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The effect of zolpidem-CR on the suicide item of the Hamilton Rating Scale for Depression in outpatients with depression, insomnia and suicidal ideation: lessons learned

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Abstract

The REST-IT study found the addition of zolpidem-controlled release (CR) provided a significant reduction in observer-rated measurement of suicidal ideation (the Columbia Suicide Severity Rating Scale) in 103 depressed outpatients with insomnia and suicidal ideation, but without significant change in a self-report measure of suicidal ideation (the Scale for Suicide Ideation). This secondary analysis of the REST-IT data examined the suicide item of another observer-rated scale, the Hamilton Rating Scale for Depression (HRSD), further clarifying the impact of insomnia-focused treatment on suicidal ideation. This analysis established a significant advantage for zolpidem-CR compared with placebo on the HRSD suicide item.

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Ruth M. Benca: Conceptualization and approved final version

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Keywords

hypnotic; observer-rated; self-report

1. Introduction

Insomnia is a risk factor for suicidal ideation (SI), suicide attempts (SA), and suicide death after taking into account other symptoms of major depressive disorder (MDD).(Bernert et al., 2005) Randomized clinical trials (RCTs) of hypnotics or digital cognitive behavior therapy for insomnia (CBT-I) in persons with MDD complicated by insomnia and SI have shown superior reductions in SI when contrasted with placebo. One digital CBT-I trial used the suicide item of the self-reported Quick Inventory of Depressive Symptomatology (QIDS-SR16) as the measure for SI (Kalmbach et al., 2022) while a hypnotic trial REST-IT(McCall et al., 2019) used both the Scale for Suicide Ideation (SSI, a self-report measure of SI) (Beck et al., 1979) and the Columbia Suicide Severity Rating Scale (C-SSRS, an observer-rated scale).(Posner et al., 2011) REST-IT showed a significant advantage of zolpidem controlled release (zolpidem-CR) compared with placebo in reducing the C-SSRS SI ($p = .035$), while the SSI did not show a significant difference.(McCall et al., 2019) Therefore, subsequent commentators understandably described the literature as "mixed" regarding whether or not targeted treatment of insomnia "leads to reductions in suicidal ideation".(Batterham et al., 2021)

We are not aware of any consensus on the optimal instrument for detecting change in SI in a pharmacologic RCT. Decades of experience from RCTs in MDD have led to a reliance upon either the Hamilton Rating Scale for Depression (HRSD) or the Montgomery Asberg Depression Rating Scale in most studies.(Zimmerman et al., 2004) There is comparatively little to guide the choice of instruments for suicide risk-reduction studies, leading to greater uncertainty in a priori outcome selection and perhaps greater likelihood of mixed results.

In addition to the C-SSRS and the SSI, the REST-IT study included the observer-rated 24-item HRSD (hereafter referred to as HRSD) as a general measure of depression severity, but the main paper did not examine the suicide item within the HRSD as an outcome. In this article, we report the effects of zolpidem-CR on the suicide item of the HRSD, especially as it relates to better understanding the relative merits of different measurement instruments for SI within a clinical trial.

2. Methods

2.1 Overview

REST-IT was a double-blind RCT. (McCall et al., 2015; McCall et al., 2019) Briefly, the three-site study recruited adult outpatients 18–65 years old with MDD, insomnia, and suicidal ideation who were free of all psychotropic medications for at least a week. Participants provided informed consent, and each local institutional review board approved the study. The participants' lifetime history of SA was assessed using the C-SSRS. The participants were randomized 1:1 to either a selective serotonin reuptake inhibitor (SSRI,

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initial dose fluoxetine 20 mg) plus zolpidem-CR (up to 12.5 mg) or a SSRI plus placebo at bedtime for 8 weeks. Flexible dosing was allowed for the SSRI and for the bedtime study drug, with no rescue treatments allowed. Treatment visits occurred at 1, 2, 4, 6, and 8 weeks.

The principal outcome measures in REST-IT were the SSI and the suicidal ideation scale within the C-SSRS, with the HRSD as a secondary outcome. The HRSD has a single item for measuring SI, scaled as “absent = 0”, “feels that life is not worth living = 1”, “wishes were dead or any thoughts of possible death to self = 2”, “suicide ideas or gestures = 3”, and “attempts at suicide = 4”.(Hamilton, 1960) The SSI and HRSD were administered and scored by blinded non-doctoral research staff, while the principal investigator psychiatrist administered the C-SSRS.

2.2 Statistical Approach

To be consistent with the analysis for the REST-IT study, a mixed-model analysis of covariance (ANCOVA) was used to perform a repeated measures analysis for the HRSD suicide item, with one between factor (treatment group) and one within factor (visit), after adjusting for the baseline value of the suicide item and the design parameters: clinic site, sex, and lifetime SA history, with SA history coded as yes/no based on the C-SSRS. This ANCOVA was used to test the significance of the treatment group effect, the visit effect, and the treatment group by visit interaction. Because the HRSD suicide item was not normally distributed, a rank-based repeated measures ANCOVA was used, as in the REST-IT study. (McCall et al., 2019) The Tukey-Kramer method for repeated measures designs was used to perform relevant pairwise comparisons.

A two-sided significance level of 0.05 was used for all statistical tests and all analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, 2016). The PROC MIXED procedure in SAS was used to fit the ANCOVA models in order to account for the repeated measures nature of the REST-IT data.

