) 1 (1.3)	 1 (3.9) 0 25 (96.2) 0	 1 (20.0) 0 4 (80.0) 0	 80 (10.5) 15 (2.0) 649 (85.0) 20 (2.6)
Oral antidepressant, n (%) Duloxetine Escitalopram Sertraline Venlafaxine XR	 213 (32.6) 173 (26.5) 130 (19.9) 138 (21.1)	 19 (24.4) 36 (46.2) 17 (21.8) 6 (7.7)	 10 (38.5) 9 (34.6) 3 (11.5) 4 (15.4)	 1 (20.0) 3 (60.0) 1 (20.0) 0	 243 (31.9) 221 (29.0) 151 (19.8) 148 (19.4)
Age when diagnosed with MDD, mean (SD), years	36.0 (13.9)	32.8 (11.5)	28.7 (11.0)	24.0 (5.4)	35.3 (13.7)
Baseline MADRS total score, mean (SD)	31.3 (5.3)	30.7 (5.2)	31.4 (4.6)	28.4 (2.9)	31.2 (5.3)

MADRS, Montgomery and Asberg Depression Rating Scale; MDD, major depressive disorder; SD, standard devision; XR, extended release.

Clinician Report of Dissociation as an AE

- At the time point examined (ie, day 1), 109/764 (14.3%) of the sample patients were identified as experiencing dissociation as an AE (Table 1)
- Among these participants, the majority of AEs of dissociation were characterized as mild (n = 78), some were characterized as moderate (n = 26), and very few (n = 5) were characterized as severe

What Does the Sample Tell Us About the CADSS?

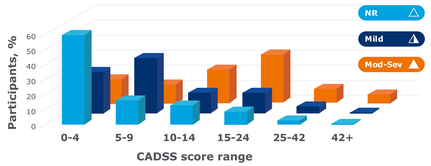
The CADSS appears to be unidimensional

- Results from confirmatory factor analyses suggest that neither the published 3-factor nor the published 1-factor solutions provided a good fit to our data, based on the results of a goodness-of-fit test and goodness-of-fit based on skewed distribution. The criteria for variable inclusion are much more stringent in a confirmatory factor analysis than in an exploratory factor analysis
- A new exploratory factor analysis, using principal axis factoring and promax rotation, identified 1 factor with an eigenvalue of 8.5, with no other factor reaching 1.0
  - This single factor accounted for 86% of the variance, with 22 of the 23 items of the scale having loadings of at least 0.35
  - Hence, **the CADSS appears to be measuring a single construct, not multiple factors**

Clinician-reported AE severity is correlated with CADSS total scores but with substantial overlap between categories

- **Figure 1** demonstrates that CADSS total scores tend to follow the expected pattern, although with substantial variability
- Specifically, approximately 60% of participants for whom dissociation was not reported as an AE have CADSS total scores in the 0-4 range, whereas the CADSS total scores of those for whom dissociation was reported to be of mild severity are most commonly in the 5-9 range (37% of this group)
- In contrast, the majority of participants for whom dissociation was reported to be of moderate severity have CADSS total scores >9, and the 5 participants with reported severe dissociation had CADSS total scores >14. The moderate and severe groups are combined in the graph due to the small number of participants rated as severe

Figure 1. CADSS score distributions by clinician-perceived dissociation severity



CADSS, Clinician-Administered Dissociative States Scale; NR, not reported.

There is no single CADSS cutoff score that best discriminates between the presence and absence of the clinician-reported AE of dissociation. The instrument may work best as a measure of change or when specific emphasis can be placed on either sensitivity or specificity

- As noted in **Table 2**, the CADSS total score with the optimal discriminative properties, per the Youden Index,[6] is 5; however, this value does not discriminate very well
- The Youden Index value suggests that, when this cutoff is used, the likelihood of a positive test result is only 34.6% in those for whom dissociation is identified as an AE compared with those for whom it is not identified
- More specifically, although this value correctly detects 75% of participants for whom dissociation is reported (true positives), it would identify 41% of participants for whom clinicians did not identify dissociation as an AE as suffering significant dissociative symptoms; thus, specificity is poor

Table 2. Diagnostic Characteristics of CADSS When Used to Identify Clinican-Reported Dissociation AE

