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GUEST EDITORIAL

The power of pooled analyses to inform about the effects of CBTI on outcomes beyond sleep

Several meta-analyses have examined the efficacy of cognitive behavioral therapy for insomnia (CBTI) on insomnia severity and sleep outcomes [1–3]. Based on strong evidence of its efficacy, CBTI is now considered a first line intervention for insomnia [4]. Less is known about its effectiveness in terms of impact on outcomes other than sleep. Two manuscripts in this volume begin to address this gap by examining the impact of non-pharmacological sleep interventions on different aspects of wellbeing. This editorial will focus on outcomes following behavioral and cognitive behavioral interventions, which were utilized in the majority of included studies.

The review by Perach and colleagues [17], which included 29 studies, is limited to older adults and encompasses a broad range of interventions including dietary supplements, mind-body interventions and psychological interventions, with only seven studies of CBTI. This review examined a number of non-sleep outcomes, including depressive symptoms (15 studies), anxiety (nine studies), mental health-related quality of life (five studies), and fatigue (six studies). The review by Gee and colleagues [18], which included 49 studies and had broad age range, assesses the impact of non-pharmacological sleep interventions on a single non-sleep outcome: depressive symptom severity. It includes only psychological interventions with the majority of the studies (39 studies) involving CBTI or "CBT-informed interventions". Both reviews include meta-analyses as well as qualitative reviews and synthesis.

Among non-sleep outcomes following CBTI, the one that has received the most attention to date is depressive symptom severity. This line of inquiry has a high public health relevance because depression is the leading cause of disability worldwide in terms of number of people affected [5]. Several meta-analyses, including one in this volume, indicate that insomnia incurs risk for a future depressive episode a year or more later [6,7]. It is tempting to apply the mathematical transitivity law and conclude that improving insomnia will reduce the risk for depression. However, simple transitive logic oversimplifies the complex relationship between insomnia and depression, underscoring the importance of the single and meta-analytic studies that directly test if CBTI for insomnia reduces depression symptom severity and associated risk for future depressive disorders.

The meta-analyses by Perach and Gee suggest that CBTI might have a small to moderate impact on depression symptom severity immediately post treatment. Although the interventions used in the majority of the studies included in each of the two meta-analyses were CBTI and CBTI-like, the inclusion of other non-pharmacological interventions limits inference about the specific effects of CBTI on depressive symptoms. The meta-analysis by Perach and colleagues, which combined the effects of 11 non-pharmacological interventions, found a small effect size overall for reduction in depressive symptom severity among older adults who have insomnia symptoms. Although the review did not provide a separate pooled effect size for the seven studies that involved CBTI and its components, their qualitative review on individual studies indicates equivocal findings. Specifically, three of the seven studies utilizing CBTI interventions found positive effects on depressive symptom severity and four did not.

The review by Gee and colleagues had no age restriction and included only psychological interventions for insomnia, with the vast majority evaluating CBTI or "CBT-informed interventions". Therefore, this review has the potential to better inform on the impact of CBTI on depressive symptom severity among individuals with insomnia symptoms. The findings indicate a moderate effect size for the combined interventions, with the smallest effects among four teen trials and the largest among the three older adult trials. Of note, the three older adult studies were not included in the review by Perach and colleagues, likely because they had a higher age cutoff for classifying "older adults".

In interpreting the results from these two review manuscripts, it is important to consider several factors. First, unlike studies of CBTI that identify depressive symptom severity as a primary outcome, the studies included in the meta-analyses may not have removed sleep items from the depressive measures prior to the analysis. This makes it difficult to determine the true effect of the sleep interventions on depression. This limitation is further compounded by the inclusion of other insomnia symptoms, such as low energy and poor concentration, in many measures of depression symptom severity. Second, the analyses pooled post-treatment summary data, which in many cases were based only on treatment completers. As a result, conclusions may be relevant only to treatment completers. This is unfortunate since individuals with high depressive symptom severity are more likely drop out of CBTI [8]. Lastly, of particular clinical relevance is the fact that many studied included in the meta-analyses excluded participants with diagnosis of depressive and other psychiatric disorders. Specifically, samples with comorbid depressive and insomnia disorder were excluded from all studies in the meta-analysis by Perach and colleagues and from half the studies in the Gee et al. meta-analysis. Although the latter found a larger effect on depression for studies that recruited from mental health clinics, the designs of these studies makes it is difficult to draw conclusions about the effect of CBTI on improving depressive symptom severity among patients with a diagnosis depressive disorder; specifically because systematic documentation of comorbid disorders and concomitant treatments were not included in some of the studies included in the review. As a result, the current two reviews cannot inform clinical guidelines relevant to patients with depressive disorders.

