Symptom-specific effects of zolpidem and behavioral treatment for insomnia: a network intervention analysis

Lancee, J.; Morin, C.M.; Edinger, J.D.; Ivers, H.; van der Zweerde, T.; Blanken, T.F.

DOI
10.1093/sleep/zsad240

Publication date
2023

Document Version
Final published version

Published in
Sleep

SLEEP, 2023, 46, 1–4
https://doi.org/10.1093/sleep/zsad240
Advance access publication 11 September 2023
Research Letter

Research Letter

Symptom-specific effects of zolpidem and behavioral treatment for insomnia: a network intervention analysis

Jaap Lancee[1,*], Charles M. Morin[2,3], Jack D. Edinger[4,5], Hans Ivers[2,3], Tanja van der Zweerde[6] and Tessa F. Blanken[1,7]

[1]Department of Clinical Psychology, University of Amsterdam, Amsterdam, The Netherlands,
[2]School of Psychology, Université Laval, Quebec City, QC, Canada,
[3]Centre d'étude des Troubles du Sommeil, Centre de Recherche de l'Institut Universitaire en Santé Mentale de Québec, Quebec City, QC, Canada,
[4]National Jewish Health, Denver, CO, USA,
[5]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA,
[6]Geestelijke gezondheidszorg (GGZ) InGeest Specialized Mental Health Care, Amsterdam, The Netherlands and
[7]Department of Psychological Methods, University of Amsterdam, Amsterdam, The Netherlands

*Corresponding author. Jaap Lancee, Department of Clinical Psychology, University of Amsterdam, PO Box 15933, 1001NK Amsterdam, the Netherlands. Email: j.lancee@uva.nl.

Both cognitive behavioral therapy (CBT-I) and sleep medication have short-term treatment effects on insomnia [1], but the effects of CBT-I last longer and it has fewer side effects. Therefore, CBT-I is the gold standard and first treatment option for someone with insomnia [2]. Pharmacological agents can be offered if CBT-I is not effective or available.

One of the alleged benefits of pharmacological treatment is that it produces more rapid symptomatic relief [3]. The few studies that compared differences in immediate treatment effects indeed showed that triazolam produced faster treatment effects than behavioral treatment [4] and CBT-I combined with zolpidem had faster effects than CBT-I alone [5]. While these studies thus support the fast treatment effects of sleep medication, none of these studies mapped these treatment differences to specific symptoms. Knowledge about symptom-specific effects can guide clinicians in their choice of what treatment to offer.

In investigating symptom-specific effects, it is important to consider that the symptoms themselves are related. Network Intervention Analysis (NIA) provides a powerful tool to get a more fine-grained understanding of symptom-specific treatment effects while taking the associations between the symptoms into account, thereby distinguishing direct from indirect treatment effects [6]. A first step would be to employ NIA in single-component treatments since these treatments target specific components and thus give the most clear-cut signal on these symptom-specific effects.

For this paper, we applied NIA to a dataset from a randomized controlled trial comparing behavior therapy (BT) to zolpidem treatment for the initial 6-week treatment stage [7]. Of the several classes of medication available for the treatment of insomnia, zolpidem was used because it is an effective, short-acting hypnotic [8]. BT is an interesting comparator because it specifically targets sleep timing, is effective in a stand-alone format, and shows faster treatment effects than cognitive therapy [9]. At post-test, BT and zolpidem had similar response and remission rates on the Insomnia Severity Index (ISI).

We expected zolpidem to work faster, which would be shown in the network by direct effects of zolpidem in the early weeks of treatment. We had no specific expectations of which particular symptoms would be affected and stress the exploratory nature of the current analyses.

Methods

The data for this study came from a randomized controlled trial investigating sequential treatment effects where BT ($n = 104$) and zolpidem ($n = 107$) were the first-stage therapies (NCT01651442). BT consisted of sleep restriction and stimulus control. Medication treatment consisted of zolpidem, sublingual, 5–10 mg, taken nightly at bedtime. The original sample consisted of 211 adults, predominantly female (63%) with a mean age of 45.6 (SD = 14.9) years. See [7] for the study procedures.