Test-Positive Criteria on CADSS	Sensitivity	Specificity	Youden Index: Sensitivity+ Specificity-1	
0+	1.000	0.000	0.000	
1+	0.954	0.273	0.227	
2+	0.908	0.385	0.293	
3+	0.862	0.467	0.330	
4+	0.798	0.527	0.325	
5+	0.752	0.594	0.346	CADSS total score with the optimal discriminative properties, per the Youden Index[6]
6+	0.697	0.640	0.337	
7+	0.642	0.667	0.309	
8+	0.606	0.693	0.299	
9+	0.560	0.721	0.280	
10+	0.450	0.756	0.205	
11+	0.413	0.791	0.204	
12+	0.367	0.818	0.185	
13+	0.339	0.837	0.176	
14+	0.303	0.860	0.162	
15+	0.284	0.882	0.167	
16+	0.248	0.904	0.152	
17+	0.229	0.911	0.141	
18+	0.220	0.925	0.145	
19+	0.193	0.933	0.125	
20+	0.193	0.939	0.132	
21+	0.174	0.948	0.122	
22+	0.147	0.951	0.098	

CADSS, Clinician-Administered Dissociative States Scale.

What Does Combining CADSS and Clinician-Reported AE Severity Data Tell Us About Dissociation?

There is no single profile, but some CADSS items are reported more frequently than others

- Based on AE severity, clinicians rated 78 participants as experiencing mild dissociation, 26 as experiencing moderate dissociation, and 5 as experiencing severe dissociation. Dissociative symptoms generally resolved by 1.5 hours. Dissociation was not reported as an AE in 655 participants
- CADSS items were endorsed in each of these groups (**Table 3**)

Table 3. CADSS Item Endorsements by Severity Group

at least **one-quarter** of participants received nonzero ratings | more than **one-third** received nonzero ratings | more than **half** received nonzero ratings

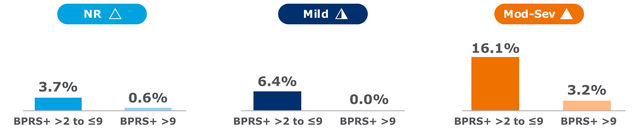
CADSS Item	Not Reported n = 655		Mild n = 78		Moderate n = 26	
	Particpants with nonzero ratings, %	Mean severity	Particpants with nonzero ratings, %	Mean severity	Particpants with nonzero ratings, %	Mean severity
Things seem to be unreal	42.29	0.55	73.08	1.04	76.92	1.27
Things moving in slow motion	39.69	0.51	65.38	0.91	69.23	1.08
Body feels changed	27.63	0.35	56.41	0.85	61.54	1.19
Separation from what is happening	27.02	0.36	48.72	0.62	50	0.92
Watching situation as an observer	26.56	0.35	46.15	0.67	38.46	0.69
Spaced out, lost track	27.48	0.36	44.87	0.65	73.08	1.46
Disconnected from own body	29.16	0.37	42.31	0.62	57.69	1
Sounds disappeared or stronger	20.46	0.28	42.31	0.55	46.15	0.85
Things seem foggy and unclear	29.16	0.34	39.74	0.51	53.85	0.85
Looking from outside of your body	22.6	0.27	35.9	0.45	38.46	0.58
Interview longer than expected	16.95	0.2	30.77	0.36	42.31	0.62
Objects different than expected	18.47	0.24	25.64	0.38	26.92	0.46
Tunnel vision/wide-angle vision	16.34	0.2	24.36	0.32	23.08	0.38
Gaps in memory	14.96	0.19	23.08	0.37	38.46	0.65
Things cannot be accounted for	20	0.25	20.51	0.32	38.46	0.73
Colors diminished in intensity	13.13	0.15	17.95	0.26	30.77	0.46
Confused about who you really are	9.01	0.11	17.95	0.27	30.77	0.58
People seem dead, mechanical	9.92	0.13	14.1	0.19	23.08	0.38
Things happening very quickly	13.44	0.18	14.1	0.22	23.08	0.35
Color much brighter than expected	10.99	0.13	12.82	0.17	23.08	0.27
Parts of self do not fit together	10.38	0.13	12.82	0.24	19.23	0.38
More than 1 identity	4.12	0.05	12.82	0.17	19.23	0.27
Things very real, special clarity	14.35	0.19	11.54	0.15	19.23	0.23

CADSS, Clinician-Administered Dissociative States Scale.

