https://doi.org/10.5664/jcsm.10088

JCSM | Journal of Clinical Sleep Medicine

LETTERS TO THE EDITOR

Recruiting "clean" chronic insomnia participants: the unicorn of sleep research

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Our laboratory team is currently conducting a placebo-based, double-blind, randomized controlled trial to determine if Suvorexant (Merck, Rahway, NJ) reduces muscle sympathetic nerve activity and/or improves baroreflex control of blood pressure, building upon our previous findings indicating sympathetic dysfunction in chronic insomnia.[1] While designing our study, we planned to allow inclusion of participants with chronic insomnia whose anxiety and depressive symptoms were well controlled, while excluding uncontrolled anxiety or depression, serious psychiatric diagnoses, and current use of sleep/hypnotic medication, antihypertensive medications, and any uncontrolled medical diagnoses such as hypertension. With over 2 years of recruitment efforts, these "clean" chronic insomnia participants have proved to be exceedingly rare. This led us to wonder how generalizable will our findings be if we include only "clean" chronic insomnia participants? It turns out we are not the only research group with this question.[2] Even with our approach of not excluding "all comorbidities," we still struggled with recruitment. After analyzing our recruitment data of the first 197 individuals, 127 (64%) met 1 or more of the initial exclusion criteria (**Table 1**). Furthermore, of the 70 participants who matriculated past initial screening, only 9 (~5%) proceeded to treatment randomization (**Figure 1**).

Our research group decided to amend the recruitment strategy to allow for more generalizable recruiting. Modifications included allowing participants with controlled hypertension, inclusion of chronic insomnia participants with varying levels of habitual sleep duration (our original design aimed for the "short sleeping" insomnia phenotype[3]), and exclusion of only severe obstructive sleep apnea (changing from an apnea-hypopnea index cutoff of > 10 to > 30 events/h). Clearly, if it was so challenging to include our initially hypothesized "appropriate" study group, the inclusion/exclusion criteria were not a reasonable reflection of the large population of people with chronic insomnia.

This led us to wonder, what do these recruitment challenges suggest, and what advice do we have for others considering research with this important population?

Perhaps our initial aim of better understanding the hyperarousal theory is relevant to this dilemma. Hyperarousal in the current context refers to a broad dysregulation of both central and peripheral autonomic processes. Previous research from our team[1] reported excessive sympathoexcitation in chronic insomnia, supporting the hyperarousal theory. However, insomnia is often associated with numerous comorbidities, including anxiety and mood disorders, which are similarly associated with altered sympathetic regulation.[4] Stringent controls in our previous study indicate a direct relationship between insomnia and sympathoexcitation.[1] These findings infer that the presence of insomnia within other disorders may influence sympathetic neural control, leading to an underestimation of the importance of sleep in the pathology observed in other disorders. To adequately assess autonomic dysregulation as it relates to insomnia, it is paramount to account for differences in psychological health and well-being, as differing severities of comorbid conditions may influence autonomic control.[4] Accounting for different insomnia subtypes and severities, as well as comorbidities in autonomic research, may offer a chance to assess interindividual cardiovascular risk factors, leading to improved preventative care.

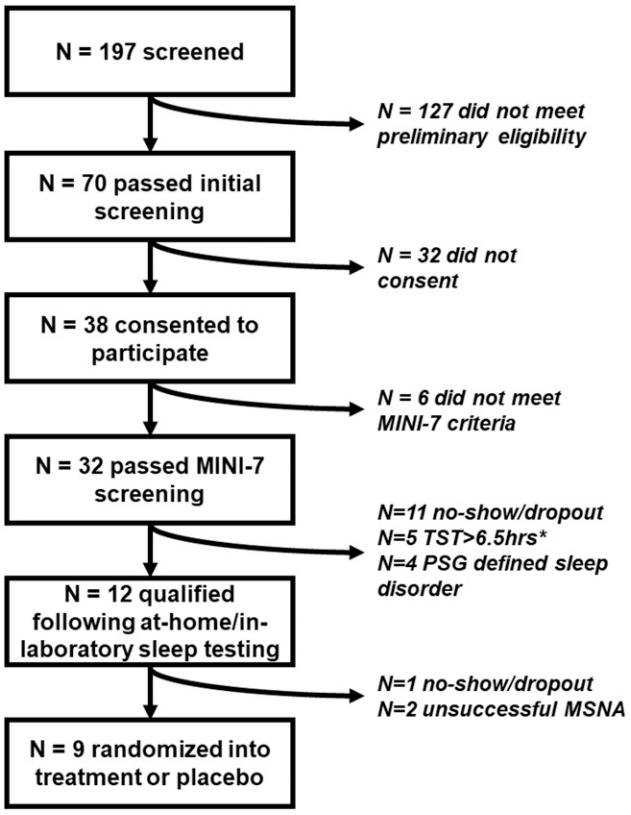
Years ago, the *International Classification of Sleep Disorders: Diagnostic and Coding Manual*, second edition (ICSD-2),[5] and *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR),[6] required clinicians to consider whether insomnia was a primary or secondary diagnosis.