Analytic procedure

In this study, we included the individual ISI items and sleep diary-based sleep efficiency (SE). To investigate the symptom-specific effects for BT and zolpidem we used NIA [6] and estimated a Mixed Graphical Model (mgm [10];) on the change scores relative to baseline for each assessment. Links between the treatment variable and symptoms indicate differential treatment outcomes: orange dashed links indicate BT led to a greater reduction in complaints, whereas green dashed links indicate zolpidem led to a greater reduction. Absent links may indicate no direct treatment effect or that there were no marked differences between the two treatments. See Supplementary Materials for more details.

Results

In week 1, a differential effect of BT on "early morning awakening" was observed (Figure 1). In week 2, we observed differential effects of BT on "SE" and of zolpidem on changes in "daily functioning"

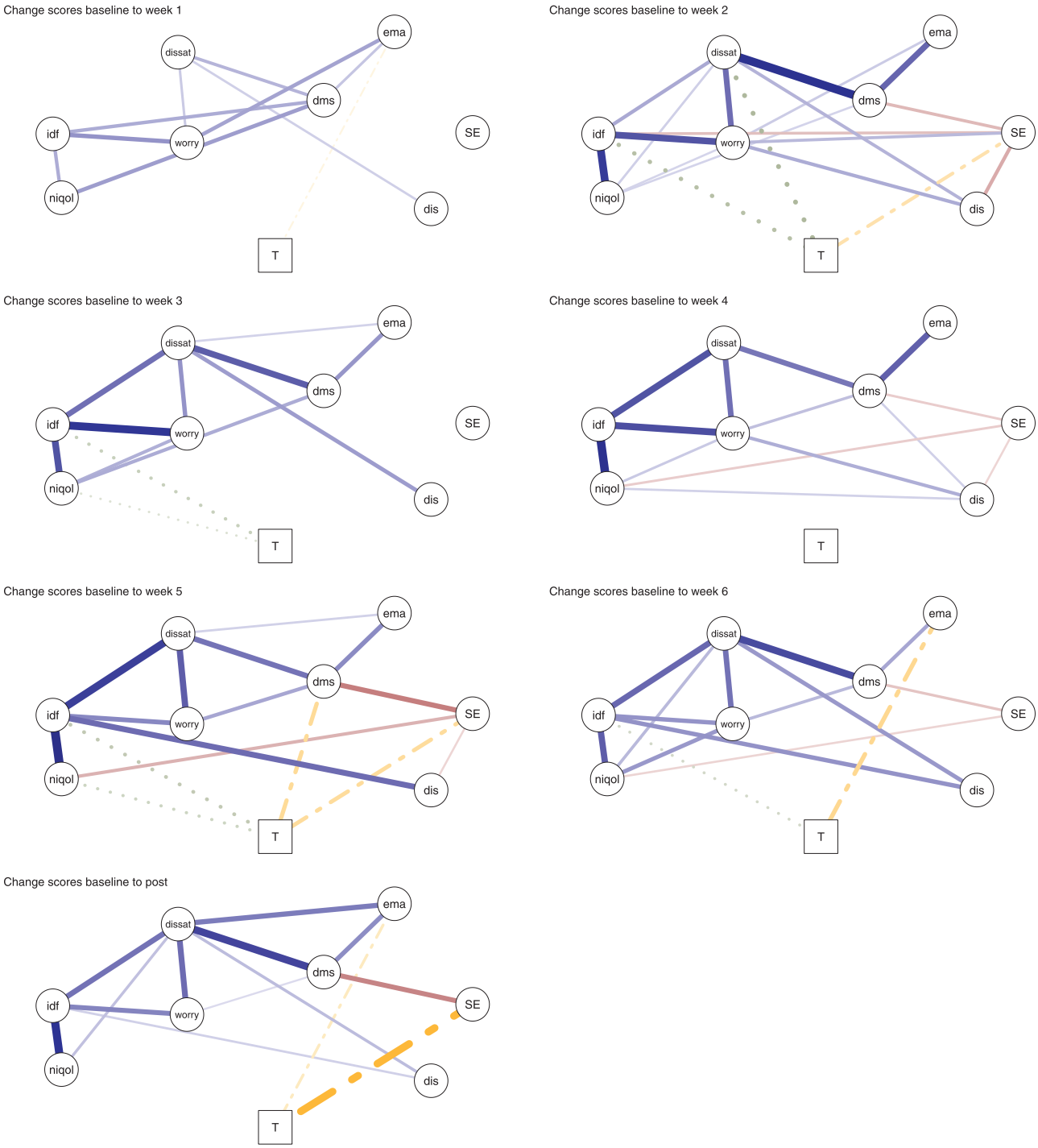

Figure 1. Symptom-specific effects of behavior therapy (BT) and zolpidem on insomnia symptoms and sleep efficiency. Estimated networks during treatment (week 1–6) and posttreatment. The nodes in the networks represent the change scores (assessment–baseline) for the seven ISI items and sleep efficiency (circles), and a binary treatment variable (square). A connection (edge) represents the unique association between two variables after conditioning on all other variables in the network. Positive associations (blue solid edges) indicate that two symptoms change in the same direction (i.e. a decrease in severity of one symptom is associated with a decrease in severity of the other symptom, given the change in all other symptoms), whereas negative associations (red solid edges) indicate that the two symptoms change in opposite directions (i.e. a decrease in severity of one symptom we associated to an increase in severity of the other symptom, given the change in all other symptoms). Any edge between the treatment node and another symptom delineates a treatment-specific effect. Effects in favor of zolpidem are represented by a green dashed edge, and effects in favor of BT are represented by an orange dashed edge. Abbreviations: dis, difficulty initiating sleep; dms, difficulty maiintga insleep; ema, early morning awakenings; dissat, dissatisfaction with sleep; idf, interference with daily functioning; niqol, noticeability of impaired quality of life; worry, worry about sleep; SE, sleep efficiency; T, treatment.

and "dissatisfaction with sleep." In week 3 only treatment-specific effects for zolpidem were observed on changes in "daily functioning" and "impaired quality of life." After four weeks, no differential effects were observed, but in week 5 we again observed treatment-specific effects for BT on changes in "difficulty maintaining sleep" and "SE" and treatment-specific effects for zolpidem on

