

Sleep Disorders Among People With Schizophrenia: Emerging Research

Elizabeth A. Klingaman^{1,2} · Jessica Palmer-Bacon² · Melanie E. Bennett^{1,2} · Laura M. Rowland³

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Abstract Up to 80 % of individuals with schizophrenia spectrum disorders experience sleep disturbances, which impact physical and mental health, as well as quality of life. In this paper, we review and integrate emerging literature, published between 2012 and 2014, regarding approaches to diagnosis and treatment of major sleep disorders for people with schizophrenia spectrum disorders, including insomnia, obstructive sleep apnea (OSA), circadian rhythm dysfunction, and restless legs syndrome (RLS). We advocate for (1) the need to evaluate the utility of nonpharmacological approaches in people with schizophrenia spectrum disorders; (2) documentation of guidelines to assist providers in clinically tailoring such interventions when their clients experience positive, negative, and/or cognitive symptoms; (3) research on the best ways providers can capitalize on clients' self-identified needs and motivation to engage in sleep treatments through shared decision making; and (4) the importance of investigating whether and how mental health and sleep treatment services

should be better connected to facilitate access for people with schizophrenia spectrum disorders. Assessment and tailored treatment of sleep disorders within mental health treatment settings has the potential to reduce sleep problems and improve functioning, quality of life, and recovery of this population.

Keywords Sleep · Schizophrenia · Psychosis · Insomnia · CBT-I

Introduction

Sleep plays a vital role in optimal cognitive, brain, immune, metabolic, and cardiovascular health [1–4]. Sleep problems are prominent in people with schizophrenia spectrum disorders (up to 80 % [5]), compared to the general population. The mechanism of poor sleep in people with schizophrenia spectrum disorders is unknown but studies indicate both sleep homeostasis and circadian rhythms are disrupted [5, 6]. Specifically, polysomnography (PSG), actigraphy, and subjective sleep quality assessments indicate increased sleep latency and awakenings during the sleep period, shifted wake/sleep periods, increased naps, and reduced sleep efficiency in schizophrenia [5, 6]. Disturbed sleep occurs in the prodromal phase [7], commonly precedes psychotic exacerbation [8], and occurs in both antipsychotic medicated and unmedicated states [9, 10].

In schizophrenia, poor sleep quality is associated with diminished quality of life [11, 12], greater positive symptoms [13], peripheral immune measure alterations [14], and impaired cognitive functions [15], including impaired sleep-dependent memory consolidation [16–19]. Sleep deprivation in healthy individuals shares many similarities to clinical manifestations observed in schizophrenia. Sleep deprivation can

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✉ Elizabeth A. Klingaman
Elizabeth.Klingaman@va.gov

¹ Mental Illness Research, Education, and Clinical Center (MIRECC), VA Capitol Health Care Network (VISN 5), 10 North Greene Street (Annex Suite 720), Baltimore, MD 21201, USA

² Department of Psychiatry, School of Medicine, University of Maryland, 737 W. Lombard St., Room 551, Baltimore, MD 21201, USA

³ Maryland Psychiatric Research Center, School of Medicine, University of Maryland, P.O. Box 21247, Baltimore, MD 21228, USA

cause psychotic features such as perceptual alterations and paranoia [20, 21], severe cognitive impairments [22–24], reduced frontal cortical and thalamic metabolism [25] and functional connectivity [26], increased proinflammatory cytokine production [27], and altered cortisol and melatonin levels [28]. Sleep problems are also a major contributor to obesity and cardiovascular illness [29], which are highly prevalent in schizophrenia [30]. The evidence of altered sleep in schizophrenia, coupled with some similarities between the chronic sleep deprived state in people with and without schizophrenia, suggests that sleep alterations may play a role in the pathophysiology or severity of illness in schizophrenia spectrum disorders. Prevention, screening, diagnosis, and treatment for sleep disorders should be incorporated into standard clinical care for individuals with schizophrenia spectrum disorders. Experts in the fields of sleep and schizophrenia have recently called for empirical research to inform improved management of these conditions for this population [31–35].

