Title

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Efficacy of the Transdiagnostic Intervention for Sleep and Circadian Dysfunction for depression symptoms and sleep-wake disruption in older and younger adults: secondary age-stratified analysis of a randomized controlled trial

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Abstract

Objective: Perform a secondary analysis examining the efficacy of the Transdiagnostic Intervention for Sleep and Circadian Dysfunction (TranS-C) for depression symptom responses, and explore changes in potential target mechanisms.

Design: Secondary analysis of a randomized controlled trial with convenience age subsamples (younger (20-49 year; n=52) versus and older (50-71 years; n=35)).

Setting: Community mental health clinics

Participants: Eighty-seven adults with serious mental illness

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Author Contributions: All authors listed contributed to conceptualizing the paper and analysis. SFS and RTK conducted the analysis. CEG, DJB, AGH, conceptualized and/or implemented the study. SFS drafted the paper with writing assistance and critical revisions from all authors.

Intervention: TranS-C versus treatment as usual (TAU)

Measurements: Outcomes were depression symptoms (Quick Inventory of Depression Symptoms), insomnia symptoms (Insomnia Severity Index), and objective sleep-wake rhythm measures (inter-daily stability and relative amplitude).

Results: Depression response rates (≥50% symptom reductions) were higher in the TranS-C (35.0%) than the TAU (8.8%) group six-months post-intervention (Chi-square =10.3, p=0.001). There was a medium effect of TranS-C versus TAU on depression symptoms six-months post-intervention (Cohen's d=−0.40, 95% confidence interval (CI): −0.81, 0.01). In both age groups, there were large treatment effects on insomnia symptoms post-treatment (Cohen's d>0.90). In the older subsample, there were additionally medium treatment effects on post-treatment inter-daily stability (Cohen's d=0.60, 95% CI: −0.11, 1.61). Post-treatment reductions in insomnia symptoms correlated with depression symptom reduction six-months later in the younger subsample (Spearman rho=0.59, n=20, p=0.008). In older adults, post-intervention increases in inter-daily stability correlated with depression symptom reductions six-months later (Spearman rho=−0.52, n=15, p=0.049).

Conclusions: Confirmatory trials are needed, given the low age-specific sample sizes here, to determine if TranS -C's produces durable depression responses by increasing sleep-wake rhythm stability in older adults and improving insomnia symptoms in younger adults.

Brief article summary:

We evaluated preliminary efficacy of a behavioral intervention that targets sleep/sleep-wake rhythms, the Transdiagnostic Intervention for Sleep and Circadian Dysfunction (TranS-C), for depression symptoms in people with serious mental illness. TranS-C was associated with higher depression response rates than treatment as usual six-months post-intervention. The degree of depression symptom response six-months later was related to the degree of treatment phase improvements in inter-daily stability (in older adults) and reduction in insomnia severity (in younger adults).

A pragmatic non-pharmacologic intervention, the Transdiagnostic Intervention for Sleep and Circadian Dysfunction, has preliminary efficacy for improving sleep-wake factors and depression symptoms.

Based in part on decades of observational evidence (1, 2), it has been suggested that treatments for sleep-wake disturbances may be useful depression interventions (3, 4). Recently, a randomized controlled trial provided evidence that that a non-pharmacologic treatment (Cognitive Behavioral Therapy for Insomnia or CBT-I) could prevent incident/recurrent episodes of major depression in older adults with insomnia disorder (5). Interventions targeting sleep-wake dysfunction may also be useful as a depression treatment. Effects of CBT-I on depression in people with insomnia have been mixed (e.g., see significant (5-17) and null findings (18-20)). Note, however, that insomnia is not the only relevant aspect of sleep-wake dysfunction that could be targeted to improve depression symptoms. People with depression often have co-occurring insomnia/hypersomnia (21), and in older adults, and rhythm disruption are more strongly related to depression than sleep problems themselves (22). Thus, the potential of treating sleep-wake dysfunction to improve depression goes beyond treating insomnia.