Table 1—Preliminary eligibility.

Criteria	Number of Excluded Applicants	Percentage of Excluded Applicants
Absent/subclinical insomnia	44/127	35%
Sleep/hypnotic medication usage	44/127	35%
BMI > 35 kg/m^2	35/127	28%
Hypertension or diabetes	28/127	22%
Chronic smoker/alcohol use	22/127	17%
Shift-worker	12/127	9%
Age > 65 years	8/127	6%
Other	9/127	7%

Chronic smoking is classified as 6 or more cigarettes per week, while excessive alcohol use was defined as consumption of greater than 2 alcoholic drinks per day. BMI = body mass index.

Figure 1—Flow chart of recruitment.



A representative recruitment flow diagram indicating the rate of participant dropout at various stages of the protocol. *The criteria for an actigraphy defined total sleep time < 6.5 hours/night was an initial inclusion criterion but was subsequently removed due to recruiting difficulty. MINI-7 = Mini International Neuropsychiatric Interview 7.0.2, MSNA = muscle sympathetic nerve activity, PSG = polysomnography, TST = total sleep time.

While this was appropriately adjusted due to poor interrater reliability,[7] it previously existed for a reason—insomnia patients are significantly likely to have comorbidities. While other diagnoses in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5),[8] include "due to _____," it is rare that a diagnosis has such a high prevalence of comorbidities that there has ever been an element of primary vs secondary. Perhaps the next iteration of the ICSD should reconsider these common comorbidities? The DSM-5 encourages us still to note comorbidities in our diagnosis (eg, Insomnia Disorder, Persistent, Comorbidities: Generalized Anxiety Disorder). While primary vs secondary insomnia might be too challenging to tease apart, should insomnia as a comorbidity be listed more frequently as a subcategory in other diagnoses such as major depressive disorder, hypertension, chronic pain, etc.? What is the best way to diagnostically attend to the highly prevalent comorbidities in patients with chronic insomnia?

The American College of Physicians released a paper in 2016 reviewing the overwhelming support for cognitive behavioral therapy for insomnia (CBT-I) and recommended the use of CBT-I as a first-line treatment.[9] Although most research used to establish these guidelines excluded comorbid conditions,[9,10] CBT-I has shown similar efficacy when insomnia is comorbid with psychiatric or medical conditions.[11] Despite these guidelines, of those participants excluded after initial screening, 35% reported taking an exclusionary medication in the current study, indicating that treatment practices have not yet caught up with American College of Physicians recommendations. This highlights a long-standing problem in the field of behavioral sleep medicine—there is a dearth of board-certified behavioral sleep medicine specialists. More training options are necessary to increase the number of providers, yet without enough providers, it is challenging to build more training options.

While we recognize the statistical challenges of choosing to include participants with varying comorbidities, we did not feel the data would be as helpful to the community if we did not present generalizable findings. Additionally, our utilization of a repeated-measures design with gold-standard assessment of sympathetic neural activity (ie, microneurography) with high levels of reproducibility[12,13] allows participants to serve as their own controls, allowing for more meaningful interpretations of our findings.

Looking ahead, the insomnia research field would benefit from a consensus paper outlining "best practices" when researching this complex population. Greater consideration of necessary exclusion criteria appears warranted,[2] particularly in reference to specific outcome variables between studies. Aligning on guidelines pertaining to exclusionary psychological/medical comorbidities, symptom severity allowance, medication usage, and statistical norms might help improve the utilization of future research findings. Even if reigniting this challenge of "finding unicorns" does not ignite a consensus paper, we hope our readers may benefit from learning how we approached this challenge, or at the very least, we hope our readers commiserate with the challenges we faced!

CITATION

Medalie L, Bigalke JA, Tikkanen AL, Mokhlesi B, Carter JR. Recruiting "clean" chronic insomnia participants: the unicorn of sleep research *J Clin Sleep Med*. 2022;18(8):2081–2083.

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ACKNOWLEDGMENTS

The authors acknowledge the many participants that have participated in our screening and recruitment efforts, particularly those who have met our stringent criteria and formally enrolled in this ongoing randomized clinical trial. They also acknowledge the Merck Investigators Studies Program (MISP), which is funding this project.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication April 6, 2022
Submitted in final revised form April 19, 2022
Accepted for publication April 20, 2022
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DISCLOSURE STATEMENT

All authors have seen and approved this manuscript. Work for this study was performed at Montana State University. This study was funded by the Merck Investigators Studies Program (MISP) (J.R.C). Additionally, the main study sponsor (Merck) has an FDA-approved drug for insomnia (Suvorexant) on the market in the USA and elsewhere. Clinical Trial Information: Information presented in the manuscript is part of an ongoing clinical trial. Title: Impact of Suvorexant on Sympathetic Nerve Activity and Baroreflex Function in Chronic Insomnia, URL: https://clinicaltrials.gov/ct2/show/NCT03768713, ClinicalTrials.gov Identifier: NCT03768713.