Therefore, this paper reviews emerging research regarding treatment of major sleep disorders experienced by individuals with schizophrenia-spectrum disorders: insomnia, obstructive sleep apnea, circadian rhythm dysfunction, and restless legs syndrome (RLS). As there have been several recent reviews in this area [31–34], the current review is focused on emerging research published from 2012 to 2014, and on placing this new research in the context of previous findings. For each sleep disorder, issues related to diagnosis, assessment, and management are reviewed. The American Academy of Sleep Medicine (AASM) provides practice guidelines for the treatment and management of these disorders; guidelines were reviewed and implications for their application for individuals with schizophrenia spectrum disorders are discussed.

Methods

A literature search of publications detailing the results of clinical trials published in academic journals in PubMed, PsycInfo, and Medline databases was conducted using the following search terms: schizophren*, schizoaffect*, or schizotyp* and insomnia, sleep, circadian, restless leg syndrome, restless legs syndrome, and RLS. Databases were selected because they are considered comprehensive in health, medicine, and psychiatry. Resulting English-language articles published from January, 1, 2012 to December 31, 2014 were searched manually and all abstracts were analyzed by the authors for inclusion. Two authors (E.K. and L.R.) critically examined the remaining literature.

Results

Insomnia

Diagnosis

It was previously thought that insomnia was caused by psychiatric illness among people with both disorders. There is now increasing evidence that sleep disturbances among people with psychiatric disorders may not improve with treatment of the psychiatric illness [36]. While the DSM-IV required insomnia to be coded as a secondary disorder in those with other psychiatric conditions, DSM-5 allows coding insomnia as a primary disorder alongside other psychiatric conditions [37]. This reflects a consensus that insomnia warrants treatment as a condition in its own right and can be treated simultaneous to other disorders. Diagnosis of insomnia should include a comprehensive sleep history and administration of sleep diaries [38]. Few studies have reported the rate of insomnia among persons with schizophrenia; in one study of 175 people receiving outpatient treatment for schizophrenia, 44 % had insomnia severity index (ISI) scores within the moderate to severe clinical range [39]. Another study among 300 individuals with current persecutory delusions and a clinical diagnosis of schizophrenia, schizoaffective disorder, or delusional disorder found 54 % with moderate or severe clinical insomnia based on the ISI, with 30 % additionally scoring at the subthreshold level [40].

Treatment and Management

Treatment and management of insomnia, as recommended by the AASM [41], include (1) psychological and behavioral and (2) pharmacological interventions. Evidence-based psychological and behavioral treatments include stimulus control therapy, relaxation, paradoxical intention, sleep restriction, biofeedback therapy, and cognitive-behavioral therapy for insomnia (CBT-I) [41]. CBT-I is classified by the NIH as a first-line treatment for insomnia due to its comparable efficacy and better durability of treatment gains compared to medication [36]. This is likely due, at least in part, to its focus on teaching clients to use sleep strategies on their own after treatment discontinuation; a unique advantage over pharmacological approaches [36]. For those with severe or refractory insomnia or chronic comorbid illness, which characterizes many individuals with schizophrenia, long-term use of sleep aids may be warranted. However, clinical guidelines for the treatment of insomnia outline the importance of administering an adequate of trial cognitive and behavioral psychotherapy when using medications to treat both acute and chronic insomnia, rather than relying on pharmacological treatment as a standalone intervention [38].

Since 2012, one clinical trial has been published that focused on the treatment and management of insomnia in people with schizophrenia spectrum disorders. Tek and colleagues tested whether eszopiclone improved sleep and cognition in a double-blind, randomized placebo-controlled trial in 39 people with schizophrenia or schizoaffective disorder and insomnia receiving care in a large community outpatient mental health center [42•]. Eszopiclone was efficacious for insomnia as assessed by the insomnia severity index (ISI) but not according to sleep diaries. Results also revealed a possible beneficial short-term effect of eszopiclone on working memory. Importantly, memory deficits are related to reduced sleep spindle activity [16, 19], and eszopiclone has been shown to increase sleep spindles in a recent double-blind, randomized placebo-controlled trial of 21 people with schizophrenia but without insomnia who were taking second-generation antipsychotic medication [43•]. Although eszopiclone did not improve procedural memory in that sample, it appeared to selectively enhance spindle activity, with sleep spindle number and density predicting procedural memory. Taken together, both studies indicate the need for larger trials using objective sleep measures to determine eszopiclone's possible impact on sleep parameters as well as cognition among people with both schizophrenia and insomnia.