A behavioral approach, called the Transdiagnostic Intervention for Sleep and Circadian Dysfunction (TranS-C) (23), was recently developed to address insomnia *and* the host of potentially co-occurring sleep-wake factors that can compromise sleep-wake rhythms including insomnia, hypersomnia, timing shifts, and daytime impairment. TranS-C includes components of Cognitive Behavioral Therapy for Insomnia, Motivational Interviewing, Social Rhythm Therapy, and Chronotherapy (23, 24). Members of our team recently published the main results from a randomized controlled efficacy trial comparing TranS-C to treatment as usual (TAU) (25) for people with serious mental illness. This trial, conducted in a community mental health clinic setting, found that TranS-C intervention was efficacious for key primary outcomes including measures of self-reported sleep, sleep-related functional impairment, general psychiatric symptoms (DSM-V cross-cutting instrument total scores), and functional impairment. There was also a non-statistically significant trend in the sample overall for reductions in continuously expressed depression symptoms six-months post-intervention (a secondary trial outcome). While suggesting that TranS-C may have efficacy for depression treatment, this prior paper (25) did not report clinically significant categorical depression outcomes.

We therefore conducted a secondary analysis of depression response rates in this prior trial. In addition, we conducted exploratory analyses evaluating if TranS-C's effects on depression were similar in older and younger participants. Effects of TranS-C may differ by age, since different types of sleep/sleep-wake factors can be disrupted in older and younger people (26-29), and the sleep-wake correlates of depression symptoms may vary by age (30). One report found that older adults were less likely to benefit from TranS-C in terms of some self-reported sleep outcomes (31). Age, categorized as ≥50 years, was a stratification factor for randomization in this past trial. We leveraged these existing age subsamples as convenience samples to explore the effects of TranS-C versus TAU on depression symptoms in *relatively* younger (age <50 years) and older (age ≥50 years) trial participants separately.

We also sought to generate hypotheses regarding the potential mechanisms of TranS-C's antidepressant effects. TranS-C improves insomnia symptoms (25) and plausibly also affects objectively measured sleep-wake rhythm disruption. We therefore evaluated if, in addition to improving insomnia symptoms, TranS-C affects behavioral sleep-wake rhythm disruption: interdaily stability and relative amplitude of the rest-activity rhythm. We included measures of sleep-wake rhythms based on evidence that rhythm measures may be as/more relevant to depression than sleep measures in older adults (22); and chose these measures, in particular, as they are relatively commonly used standard ways of measuring sleep-wake/rest-activity rhythm strength (relative amplitude) and stability (inter-daily stability). To generate hypotheses regarding potential mechanisms of TranS-C's effects on depression, we evaluated if changes in insomnia symptoms and/or objective sleep-wake measures correlated with reductions in depression symptoms following TranS-C.

Methods

Experimental design and protocol:

We conducted a secondary analysis of a two-arm randomized controlled trial (comparing TranS-C to TAU) that has been described previously (23, 25). Randomization was stratified

by age group (50+ vs. <50 years of age) and lifetime psychotic disorder diagnosis. Assessments were conducted at pre-treatment (baseline), post-treatment (after at least 8-12 weeks of treatment), and six-months follow-up. Assessors, but not participants, were blinded to the treatment condition. TranS-C was delivered by master's level therapists and typically included 8 sessions that were each targeted to be 50 minutes long. Additional details on the TranS-C program are available in prior publications and the supplemental materials section.

Participants:

Eligibility criteria aimed to be broadly representative of and generalizable to people with Serious Mental Illness (SMI) being treated in Alameda County Behavioral Health Care Services (Alameda County, California) sites. Descriptions of eligibility criteria have been published previously (23, 25) and are available in the Supplement. As described previously, 121 eligible participants were randomized (25). The analytic sample for the current analyses was restricted based on the availability of follow-up data. The trial accommodated delays/postponements to provide participants with a sufficient dose of TranS-C. However, 23 participants were excluded due to failing to complete their treatment and post-treatment assessments within a reasonably comparable time frame (defined as within 24-weeks of the pre-treatment baseline assessment). Additionally, one participant was missing the depression symptoms assessment at the six-month post-intervention timepoint. Therefore, the analyzable sample for mood changes included 97 individuals. Analyses for our second aim were further restricted to the subsample of 87 participants who had adequate pre- and post-treatment actigraphy data (as defined below). All participants provided written informed consent.

Sleep-wake quality control standard and assessments:

Insomnia symptom severity was measured as total scores on the Insomnia Severity Index (32).

