

Digital health intervention for comorbid insomnia and neurocognitive impairment in adult survivors of childhood cancer: Results from a randomized clinical trial in the Childhood Cancer Survivor Study

Tara M. Brinkman, PhD¹, Kayla L. Stratton, MS², Lee M. Ritterband, PhD³, Kathryn Ruble, CRNP, PhD⁴, Chiara Papini, PhD, MPH¹, Ramona Vejandla, MA⁵, Shani Alston, MPH⁵, Vikki Nolan, DSc⁵, Nazneen Kaleem Shaikh, MBBS, MPH¹, Karen Ingersoll, PhD,³ Daniel A. Mulrooney, MD, MS ^{5,6}, Gregory T. Armstrong, MD, MSCE⁵, Wendy Leisenring, ScD², Kevin R. Krull, PhD¹

¹Department of Psychology and Biobehavioral Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA

²Clinical Research and Public Health Sciences, Fred Hutchinson Cancer Center, Seattle, WA, USA

³Center for Behavioral Health & Technology, University of Virginia School of Medicine, Charlottesville, VA, USA

⁴Division of Pediatric Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

⁵Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN, USA

⁶Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN, USA

Background-Aim: Survivors of childhood cancer are at risk of developing both insomnia and cognitive impairment, which may persist decades following treatment. Cognitive behavioral therapy for insomnia (CBT-I) focuses on changing maladaptive thoughts and behaviors that interfere with sleep and is the gold-standard treatment for insomnia; yet the impact of improved sleep on comorbid cognitive dysfunction has not been evaluated in survivors.

Methods: Survivors enrolled in the Childhood Cancer Survivor Study (CCSS; median age 44 [range 23-66] years; 73% female; 37% leukemia, 23% lymphoma, 18% sarcoma, 14% Wilms, 8% neuroblastoma) with comorbid insomnia and neurocognitive impairment were randomized 1:1 to 9-week digital CBT-I vs. online sleep education (SE). Insomnia severity index (ISI, range 0-28, higher=worse), neurocognitive problems (CCSS-Neurocognitive Questionnaire [NCQ]), emotional health (Patient Health Questionnaire/Generalized Anxiety Disorder), and quality of life (PROMIS) were measured at baseline and 9-week and 6-month follow-ups. Intent-to-treat models estimated treatment effects for ISI (mean difference [MD] between CBT-I and SE of change from baseline to follow-ups) adjusted for age, sex, and cranial radiation. Cohen's *d* estimated effect size. Additional models estimated treatment effects on secondary outcomes and mediation by improved ISI.

Results: 439 of 541 randomized survivors completed baseline assessments and started the intervention (82% CBT-I; 81% SE); 353 of those completed 9-week (76% CBT-I; 85% SE) and 305 completed 6-month (61% CBT-I; 78% SE) post-intervention assessments. Mean ISI scores at baseline did not differ significantly between groups (CBT-I=14.3 vs. SE=15.0, $p=0.07$). Survivors randomized to CBT-I reported improved ISI scores at 9 weeks (MD=-2.4[95%CI -3.4, -1.4]; Cohen's $d=0.50$) and 6 months post-intervention (MD=-3.5[-4.6, -2.4]; $d=0.72$) vs. SE (both p 's<0.001). Survivors randomized to CBT-I reported greater improvement in memory (9wks: MD=-0.3SD [-0.5, -0.1], $p=0.003$; 6mos: MD=-0.5SD [-0.7, -0.3], $p<0.001$) and task efficiency (9wks: MD=-0.3SD [-0.5, -0.1], $p=0.003$; 6mos: MD=-0.5SD [-0.7, -0.3], $p<0.001$) vs. SE. Survivors randomized to CBT-I were also more likely to be responders (a decrease of >7 points on ISI) compared to SE (9wks: 40% vs. 18%; 6mos: 49% vs. 20%, both p 's<0.001). Effects of CBT-I on cognitive function were mediated by improved ISI scores (42-65% mediated, all p 's<0.001). Insomnia remitters (those who reported a change in ISI from ≥ 8 [mild to severe insomnia] to <8 [no insomnia]; 9wks: 49% CBT-I vs. 24% SE; 6mos: 60% vs. 25%, both p 's<0.001) also reported improved quality of life (9wks: mental beta=1.7[95%CI 0.4, 3.0], physical=2.1[1.0, 3.1]; 6mos: mental=3.5[2.0, 5.0], physical=3.3[2.1, 4.5]), and emotional health (9wks: anxiety beta=-1.3[-2.1,-0.5], depression=-1.8[-2.6, -1.0]; 6mos: anxiety=-1.8[-2.7, -0.8], depression=-2.4[-3.4, -1.4]).

Conclusion: Use of a fully automated digital health treatment of insomnia confers short and long-term benefits to cognitive impairment and quality of life in survivors of childhood cancer. Given its efficacy and availability, digital CBT-I should be considered for the behavioral treatment of insomnia and comorbid symptoms in survivors.