There has been a paucity of clinical trials testing psychological and behavioral interventions for the treatment of insomnia among individuals for schizophrenia-spectrum disorders. It could be argued that because CBT-I is the first-line insomnia treatment and an evidence-based practice, it should work for those with serious mental illnesses [31]. Conversely, some argue that positive, negative, and/or cognitive symptoms could interfere with sufficient use of behavioral strategies [44]. We believe that application of cognitive and behavioral interventions such as CBT-I for individuals with schizophrenia spectrum disorders is possible. Research examining the best ways to tailor the clinical delivery of this intervention to the challenges experienced by this population is critically needed.

Our perspective is based on (1) evidence that people with schizophrenia and related psychoses do participate and benefit from behavioral treatments [45] and (2) two open CBT-I trials revealed preliminary evidence for the efficacy of CBT-I and a need to accommodate to the challenges faced by this population when using this intervention. Freeman, Myers, and colleagues provided 4 sessions of CBT-I to 18 people with persistent, persecutory delusions [46]. Two thirds ($n=12$) showed a clinically significant change in self-reported insomnia symptoms; half of these ($n=6$) maintained 50 % improvement over 1 month. Dopke and colleagues enrolled 11 people with mental health disorders (including three with schizophrenia spectrum) and provided 10 CBT-I group sessions, resulting in significant improvements in self-reported sleep satisfaction, interference of sleep on daily functioning,

sleep concerns, and number of skills used (e.g., positive sleep habits such as stimulus control) [47]. However, sleep diaries did not show significant changes in sleep parameters, an unexpected finding given their significant change in CBT-I trials with other populations [47] and their importance as a standard outcome measure in CBT-I trials [48]. While these results are encouraging, authors acknowledged challenges to delivering CBT-I with this population. They stressed the need to attend to the symptoms and experiences of people with psychotic disorders when administering CBT-I. Both studies simplified intervention materials and explanations; Dopke and colleagues additionally allowed for repetition in presentation and taught people how to adjust CBT-I skills to their symptom levels and medication side effects [47]. They noted comprehension difficulties for some participants suggesting the need for more accommodation to cognitive deficits and cited a need to build in more practice and motivational enhancement to help clients use behavioral strategies consistently. In sum, while these trials provide preliminary support for the utility of CBT-I among people with psychotic disorders, both suggest the need for guidelines for tailoring cognitive and behavioral treatments such as CBT-I to the needs of this population.

At least two current projects are responding to this need. Freeman and colleagues are currently completing the first randomized controlled trial of CBT-I with people who have distressing delusions or hallucinations in the context of a schizophrenia spectrum diagnosis [49], as a follow-up to their open trial [46]. They aim to demonstrate the efficacy of CBT-I on both sleep and psychotic symptoms, as well as examine outcomes such as well-being, fatigue, and cost-effectiveness and durability of effects on sleep and psychotic symptoms. In addition, our team is developing guidelines for the clinical tailoring of CBT-I materials and procedures for US Veterans who have psychotic disorders, through input from Veteran clients, CBT-I providers, and psychosis experts. This project will yield empirically derived guidelines that can improve access of CBT-I for people with psychosis both in the Veterans Health Administration and more widely by providing guidance and encouragement to VA and community clinicians. Our subsequent field test will yield information on the acceptability, feasibility, and preliminary efficacy of CBT-I delivered in accordance with these guidelines, for improving not just sleep, but also psychiatric symptoms and functional outcomes more broadly among people with psychotic disorders.

Obstructive Sleep Apnea

Diagnosis

Routine assessment for obstructive sleep apnea (OSA) should include a history of snoring and daytime sleepiness,