Participants were also asked to wear an ActiGraph GT9X, an accelerometer-containing device (also known as actigraphy), on their wrist for 7 days. Note our actigraphy methods follow pertinent guidelines (33) including our choice of a 60-second epoch (one of the two most validated epoch lengths), placing the device in the nondominant wrist, asking participants to wear the device continuously (24 hours a day) for a week, and our handling of missing data. See our supplemental materials for more information on the quality control criteria used.

For those recordings meeting the quality control criteria, we used custom R code to extract two sleep-wake rhythm measures from the time series of activity counts (one per minute): (1) inter-daily stability (IS), which was computed using the entire time series and not subsampling to hourly activity levels, measures the consistency (stability) of circadian sleep-wake activity patterns across days (lower IS indicates less stable rhythms); and (2) relative amplitude (RA), which measures the peak-trough difference of 24-hour activity patterns (lower values indicate weaker rhythms). To standardize scales for these measures, we re-scaled each measure to a mean of zero and standard deviation of one based on

each pre-intervention sample distributions. Technical definitions and methods for these two measures, which are commonly used, have been published previously (34).

We calculated changes in three variables as the difference between their post-intervention and baseline values, including (1) insomnia severity, (2) inter-daily stability, and (3) relative amplitude. For these change scores, negative values indicated decreases (e.g., in insomnia symptoms over time), whereas positive values indicated increases (e.g., in IS or RA).

Depression symptoms: Depression symptoms were assessed using the self-report version of the 16-item Quick Inventory of Depression Symptoms (QIDS) (35) at pre-intervention, post-intervention, and six-months post-intervention. For this secondary analysis, we categorized response at both time points as having achieved at least a 50% reduction in baseline depression symptom severity. To maximize statistical power for the exploratory age-stratified secondary outcome analyses, we also utilized total QIDS scores expressed continuously to analyze change. We subtracted total QIDS scores taken at pre-treatment from both follow-up visits, thus creating change scores where negative values reflect decreases in depression symptoms.

Based on its potential additional clinical significance, we also analyzed the single QIDS item (item #12) that assesses SI. The response options on the self-report QIDS item 12, which is labeled Suicidal Ideation, include: (0) “I do not think of suicide or death;” (1) “I feel that life is empty or wonder if it's worth living,” (2) “I think of suicide or death several times a week for several minutes,” or (3) “I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.” None of the participants endorsed the latter category (serious suicidality was an exclusion criterion as stated above), and only eight participants endorsed the second highest category. We therefore analyzed the QIDS item 12 as a categorical variable dichotomized as any endorsement other than “I do not think of suicide or death” reflecting the presence of any SI.

Statistical analyses: To check if randomization created balanced arms in terms of demographics and baseline variables of interest (sleep-wake patterns and depression symptoms), we compared baseline characteristics using the appropriate inferential statistical tests. These were t-tests for continuous variables and Chi-Squared tests for categorical variables (we used non-parametric alternatives and Fischer’s exact text as needed and noted in Table 1). For depression response and SI outcomes, which were categorical variables, we also used Chi-Squared tests comparing frequencies at each time point. For significant differences in categorical outcomes between the groups, we calculated the number needed to treat (NNT) and its 95% confidence interval (36) using the Wilson score method (37) implemented in SAS (38).

Explortatory age subgroup analyses were conducted stratifying the sample based on whether participants were 50 years and older versus those younger than 50 years of age. Since these were exploratory secondary analyses with relatively low sample size within age strata, we focused on effect sizes for continuous outcomes rather than inferential statistics. We calculated Cohen’s d values and their 95% confidence intervals with the R package “effsize” as a measure of treatment effect size for the main outcome variables (changes in

depression severity, inter-daily stability, and relative amplitude). Specifically, the Cohen's d values reported indicate the effect of TranS-C versus TAU on changes in these outcomes. Absolute values of Cohen's d greater than or equal to 0.5 (39) represent potentially clinically meaningful moderate effect sizes. Finally, we used Spearman correlations and scatter plots to examine associations between the changes in self-reported insomnia severity and sleep-wake rhythms with changes in depression symptoms.