changes in "daily functioning" and "impaired quality of life." In week 6 the treatment-specific effects of BT on changes in "difficulty maintaining sleep" and for zolpidem on changes in "daily functioning" remained. Finally, in week 7 BT showed a differential effect on changes in "difficulty maintaining sleep" and "SE." See supplementary details for effects per item over time and for networks with other sleep diary items.

Discussion

In this study, we aimed to identify symptom-specific effects of BT and zolpidem during treatment. We expected zolpidem to have more rapid effects and we explored if these effects could be pinned to specific symptoms.

Overall, we observed symptom-specific effects for both BT and zolpidem. While the first differential effect was for BT, in general, more symptom-specific effects were observed for zolpidem, especially in the early phases of treatment. Interestingly, over the course of treatment a pattern seemed to emerge that zolpidem showed symptom-specific effects on daytime functioning (daytime, quality of life) whereas BT showed symptom-specific effects on nightly wakefulness (SE, early morning awakenings). We observed the same pattern when sleep diary items were added instead of the first three ISI items (Supplementary Figure S2c). The BT effects on SE could be seen as a direct result of the sleep-restriction manipulation. However, we hold that this is also clinically relevant because time awake is part of what constitutes an insomnia disorder.

The differences in wakefulness are surprising because sleep medication is also thought to affect time awake [8]. Possibly, BT has such blunt effects on sleep (through restriction) that it surpasses the effects of medication. Another option is that it is related to the pharmacokinetic profile of zolpidem that is not indicated for sleep maintenance problems [8], which may explain the differential effects on "difficulty maintaining sleep" and "early morning awakenings."

The additional analyses did show differential treatment effects in favor of zolpidem on total sleep time (TST; Supplementary Figure S2b). Zolpidem augmented TST while BT decreased TST (Supplementary Figure S1), resulting in a 77-minute difference after week one. After the initial drop, BT steadily increased again, although a 22-minute difference in TST remained at the end of treatment. The extended sleep time for zolpidem may explain its beneficial effect on daytime complaints. Conversely, the shorter TST may have resulted in beneficial effects on wakefulness for the BT condition.