witnessed apneas, gasping/choking episodes, sleep fragmentation, and evaluation for obesity, retrognathia, or hypertension, leading to a more comprehensive sleep history and physical exam as needed. Follow-up objective testing with in-laboratory polysomnography or home portable monitors may be warranted [50]. A high prevalence of sleep disordered breathing has been found among individuals with schizophrenia [51]; one study found that nearly half of people with schizophrenia who were referred to a sleep clinic while hospitalized on a psychiatric inpatient unit met criteria for OSA, defined as a respiratory disturbance index greater than 10 events per hour [52]. Compared to others from the inpatient unit who were referred to the sleep clinic, those with schizophrenia were significantly heavier and experienced higher rates of OSA; when present, OSA was in the severe range. Being older, male, and having a higher BMI predicted OSA, echoing risk factors in the general population. However, an unanticipated finding was that antipsychotic use for 6 months prior to hospitalization additionally and independently predicted OSA when defined as greater than 20 events per hour. It is possible that such agents may be a unique OSA risk factor beyond their obesogenic properties [53]. Larger trials should continue to explore this possibility; one option for doing so may be to examine the prevalence of OSA among those taking antipsychotics but who are not overweight or obese.

Treatment and Management

Treatment and management of OSA includes education about the condition, offering of continuous positive airway pressure (CPAP) to all clients and weight loss as an adjunctive measure to those who are overweight. Treatment alternatives to CPAP include behavioral (e.g., positioning), oral appliances (e.g., mandibular repositioning appliances, tongue retaining devices), or surgical interventions. The clients' treatment preference, anatomy, and risk factors should be considered when developing or deciding on treatment management. A review of updates on the treatment and management of OSA among people with schizophrenia spectrum disorders revealed no new clinical trials. Based on prior literature on two case reports, it appears possible for people with schizophrenia to use CPAPs [54, 55], although the feasibility, efficacy, and effectiveness need to be tested in larger-scale studies. Rates of overweight and obesity are higher among people with schizophrenia than the general population [56] and obesity promotes OSA [57]. Given that psychosocial weight loss programs of at least 3 months in duration are beneficial among those with schizophrenia [45], such programs should be discussed with clients and offered as a preventative strategy or treatment option for those who are overweight or obese.

Circadian Rhythm Sleep Disorders

Diagnosis

Diagnosis of circadian rhythm disruption should utilize sleep diaries and actigraphy [58]. There are no large-scale studies that have examined the incidence of circadian rhythm disruption among those with schizophrenia. A recent small-scale study of 20 clinically stable individuals with schizophrenia and sleep complaints revealed two distinct subgroups based on sleep/wake characteristics. One half of the sample had a circadian rhythm abnormality characterized by severe abnormalities in circadian timing, namely sleep/wake patterns misaligned to environmental day/night, excessive sleep, and less activity while awake [59]. Of these individuals, sleep phases and melatonin cycles were either delayed or both delayed and free-running [59]. The other half of the sample, while not displaying a circadian or melatonin cycle abnormality, did show prolonged, irregular, or fragmented sleep [59]. Results suggest the importance of screening for circadian rhythm sleep disorders among people with schizophrenia, to appropriately tailor clinical treatment and management. In our experience, people with schizophrenia are able to complete sleep diaries and use actigraphy successfully for multiple nights at home without problem. Mental health care providers are strongly encouraged to use these assessment strategies as needed.

Treatment and Management

Treatment and management of circadian rhythm sleep disorders depends on the type of disorder diagnosed. For instance, options for advanced sleep phase disorder include prescribed sleep/wake scheduling, timed light exposure, or timed melatonin administration. Guidelines for delayed sleep phase disorder include morning light exposure and evening melatonin; chronotherapy is also an option. Options for free running disorder include prescribed sleep/wake scheduling and circadian phase shifting by timed light exposure or melatonin. Irregular sleep and wake rhythm disorder options include daytime bright light exposure, melatonin, or combined treatments that include bright light exposure, physical activity, and other behavioral elements. Our review of updates on the treatment and management of circadian rhythm disorder revealed no new clinical trials among people with schizophrenia spectrum disorders. Although no published studies have reported its use with individuals with schizophrenia disorders, interpersonal and social rhythm therapy [60], which emphasizes education on the importance of circadian rhythms and routines and improving interpersonal relationships and skills, is promising. These strategies seem especially important for people with schizophrenia, many of whom may experience social

anhedonia and may need assistance in developing activities to replace their daily time-in-bed.