Results

Baseline characteristics:

There were no statistically significant differences between the TranS-C and TAU groups in terms of the main study variables, overall (Table 1), or within age strata (Table 2). The older sample was in their late 50's/early 60's on average, whereas the younger sample was in their mid-to-late 30's on average. Depression severity at baseline measured with the QIDS-16 was on average around 12, indicating mild-to-moderate depression symptomology. There were no statistical differences between TranS-C and TAU arms in terms of primary diagnosis (p=0.73), with ~45% of the sample were primarily diagnosed with a Schizophrenia Spectrum Disorder, ~22% with Bipolar Disorder, ~22% with Major Depressive Disorder, ~3% with an other Psychotic Disorder, ~3% with an Anxiety Disorder, and ~2% with a Substance Use Disorder.

There were no statistically significant differences between older and younger subsamples them in terms of depression symptoms or the objective sleep-wake measures (p>0.20). Average ISI scores were numerically higher in the older (mean ISI scores = 19.2 (STD = 5.6)) compared with the younger (mean ISI scores = 17.3 (STD = 5.9)) age group, but this difference was not statistically significant (t-value = −1.47, df=85, p=0.14).

Effect of TranS-C versus TAU on depression symptoms:

In the sample overall and in both age groups, there were no effects of treatment on depression response or rates of SI at the post-treatment assessment (Table 4). However, at six-months post-intervention, depression response rates were higher in the TranS-C compared with TAU groups across age groups. The absolute differences in response rates between the TranS-C and TAU groups were similar across age groups. In the sample overall, the estimated NNT for TranS-C versus TAU to obtain depression symptom responses six-months post-treatment was 4 (95% confidence interval: 3-8). Similar effects of TranS-C versus TAU on six-month depression response rates were observed in participants with only mood disorder diagnoses (n=19), and people with mood disorders plus psychotic disorders/features (n=53), but not in people with single psychotic disorder diagnoses (n=22 in whom depression response rates were lowest; see Supplemental Table).

Among older adults after treatment, there was a numerically lower rate of SI endorsement in the TranS-C versus TAU groups. However, the actual numbers of SI cases were very low in this sample and these differences were not statistically significant. Rates of SI did not differ by treatment arm in the younger group.

In terms of continuous effect sizes, at post-intervention, none of the effect sizes for treatment on depression symptoms changes met the criteria for being at least moderate/potentially clinically meaningful (i.e., all Cohen's d < 0.5; Table 3). In the older sample only, there was a large effect size difference between TranS-C and TAU in terms of changes in depression symptoms six-months post-intervention. To provide a sense of this effect size in terms of the original QIDS-16 scale, older adults given TranS-C had average reduction in QIDS-16 scores of 4.2 points (standard deviation=4.2) at six-months post-intervention, compared with 0.9 points (standard deviation=3.4) in the TAU group (t-value = 2.81; df=33; p=0.008).

Effect of TranS-C vs. TAU on objective sleep-wake rhythm measures:

Overall, there was a small-to-medium effect size (Cohen's d = −0.40) difference between the treatment groups, wherein TranS-C was associated with greater increases in IS than TAU (Table 3). This was driven by a medium size effect of TranS-C versus TAU on IS in the older group, whereas there was only a small treatment effect on IS in the younger adults. Only small/negligible treatment effects on RA were observed overall and within age strata.

Evidence that TranS-C has strong effects on self-reported sleep symptoms was published previously (25). To confirm in this specific analytic sample, we note large effect size differences between TranS-C and TAU groups for pre/post changes in ISI-measured insomnia severity (estimated Cohen's d=−1.0 overall, −1.1 in the younger adults, and −0.9 in the older adults).

Correlation of changes in sleep-wake targets with changes in depression symptoms:

We analyzed if post-intervention changes in insomnia severity and inter-daily stability correlated with reductions in depression symptom severity six-months later in the TranS-C group. In the overall study sample, both increases in IS (Spearman rho = −0.34, n = 35, p = 0.048) and decreases in insomnia severity (Spearman rho = 0.40, n = 35, p = 0.019) correlated with depression symptoms reductions.

These small overall correlations appeared to be driven by different patterns of correlation in the older and younger groups. In the older adults assigned to TranS-C, depression symptom reductions six-months post-intervention were correlated with post-intervention increases in IS (Spearman rho = −0.52, n = 15, p = 0.049; left-side of Figure 1) but not decreases in ISI scores (Spearman rho = 0.13, n = 15, p = 0.64; right-side of Figure 1). In contrast, among younger adults given TranS-C, depression symptom reductions six-months post-intervention were not statistically correlated with IS changes (Spearman rho = −0.21, n = 20, p = 0.37; left-side of Figure 1) but were correlated with post-intervention improvements in ISI scores (Spearman rho = 0.59, n=20, p = 0.008; right-side of Figure 1).