A 2018 qualitative review [9] identified three randomized controlled trials (RCTs) of CBTI in carefully screened clinical samples. These studies tested therapist-delivered individual CBTI that was

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offered in conjunction with antidepressant therapy to individuals with comorbid insomnia and major depressive disorder. Although the smallest and earliest of the three studies [10] found a marked additive impact of CBTI on depression outcome, two subsequent and better powered RCTs found that adding CBTI to antidepressant medication management did not improve depression outcome [11,12]. Nonetheless, there is evidence that reduction of insomnia severity might mediate the effect on depression. For example, the TRIAD study, found that improvement in insomnia severity during the first six weeks of treatment was a mediator for remission in depression over the 16 wk trial [12]. Ashworth and colleagues also found that reduction in insomnia severity mediated depression outcomes [13]. This study focused on patients with comorbid insomnia and depression whose depression had not fully remitted after six weeks of antidepressant medications. The study found that reduction in insomnia severity from baseline to follow-up mediated differential effects of self-help and in-person CBTI on depressive symptom severity at follow-up [13]. Consistent with these two studies, a secondary meta-analysis in the Gee and colleagues review found that the impact of sleep enhancement interventions on subjective sleep quality moderated their effects on depressive symptom severity. Specifically, studies of psychological interventions for insomnia that produced greater improvement in sleep also reported larger reductions in depressive symptom severity.

Our recent work suggests that there may be subgroups of patients for whom the combination of antidepressant medication management and CBTI might be particularly advantageous. We found that among patients with comorbid depression and insomnia, those with stronger eveningness tendencies are more likely to benefit from the addition of CBTI to their depression management [14]. Given the complex relationship between insomnia and depression and the limited availability of qualified CBTI providers, we need to continue our efforts to identify whose depression management could be enhanced by the addition of CBTI.

While both meta-analyses have limitations, each has strengths that underscore the value of meta-analytic reviews. The manuscript by Perach and colleague, although it included mind-body interventions that did not specifically target sleep, exemplifies the potential of meta-analysis to inform the field on the impact of non-pharmacological sleep interventions on non-sleep outcomes. The review also examined the effects of non-pharmacological interventions on fatigue and anxiety; however results regarding these domains should be considered as tentative because only a small number of studies assessing these two outcomes were entered into the meta analyses (five studies for each domain, of which only two involved CBTI). The consequence of including only a small number of studies is further compounded by the fact that the effects of the interventions on fatigue diminished after removing studies with risk of bias. The manuscript by Gee and colleague exemplifies the potential of subgroup meta-analysis to begin to answer additional relevant clinical questions, such as moderators of effectiveness outcomes. This review included 16 studies in which the interventions were delivered in a self-help format, online or via a mobile application. Base on qualitative review, the authors concluded that low cost delivery formats may be less effective for improving depression outcomes. Together, the two manuscripts highlight clinically relevant gaps in knowledge that could stimulate future research.

The use of meta-analysis of outcomes beyond insomnia and sleep is particularly exciting because RCTs are usually underpowered for detecting an effect on secondary outcomes. As a result, the interpretation of the results from individual studies is limited. There are two general approaches to meta-analyses. The most common, and the one used in the two manuscripts reviewed here, combines aggregated data (AD) from independent individual studies. Less common, but potentially more powerful, is meta-analysis of individual patient data (IPD), which when combined with an initial systematic review, is the gold standard for evidence synthesis [15]. Whereas AD meta-analyses may bias towards treatment completers, IPD meta-analyses make it possible to examine outcomes on the intent-to-treat sample using appropriate statistical methods for handling missing data and drop outs. This could better inform clinical decision making where the clinicians and patients do not know whether the patient will complete treatment. There is currently a registered systematic review and IPD meta-analysis on RCTs of CBT-I (PROSPERO CRD42018085073; [16]), which is in the process of collecting data from multiple CBTI studies with the hope of answering clinically relevant questions that are difficult to answer in smaller individual studies. Such pooled analysis can increase statistical power for the analysis of secondary outcomes and subgroups and has an added advantage relative to AD meta-analysis in helping resolve uncertainty when results from individual studies disagree.

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