Restless Legs Syndrome

Diagnosis

Diagnosis of RLS may require differential diagnosis considerations for positional discomfort, pain, hypnic myoclonus, nocturnal leg cramps, antipsychotic-induced akathisia, and vascular or neurogenic intermittent claudication and anemia; polysomnography (PSG) may be warranted to clarify diagnosis [61]. As no diagnostic test exists for RLS, diagnosis typically begins with self-report of symptoms based on four criteria as defined by the International Restless Legs Syndrome Study Group (IRLSSG): (1) reports of symptoms being worst at night (with their absence or relief in the morning), (2) strong urge to move the symptomatic limb, (3) inactivity triggering sensory symptoms, and (4) partial or total relief of sensory symptoms provided with movement [62]. Symptoms can include uncomfortable and unpleasant sensations in the legs, periodic limb movements, and sleep disturbances [63]. One study of people with schizophrenia hospitalized on an inpatient unit ($n=182$) and age- and sex-matched controls ($n=108$) revealed that the rate of RLS was double in the schizophrenia group, with 21.4 % having RLS and nearly half meeting at least one of the RLS criteria based on the International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria and the IRLSSG rating scale [64].

Treatment and Management

Treatment and management of RLS focuses on pharmacotherapy, including dopaminergic agents, opioids, anticonvulsants, and benzodiazepines. A review of updates on treatment and management of RLS among people with schizophrenia spectrum disorders reveals no new clinical trials. While behavioral treatments (e.g., good sleep hygiene, including refraining from alcohol and caffeine in the evening) may be viable adjunctive treatments, there is little evidence to support their use even among people without mental illness, and they may pose additional challenges requiring clinical tailoring in people with schizophrenia spectrum disorders. Because periodic leg movements during sleep respond to dopaminergic agents and agonists and psychosis is a potential side effect, prescribers are posed with a difficult risk/benefit decision for these agents in this population. Since dopaminergic treatment sometimes fail to significantly reduce sleep loss in those with restless legs syndrome [65, 66], researchers are investigating other neurotransmitter systems, such as glutamate. One neuroimaging study using magnetic resonance spectroscopy reported increased thalamic glutamate plus glutamine to creatine (“Glx/Cr”) ratios in participants with RLS compared to healthy

control participants [65]. Interestingly, Glx/Cr was strongly related to wake time during sleep period, and total PSG and subjective sleep time during sleep period, but was not related to periodic limb movements per hour. These results provide some evidence for the glutamatergic system involvement in RLS. Although additional research is necessary to confirm these findings, drugs that target the glutamatergic system may prove effective for sleep loss in RLS.

Discussion

Use of pharmacotherapies and cognitive and behavioral interventions to treat sleep disorders has the potential to improve quality of life, cognitive function, and reduce psychiatric symptom severity. However, there remains little clinical guidance and a paucity of emerging clinical trials on sleep treatments for this population. We highlighted several recent discoveries on the nature of disturbed sleep for people with schizophrenia and outlined promising new treatment avenues worth future investigation, including the tailoring of CBT-I and a personalized transdiagnostic approach [67]. More research on these approaches is greatly needed.

This review identifies a number of important clinical implications and directions for future research. First, the importance of behavioral approaches as the primary intervention for insomnia is stressed. The NIH has classified CBT-I as the first line of treatment for insomnia, and clinical guidelines outline the importance of administering an adequate of trial cognitive and behavioral psychotherapy when using medications to treat chronic insomnia [38]. The majority of published research on insomnia treatments used with those with schizophrenia has been pharmacological in nature, so the use of CBT-I appropriately tailored for this population remains a promising and novel direction for future research. It is likely that this lack of treatment trials on psychotherapeutic approaches to insomnia and other sleep disorders reflects a similar reliance on pharmacological treatment approaches to sleep disorders in clinical settings. Indeed, sedative-hypnotic and antipsychotic medications are typically used to treat insomnia among people with psychotic disorders [68]. Given that individuals with mental illness often express preferences in line with taking fewer medications [69] and are interested in behavioral sleep interventions [70], it is imperative that the field also study nonpharmacological approaches and that these are offered by providers. As noted above, our team and others [40, 46, 71] are developing guidelines for the use of CBT-I with people with psychotic disorders and testing its efficacy on insomnia, psychiatric symptoms, and functional outcomes. Harvey and colleagues also posited a transdiagnostic approach to the treatment of sleep disorders [67]. This treatment includes “core” components (e.g., enhancing daily functioning, regularizing the sleep schedule, psychoeducation), supplemented by

treatment modules selected for the sleep disturbance experienced by each individual (e.g., insomnia, nightmares), and would therefore address the needs of individuals with multiple co-occurring sleep disorders within one integrated treatment protocol. Although promising in theory, her transdiagnostic approach has not been tested in individuals who have schizophrenia-spectrum disorders. This is another promising avenue for future work.