Discussion

This secondary analysis found that, compared with TAU, TranS-C had efficacy for improving depression symptom response rates six-months after treatment. The estimated NNT of 4 overall suggests that, if confirmed in a large-scale trial, TranS-C may provide a valuable targeted depression intervention. Compared with post-treatment, there were larger effects of TranS-C relative to TAU on depression symptoms six months later (i.e., evidence

of delayed efficacy). Reviewing depression response rates at each time point indicates that this was due to post-treatment depression responses in the TAU group that did not persist to the six-month follow-up (Table 4). These findings suggest that using TranS-C to target sleep-wake disruption in addition to TAU may help patients achieve more durable, sustained, depression symptom responses. Thus, TranS-C may add preventive efficacy, i.e., adding TranS-C to TAU may reduce the risk of symptom recurrence over time.

An additional strength of our study was the separate examination of the suicidal ideation item from the QIDS, which provides initial support for hypothesis that TranS-C may be efficacious for reducing rates of suicidal ideation in older adults particularly. This TranS-C intervention was delivered in community mental health care clinics by masters-level therapists to people with SMI . Thus, TranS-C appears efficacious even when disseminated in challenging real-world circumstances. An ongoing effectiveness trial is now evaluating a version of TranS-C that was further adapted for delivery in community mental health clinics (40). As such, if future large-scale efficacy trials can confirm TranS-C's preventive efficacy for reducing depression symptom recurrence and rates of other suicide risk factors, then similar benefits are likely also achievable in real-world settings.

Our findings also support new hypotheses regarding TranS-C's potential antidepressant efficacy and mechanism-of-action. Overall, improvements in insomnia symptoms and sleep-wake rhythms correlated with reductions in depression symptoms. But interestingly, exploratory age-stratified correlations (Figure 1) indicated that these sleep-wake factors had more/less relevance to improvements in depression symptoms depending on age group. Specifically, in the older adults, TranS-C reduced insomnia symptoms also had a medium-sized effect on sleep-wake rhythm stability (indexed by IS). In the older subgroup, increases in sleep-wake stability during the intervention phase, but not changes in insomnia symptoms, were statistically correlated with depression symptom reductions six-months later. These findings extend existing observational research that indicates sleep-wake rhythms may be more strongly tied with depression than measures of sleep in older adults (22). Specifically, our exploratory findings support the hypothesis that TranS-C has antidepressant effects in older adults by improving sleep-wake rhythm stability. In contrast, among younger adults, greater improvements in insomnia symptom severity (but not sleep-wake stability) correlated with greater depression reductions. This suggests that, in younger adults, improving insomnia symptoms may be critical to TranS-C's impact on mood. But due to the relatively small size of the age subsamples, results in these age subgroups should be considered preliminary and hypothesis generating. Future studies are needed to confirm these associations and related hypotheses regarding TranS-C's antidepressant mechanism(s) of action in adequately powered, age-delimited, samples.

Several limitations should be noted. The age subgroups were convenience subsamples chosen based on the parent trial using age, stratified at 50 years old, as a randomization factor. While relatively younger and older compared with each other, our study is limited by the small subsample sizes and somewhat restricted subgroup age ranges (i.e., 20-49 year olds versus 50-71 year olds). Given differences in biological aging and lifespan, both groups could include some individuals considered to be in "midlife." Future trials are required to determine the efficacy of TranS-C across a broader range of distinct age groups

including the “oldest old.” While we observed absolute differences in the rates of suicidal ideation between TranS-C and TAU groups six-months after the intervention, participants with severe suicide risk at baseline were excluded from this study. Thus, absolute numbers of participants with these outcomes were very low, and differences were not statistically significant. Future studies will be needed to evaluate the potential benefits of TranS-C for suicidal ideation, specifically, in people with high suicide risk. In addition, this was a secondary analysis of an efficacy trial conducted in a heterogeneous group of people with SMI. Results, including response rates, are likely to differ from those obtained in more traditional, highly-controlled, trials that are conducted in specialty care settings and only include people with unipolar depression. Finally, while this was a randomized trial and available data indicate that the treatment arms were balanced on key factors, we could not verify the absence of differential biases that may have been introduced between treatment ending and the six-month outcome. Especially since our sample size was relatively small, larger studies focused on patients with unipolar depression will be needed to verify that assignment to TranS-C, and not emerging group differences (e.g., in the rates of other treatment utilization or stressors), account for the delayed antidepressant efficacy observed.