Results from participants with CADSS items rated as severe are not shown, owing to the small sample size (n = 5). CADSS items are rated on a scale from 0 (not at all) to 4 (severe). Results suggest a random occurence of symptoms that systematically increase in frequency and severity around the themes of changes in bodily sensations, perceptual changes, and a general sense of being disconnected from one's own experience (depersonalization). More unusual symptoms (eg, having more than 1 identity) are less common. Notably, with the sole exception of tunnel vision, when moving from mild to moderate in severity, the percentage of participants with nonzero ratings increased at least slightly for every item as the clinician-reported severity rating increased. This is consistent with what one might expect given the unifactorial nature of the CADSS in this sample.

Presence of dissociation does not imply presence of psychosis

Figure 2. Percentage of participants with moderate (BPRS+ >2 to ≤9) or severe (BPRS+ >9) psychotic symptoms by severity of clinician-reported AE of dissociation



AE, adverse event; BPRS+, Brief Psychiatric Rating Scale plus; NR, not reported.

Results of the group rated with severe dissociation (n = 5) were combined with the group rated with moderate dissociation (n = 26) owing to the small sample size of the former. Clinicians are unlikely to report the AE of dissociation in association with moderate to severe psychotic symptoms on the BPRS+. Of the 5 BPRS+ scores of ≥10 in the sample, 4 occurred in participants for whom dissociation was not reported as an AE and 1 occurred in a participant in whom dissociation was rated as severe. Of the other 4 participants with severe dissociation, 3 had BPRS+ scores of ≥3 and 1 had a score <3. BPRS+ scores of ≥3 occurred in small percentages in the other groups. No participant was diagnosed with psychosis.

DISCUSSION

- Combining spontaneous AE reporting with structured assessment of the same clinical phenomena using a validated tool can provide valuable insights not available when either technique is used in isolation
- The time point chosen for examination in this study (40 minutes post–ESK dosing on day 1) was selected to maximize variability in CADSS scores; it is not known if these findings would extend to other time points, to other therapeutic conditions, or to other treatments
- The extent to which spontaneous reporting of dissociation as an AE was impacted by knowing that dissociation was being quantified by use of the CADSS is uncertain

CONCLUSIONS

- **There is no "universal" profile of dissociative symptoms associated with esketamine nasal spray. However, we found that, similar (but not identical) to the symptom clusters noted by van Schalkwyk and colleagues,[4] changes in bodily sensations, general perceptual changes, and a general sense of being disconnected from one's own experience (depersonalization) increase in frequency as the severity of clinician-reported AE of dissociation increases**
- **Dissociation as reported in this study had very little overlap with reported symptoms that were suggestive of potential psychosis. The majority of participants who were reported as having dissociation were not rated as demonstrating significant psychotic symptomatology on the BPRS+, although the overlap was higher in the <1% of participants (n = 5) who were rated as experiencing severe dissociation**
- **In this sample, the CADSS is a single-factor instrument**
- **Although the general pattern of clinician-reported AE severity correlates with the total score of the CADSS, total CADSS scores vary substantially within each level of AE severity, suggesting variability between clinicians in their thresholds for identifying dissociation as an AE, either in terms of total or types of symptoms. Consequently, there is no single CADSS total score in this population that would discriminate between the presence and absence of an AE of dissociation**

References

1. Wajs E et al. Poster presented at: The International College of Neuropsychopharmaccology (CINP) 31st World Congress; June 16-19, 2018; Vienna, Austria. Poster P5074.
2. Bremner JD et al. *J Trauma Stress.* 1998;11:125-136.
3. Niciu MJ et al. *J Affect Disord.* 2018;232:310-315.
4. van Schalkwyk GI et al. *J Affect Disord.* 2018;227:11-16.
5. Leucht S et al. What does the PANSS mean? *Schizophr Res.* 2005;79:231-238.
6. Youden WJ. Index for rating diagnostic tests. *Cancer.* 1950;3:32-35.

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