3. Results

The REST-IT study enrolled 103 participants. The majority of the participants were female (62%) and Caucasian (63%) with a mean age of 40.5 ± 13.2 years. Baseline total HRSD-24 scores were high, with moderately severe suicide and insomnia items. Baseline insomnia, as measured by the Insomnia Severity Index (ISI), was moderately severe (Table 1). Thirty percent of participants endorsed a prior lifetime SA as per the C-SSRS, but none endorsed SA in the week prior to randomization as per the HRSD. Furthermore, there were no suicide attempts at baseline or during the course of the 8-week randomization in either group.

After adjusting for baseline value of the HRSD suicide item, clinic site, sex, and SA history in the ANCOVA, the interaction between treatment group and visit was not significant ($p = 0.357$). Therefore, this interaction term was removed from all subsequent analyses, as was done in the REST-IT study. The least squares mean (LSM) estimate of the treatment effect over the 8 weeks of the REST-IT study for the HRSD suicide item was −0.15 (SE = 0.07), which yielded a significant advantage for the zolpidem-CR group relative to placebo ($p = 0.035$). Across combined treatment groups, there was no significant improvement over time

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for the suicide item (p = 0.061) after the first post-randomization visit. All of the covariates were statistically significant in the ANCOVA for the HRSD suicide item: baseline value (p < 0.001), sex (p = 0.001), clinic site (p < 0.001), SA history (p = 0.035).

There were no significant differences between the zolpidem-CR and placebo groups at any visit after applying the Tukey-Kramer pairwise adjustment. The largest difference in LSMs for the HRSD suicide item between the zolpidem-CR and placebo groups occurred at week 6. Prior to applying the Tukey-Kramer adjustment, the estimated treatment effect at week 6 was −0.43 (SE = 0.16, p = 0.008). However, this did not yield a significant difference between groups after applying the Tukey-Kramer adjustment (p = 0.195).

4. Discussion

This secondary analysis of the REST-IT data showed a significant benefit of adding zolpidem-CR to an SSRI for the HRSD suicide item. This result is consistent with the findings from the original REST-IT study regarding the effects of zolpidem-CR on the C-SSRS suicidal ideation scale. The two observer-rated scales (HRSD and C-SSRS) were independently rated by different individuals at each site, yet both yielded significant test results when comparing zolpidem-CR and placebo. On the other hand, the self-rated SSI failed to detect a difference between the two treatment arms. Notably, self-rated measures of suicidal ideation showed significant differences in a RCT of digital CBT-I in patients with depression, insomnia, and suicidal ideation.(Kalmbach et al., 2022) Therefore, some variation may be expected regarding whether self-rated versus observer-rated measures of suicidal ideation will detect significant differences in any RCT.

A principal strength of this study is the evaluation of the HRSD suicide item in the context of two other suicidal ideation rating scales which were simultaneously assessed, allowing for comparison among the scales. Our prior work has shown that the C-SSRS suicidal ideation scale, the SSI, and the HRSD suicide item are all responsive to a large range of SI intensities, with less sensitivity at the lowest range.(McCall et al., 2021) The SSI total score is a reflection of overall intensity of SI, while the scoring of the C-SSRS and HRSD suicide items is subject to more granular interpretation regarding planning, intent, etc., and perhaps is therefore more sensitive to discriminating different degrees of progression from suicidal rumination towards planning and intent.

Major depressive disorder RCTs often do not include patients with significant SI and/or do not have an a priori plan to analyze suicide items within the depression rating scale chosen for a given study.(Iltis et al., 2020) Advances in suicide prevention would be facilitated by secondary analyses of existing MDD RCTs data sets, and our results support the analysis of the single suicide item within the HRSD as an option.

The analysis of the HRSD suicide item as a post hoc secondary outcome is a limitation. In the meantime, future RCTs of suicide risk should consider the inclusion of both self-rated and observer-rated scales for SI and SA as co-primary end-points until a better understanding is obtained regarding the relative strengths of observer-rated versus self-rated scales in detecting treatment effects.

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Highlights

- There are multiple psychometric options for measuring suicidal ideation (SI) , but little is known regarding how each of these options performs in a clinical trial
- The single “suicide item” within the Hamilton Rating Scale for Depression (HRSD) is a potential option for measuring SI within a clinical trial
- The HRSD suicide item was successful in discerning significant differences in SI in a clinical trial comparing zolpidem controlled CR versus placebo as add-on treatments to a selective serotonin reuptake inhibitor in outpatients with depression, insomnia, and SI

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Table 1.

Baseline characteristics of participants

	All Participants (n = 103)		C ontrolled-Release Zolpidem (n = 51)		Placebo (n = 52)	
Characteristic	**Me an**	**SD**	**Mean**	**SD**	**Me an**	**SD**
Age (years)	40.5	13.2	39.7	14.5	41.2	12.0
BMI	28.2	6.0	28.3	6.4	28.2	5.6
Insomnia Severity Index	20. 9	4. 1	20.7	4. 0	21 .0	4. 3
24-item HRSD	29.1	5.9	28.7	4.7	29.6	7.0
Suicide item	1.7	0.7	1.6	0.7	1.7	0.8
	n	**%**	**n**	**%**	**n**	**%**
Female	64	62	32	63	32	62
Caucasian	65	63	32	63	33	64
Clinic						
Georgia	50	49	23	45	27	52
Duke	30	29	18	29	15	29
Wisconsin	23	22	13	26	10	19
Lifetime suicide attempt(s)	31	30	15	29	16	31
Posttraumatic stress disorder	29	28	13	25	16	31
Obsessive Compulsive disorder	5	5	2	4	3	6
Generalized anxiety disorder	41	40	20	39	21	41
Panic disorder with agoraphobia	17	17	9	18	8	15
Panic disorder without agoraphobia	17	17	10	20	7	14

* HRSD assessments excluding the suicide item and three insomnia items.