In conclusion, our findings and limitations together support the need for adequately powered studies to confirm the preventive efficacy of TranS-C for depression symptoms and suicidal ideation in adults who are undergoing treatment for these symptoms. Future studies are also needed to test the hypotheses generated here regarding TranS-C’s potential antidepressant mechanism of action (discussed above). It is also yet unclear if early changes in sleep-wake rhythm stability and/or insomnia symptoms provide clinically useful prognostic information on whether a given patient is on track for a meaningful depression response (i.e., if these measures of putative target mechanism engagement are useful to forecast treatment outcomes). Finally, we observed significant controlled average treatment effects for depression symptoms, but as with psychiatric treatments generally, there was substantial treatment response heterogeneity (variability in the degree of depression symptom reductions; see Figure 1). Large-scale trials of TranS-C that are focused on unipolar depression outcomes will be needed to identify factors that explain treatment response heterogeneity (i.e., moderators). If future studies can confirm its efficacy, mechanism, and moderators, TranS-C may provide a highly disseminable, precise, targeted depression intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflicts of Interest and Source of Funding:

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Data Statement:

As of paper submission, these data has not been previously presented orally or by poster at scientific meetings

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Highlights

- What is the primary question addressed by this study? Is there preliminary evidence for efficacy and mechanism-of-action, of the Transdiagnostic Intervention for Sleep and Circadian Dysfunction (TranS-C), for depression symptoms?
- What is the main finding of this study? TranS-C improved depression response rates six-months post-intervention. During the acute treatment phase, improvements in inter-daily stability (in older adults) and reduction in insomnia severity (in younger adults) correlated with the degree of depression symptom reductions six-months later.
- What is the meaning of the finding? Future studies are warranted to confirm that TranS-C, a targeted sleep-wake treatment, improves the durability of depression symptom response via the identified pathways.