Some limitations of this study need to be discussed. First, this study was not set up for this purpose which means we were tied to available time-points and measures. Second, analyses show conditional dependencies and not causality. However, since treatment is randomized we know treatment can only affect symptom scores, and not vice versa. Third, we had no placebo control group and therefore cannot rule out that the effects on sleep measures are related to side effects of sleep restriction rather than the advantages of zolpidem. Fourth, we compared BT to zolpidem; these data may not be generalizable to other sleep medications and/or full CBT-I.

Concluding, we found zolpidem had faster effects on daytime functioning and TST while BT had faster effects on nightly wakefulness probably due to the immediate effects of sleep restriction. These findings may have interesting clinical implications as they suggest that sleep medication may give fast relief to daytime complaints whereas in BT sleep improves first before the relief in complaints follows. This finding underpins the possible added benefit of the combined approach in the first treatment phase [5]. It also stresses the need to inform BT patients that while sleep medication may have a more rapid effect, the effects of BT may last longer.

Supplementary material

Supplementary material is available at *SLEEP* online.

Acknowledgments

We would like to thank Jonas Haslbeck and Riet van Bork for their statistical advice.

Funding

The original study was supported by the National Institute of Mental Health (MH091053). For the current study, we did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure Statement

Dr. Morin has received research support from Idorsia, Eisai, Lallemand Health Solutions and served as a consultant for Eisai, Idorsia, Pear Therapeutics, and Sunovion. He received royalties from Mapi Research Trust. Dr. Edinger has received research support from Merck and Philips/Respironics and an honorarium from Eisai for participation on an advisory panel. The other authors have no disclosures to report.

Data Availability

De-identified data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Zhang Y, Ren R, Yang L, *et al*. Comparative efficacy and acceptability of psychotherapies, pharmacotherapies, and their combination for the treatment of adult insomnia: a systematic review and network meta-analysis. *Sleep Med Rev.* 2022;**65**:101687. doi: 10.1016/j.smrv.2022.101687
2. Riemann D, Baglioni C, Bassetti C, *et al*. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res.* 2017;**26**(6):675–700. doi: 10.1111/jsr.12594
3. Cheung JMY, Ji XW, Morin CM. Cognitive behavioral therapies for insomnia and hypnotic medications: considerations and controversies. *Sleep Med Clin.* 2019;**14**(2):253–265. doi: 10.1016/j.jsmc.2019.01.006
4. McClusky HY, Milby JB, Switzer PK, Williams V, Wooten V. Efficacy of behavioral versus triazolam treatment in persistent sleep-onset insomnia. *Am J Psychiatry.* 1991;**148**(1):121–126. doi: 10.1176/ajp.148.1.121
5. Morin CM, Beaulieu-Bonneau S, Ivers H, *et al*. Speed and trajectory of changes of insomnia symptoms during acute treatment with cognitive-behavioral therapy, singly and combined with medication. *Sleep Med.* 2014;**15**(6):701–707. doi: 10.1016/j.sleep.2014.02.004

6. Blanken TF, Van Der Zweerde T, Van Straten A, Van Someren EJW, Borsboom D, Lancee J. Introducing Network Intervention Analysis to investigate sequential, symptom-specific treatment effects: a demonstration in co-occurring insomnia and depression. *Psychother Psychosom.* 2019;**88**(1):52–54. doi: 10.1159/000495045
7. Morin CM, Edinger JD, Beaulieu-Bonneau S, *et al*. Effectiveness of sequential psychological and medication therapies for insomnia disorder: a randomized clinical trial. *JAMA Psychiatry.* 2020;**77**(11):1107–1115. doi: 10.1001/jamapsychiatry.2020.1767
8. Wilt TJ, MacDonald R, Brasure M, *et al*. Pharmacologic treatment of insomnia disorder: an evidence report for a clinical practice guideline by the American College of Physicians. *Ann Intern Med.* 2016;**165**(2):103–112. doi: 10.7326/M15-1781
9. Harvey AG, Belanger L, Talbot L, *et al*. Comparative efficacy of behavior therapy, cognitive therapy, and cognitive behavior therapy for chronic insomnia: a randomized controlled trial. *J Consult Clin Psychol.* 2014;**82**(4):670–683. doi: 10.1037/a0036606
10. Haslbeck JMB, Waldorp LJ. Estimating time-varying mixed graphical models in high-dimensional data. *J Stat Softw.* 2020;**93**(8):1–46. doi: 10.18637/jss.v093.i08