In fact, the AASM guidelines for three of the four disorders reviewed here recommend psychotherapeutic or behavioral treatments. Therefore, research is needed to identify the most relevant psychotherapeutic or behavioral treatments for individuals with schizophrenia, tailor therapies to address their needs, and respond to providers' training and education needs. Preliminary qualitative work from our team indicates that some mental health care providers (e.g., psychologists and psychiatrists) who treat clients with schizophrenia spectrum disorders recognize the value of treating sleep disorders in this population, yet desire clinical treatment guidelines for which interventions to use and under what circumstances they are appropriate [71]. In addition, providers want specific training in addressing sleep disorders when their clients experience positive, negative, and/or cognitive symptoms [71]. Tools to assist providers in making these decisions such as consultation services and continuing education should be developed with input from key stakeholders including sleep experts, treatment providers, and clients.

Since there are multiple treatment strategies for sleep disorders, it is critical to offer clients a role in the decision-making process. Recovery-oriented and client-centered services, now recognized as integral to the treatment of people with serious mental illness, require actively eliciting and acting upon the preferences and needs that mental health consumers themselves identify. It is important to assess whether clients want to take an active role in decisions about sleep treatment options and whether they are motivated to engage in cognitive and behavioral strategies. We think this is likely, based on recent research revealing that many individuals with serious mental illnesses prefer to be engaged in shared decision-making regarding mental health treatments, particularly to be offered options and asked their opinions about treatment options [72, 73]. Furthermore, a recent study found that people receiving active treatment for psychiatric illnesses (e.g., schizophrenia spectrum, affective, neurotic, stress-related, and somatoform disorders) expressed a desire to partake in behavioral sleep treatments [70]. Future research is needed to investigate the specific treatments that people with schizophrenia spectrum disorders desire and how providers can collaborate with clients to optimally partake in shared decision-making around sleep treatment decisions in a manner that capitalizes on their self-identified needs and motivation.

Finally, the field is wide open to research investigators interested in how sleep disorder treatment for individuals with schizophrenia is currently handled within the mental health

service setting. As noted above, in our qualitative work, some mental health care providers working with clients with schizophrenia reported feeling poorly equipped to assess or treat sleep disorders [71]. It is our experience that mental health clinics often rely on pharmacotherapy instead of combined pharmacotherapy and cognitive and behavioral treatments (e.g., for insomnia) for people with schizophrenia and other psychotic disorders. Our work with Veterans with schizophrenia suggests that even in large systems that provide evidence-based interventions for sleep disorders, often these individuals are not provided with or referred for CBT-I [71]. Furthermore, clinicians who provide sleep disorder treatments may not have much experience working with individuals with schizophrenia. It is important to ensure that individuals with schizophrenia are assessed for sleep disorders and referred to the appropriate services. Given the link between sleep disorders and mental health symptoms, it is critical to determine how to best connect mental health and sleep treatment services to facilitate access to gold-standard care.

Conclusions

In conclusion, treatment for sleep disorders for people with schizophrenia spectrum disorders is especially important when considering the high prevalence of sleep problems in this population [5]. Sleep plays an important role in cognitive, brain, immune, metabolic, and cardiovascular functions, each of which are generally compromised in people with schizophrenia spectrum disorders; furthermore, they find sleep disorders distressing and are motivated to try new solutions [70, 71]. More research is needed to tailor and implement nonpharmacological sleep treatments to make them maximally effective in people with schizophrenia spectrum disorders, as well as examine new directions for pharmacological intervention. Addressing sleep effectively has the potential to make a lasting impact on myriad physical and mental health consequences, quality of life, and recovery trajectories for people living with schizophrenia spectrum disorders.

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Compliance with Ethics Guidelines

Conflict of Interest Elizabeth A. Klingaman, Jessica Palmer-Bacon, Melanie E. Bennett, and Laura M. Rowland declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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