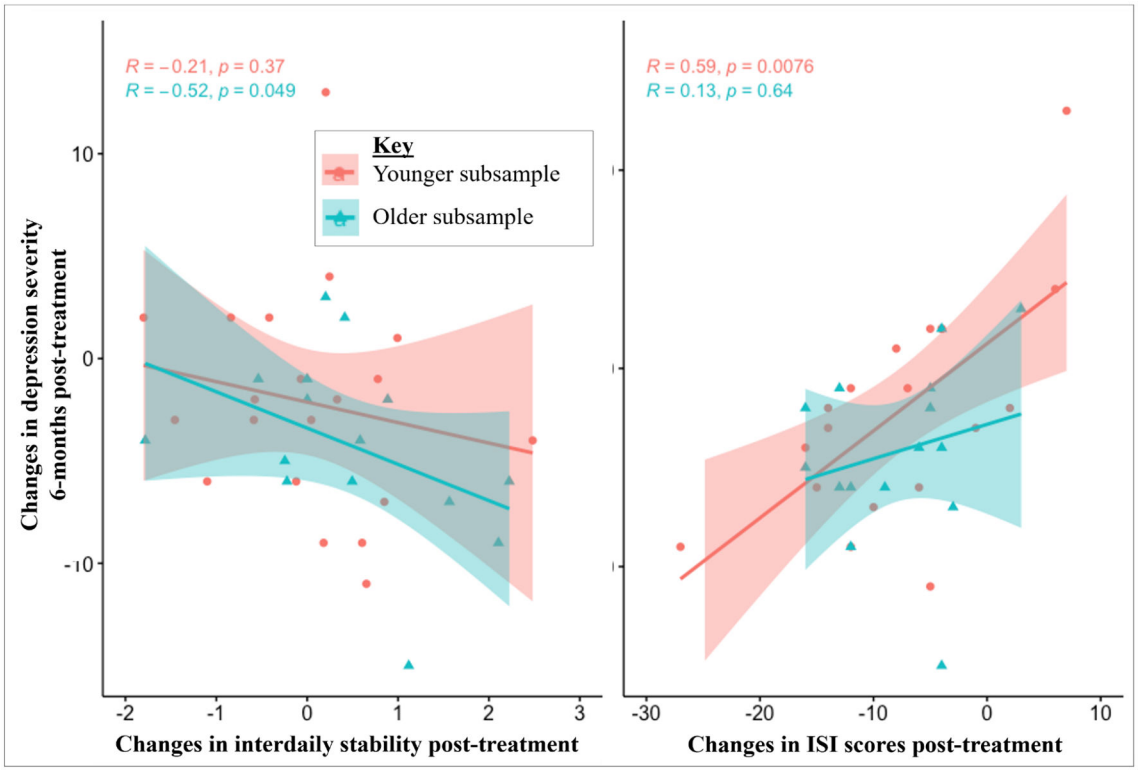

Figure 1. Scatterplots showing correlations between pre-/post- sleep-wake changes and decreases in depression symptoms six-months after the intervention among participants assigned to TranS-C.

Note that changes in sleep-wake measures were from pre- to post- intervention. Changes in depression symptoms are from pre-intervention to six-months after post-intervention, and are shown on the original QIDS-16 scale.

Table 1.

Baseline characteristics by randomly assigned treatment arm and age group

	Overall		
	TranS-C	**TAU**	**Test stat., p**
Sample size	40	57	
Age	47.75 (12.14)	45.14 (12.96)	−1.00, 0.32
Female, % (n)	50.0 (20)	54.4 (31)	0.18, 0.67
ISI total score	16.9 (5.5)	18.3 (5.9)	1.17, 0.24
Depression severity	11.78 (5)	12.4 (4.82)	0.62, 0.54
Any SI, % (n)	30.0 (12)	36.8 (21)	0.49, 0.48
Self-reported race			0.93[1]
White	36.6 (15)	35.0 (20)	
Black	41.5 (17)	43.9 (25)	
Asian	4.9 (2)	8.8 (5)	
American Indian/Alaskan Native	2.4 (1)	3.5 (2)	
Native Hawaiian/Other Pacific Islander	7.3 (3)	5.3 (3)	
Sample size for actigraphy variables	35	52	
Inter-daily stability	−0.13 (0.96)	0.09 (1.03)	1.07, 0.29
Relative amplitude	−0.01 (1.17)	−0.01 (0.88)	0.00, 0.99

Means and standard deviations shown unless otherwise noted. Depression severity was measured with the Quick Inventory of Depressive Symptomatology self-report version (QIDS). Any SI indicates QIDS Item 12 was greater than zero. Test statistics are from independent sample t-tests (for continuous variables) and Chi-Square tests (for categorical variables) unless otherwise noted. Degrees of freedom for continuous variables equaled the sample sizes minus 2 for continuous comparisons; and degrees of freedom equaled 1 for categorical variables. Bold indicates statistically significant with $p<0.05$. Notes: [1].Exact test used due to actual cell count ≤ 5; [2].Satterthqaite test (degrees of freedom = 53.5) used due to unequal group variances. Acronyms: ISI, Insomnia Severity Index; Test stat, Test statistic; TranS-C, Transdiagnostic Intervention for Sleep and Circadian Dysfunction; TAU, Treatment as usual.

Table 2.

Key characteristics within the age strata by randomly assigned treatment arm

	Age ≥50 years			Age < 50 years		
	TranS-C	**TAU**	**Test stat., p**	**TranS-C**	**TAU**	**Test stat., p**
Sample size	17	23		23	34	
Age	60.06 (6.27)	57.26 (5.5)	−1.50, 0.14	38.65 (5.41)	36.94 (9.66)	−0.85, 0.40[2]
Female, % (n)	58.8 (10)	73.9 (17)	1.01, 0.31	43.5 (10)	41.2 (14)	0.03, 0.86
ISI total score	17.9 (6.2)	19.8 (4.6)	1.1, 0.28	16.1 (5.0)	17.3 (6.6)	0.70, 0.49
Depression severity	12.71 (5.46)	12.26 (4.99)	−0.27, 0.79	11.09 (4.63)	12.5 (4.77)	1.11, 0.27
Any SI, % (n)	29.4 (5)	30.4 (7)	p=1.00[1]	30.4 (7)	41.2 (14)	0.68, 0.41
Sample size for actigraphy variables	15	20		20	32	
Inter-daily stability	−0.19 (0.76)	−0.04 (0.98)	0.51, 0.61	−0.08 (1.1)	0.19 (1.07)	0.89, 0.38
Relative amplitude	−0.16 (1.1)	−0.19 (0.95)	−0.10, 0.92	0.1 (1.23)	0.1 (0.83)	0.02, 0.99

Means and standard deviations shown unless otherwise noted. Depression severity was measured with the Quick Inventory of Depressive Symptomatology self-report version (QIDS). Any SI indicates QIDS Item 12 was greater than zero. Test statistics are from independent sample t-tests (for continuous variables) and Chi-Square tests (for categorical variables) unless otherwise noted. Degrees of freedom for continuous variables equaled the sample sizes minus 2 for continuous comparisons; and degrees of freedom equaled 1 for categorical variables. Bold indicates statistically significant with $p<0.05$. Notes: [1]·Exact test used due to actual cell count ≤ 5; [2]·Satterthqaite test (degrees of freedom = 53.5) used due to unequal group variances. Acronyms: ISI, Insomnia Severity Index; Test stat, Test statistic; TranS-C, Transdiagnostic Intervention for Sleep and Circadian Dysfunction; TAU, Treatment as usual.

Table 3.

Changes from baseline values to post-intervention and the 6-month follow-up overall and stratified by age group

	Overall	Age ≥50 years	Age < 50 years
	Cohen's d (95% CI)	**Cohen's d (95% CI)**	**Cohen's d (95% CI)**
Change in depression symptoms post-treatment	−0.32 (−0.73, 0.09)	−0.20 (−0.85, 0.45)	−0.39 (−0.93, 0.16)
Change in depression symptoms 6-months post-treatment	−0.40 (−0.81, 0.01)	**−0.90 (−1.58, −0.21)**	−0.16 (−0.70, 0.38)
Change in inter-daily stability post-treatment	0.39 (−0.05, 0.83)	**0.60 (−0.11, 1.31)**	0.26 (−0.31, 0.84)
Change in relative amplitude post-treatment	−0.06 (−0.50, 0.37)	−0.14 (−0.83, 0.56)	−0.04 (−0.62, 0.52)

Cohen’s D effect sizes are for the comparison between TranS-C and TAU groups. Bold indicates that the Cohen’s D (absolute value is at least 0.5 indicating a potential clinically meaningful effect.

Table 4.

Differences in the rates of categorical outcomes between the treatment arms

Overall Sample			
	TranS-C	**TAU**	**Test stat., p-value**
N	40	57	
SI pre-treatment	30.0 (12)	36.8 (21)	0.49, 0.48
Any SI post-treatment	17.5 (5)	29.8 (17)	1.92, 0.17
Any SI 6-months post-treatment	20.0 (8)	29.8 (17)	1.19, 0.28
Depression response post-treatment	32.5 (13)	26.3 (15)	0.44, 0.51
Depression response 6-months post-treatment	35.0 (14)	8.8 (5)	10.3, 0.001
Adults =>50 years of age			
	TranS-C	**TAU**	**Test stat. (p-value)**
N	17	23	
SI pre-treatment	29.4 (5)	30.4 (7)	(1.00)[1]
Any SI post-treatment	11.8 (2)	21.7 (5)	(0.68)[1]
Any SI 6-months post-treatment	11.8 (2)	34.8 (8)	(0.15)[1]
Depression response post-treatment	23.5 (4)	21.7 (5)	(1.00)[1]
Depression response 6-months post-treatment	29.4 (5)	0.0 (0)	(0.009)[1]
Adults <50 years of age			
	TranS-C	**TAU**	**Test stat. (p-value)**
n	23	34	
SI pre-treatment	30.4 (7)	41.2 (14)	0.68, 0.41
Any SI post-treatment	21.7 (5)	35.3 (12)	1.20, 0.27
Any SI 6-months post-treatment	26.1 (6)	26.5 (9)	0.001, 0.97
Depression response post-treatment	39.1 (9)	29.4 (10)	0.58, 0.45
Depression response 6-months post-treatment	39.1 (9)	14.7 (5)	4.4, 0.04

Percent (sample size) shown. Test statistics are from Chi-squared tests. [1]Exact two-sided test