Additional Safety Considerations Before Prescribing Opioids to Manage Restless Legs Syndrome

To the Editor: Silber et al1 are commended for espousing the merit of low and stable dose opioid treatment of refractory restless legs syndrome (RLS) given the risks of suicide and severely compromised quality of life if untreated. Opioid agreements reduce risks of RLS treatment with opioids as agreements mandate drug testing as well as frequent query of prescription drug monitoring programs. Clinicians will maximize the quality of care for patients with RLS keeping in mind several additional considerations before prescribing opioids.

Adherence monitoring should include random pill counting as it is invaluable for early identification of dangerous misuse characterized by autonomous dose escalation to self-treat medical symptoms as well as finding evidence suggesting nonmedical abuse euphoria pursuit and/or diversion.

Trials with a drug class rotation of nonopioids with the associated holiday of consumption of previously efficacious agents2 may be helpful in delaying the onset of the initiation of opioids, potentially averting a proportion of patients otherwise destined for iatrogenic addiction.

Similarly, rotation of opioids in the treatment of RLS2 may successfully minimize opioid toxicities.

Before prescribing opioids, nonpharmacological therapies should be encouraged, such as relaxing music, reading, petting the dog/cat, aromatherapy, aerobic exercise, stretching, vibration, yoga meditation, and pneumatic compression, as they are often symptomatically advantageous. Similarly, education should include avoidance of caffeine and stress before sleep.

Essential documentation of informed consent must include education that patients accept repeated findings that opioids consumed before sleep not uncommonly induce central sleep apnea, even after years of continuous consumption, as clinical expression of absence of ventilatory tolerance to opioids is “most probably grossly underreported... eventually fatal apnea may occur.”4

Walker et al.2 reported that the prevalence of chronic opioid—induced nocturnal ventilatory suppression is pervasive, affecting up to 92% of patients, without sparing those who consume methadone and with accentuated risks at higher dosing.

Aneas with clinically significant desaturation still present with appropriately low opioid dosing, which customarily characterizes most clinical scenarios for the safest opioid treatment. As such, if patients with RLS can fall asleep with only a short duration of action opioid, this minimizes the duration of opioid-induced ventilatory drive as well as rapid eye movement and stage III and IV restorative sleep suppression to which the brain is exposed, though often such patients also require a safe, long half-life, deep sleep facilitator that does not suppress ventilatory drive to maintain unconsciousness.

Although the authors stated that it is “preferable” to avoid co-consumption, the Centers for Disease Control and Prevention, Food and Drug Administration, and Federation of State Medical Boards all far more strongly advocate extreme caution about the dangers of prescribing opioids to benzodiazepine or barbiturate narcotic consumers, even designating co-ingestion of these ventilatory suppressants contrary to “best practice policy.” These agents should usually be completely tapered off before initiating opioids.

Opioids are an invaluable tool in the safe management of RLS and many medical conditions, but the authors are correct that prescribers need to exercise extreme caution in prescribing, educating, and diligent monitoring before and after the initiation of opioids and in the totality of risk vs potential benefit stratification considerations to achieve appropriate patient selection for judicious opioid dosing.

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Potential Competing Interests: The author reports no competing interests.

In Reply—Additional Safety Considerations Before Prescribing Opioids to Manage Restless Legs Syndrome

We thank Dr Geller for his interest in our article on the appropriate use of opioids in refractory restless legs syndrome (RLS).

We agree with the importance of considering whether opioids are inducing or worsening sleep apnea. We emphasized this in our article, stating that “the possibility of precipitating or exacerbating obstructive or
central sleep apnea, or the conversion of treated obstructive sleep apnea to central sleep apnea, should be considered.\textsuperscript{1,p63} We agree that the combination of opioids and benzodiazepines should be avoided whenever possible. We also agree that nonpharmacological approaches should always be tried in RLS; regrettably, these are rarely effective in patients with refractory disease and many of these relaxation techniques actually worsen RLS. Rotation of nonopioids has not been found to be an effective strategy in clinical practice in most patients with RLS, but there have not been adequate studies of this approach. Random pill counting is considered highly intrusive by most patients, and we do not feel that it adds sufficiently to abuse prevention to recommend it on a routine basis.

Dr Buchfuhrer receives consultancy fees from Xenoport; receives payment for lectures including service on speakers bureaus from UCB Pharma, Arbor Pharmaceuticals, and Xenoport; owns stock/stock options in Sensory Medical. Dr Earley receives grants from Luitpold Pharmaceuticals and honorarium from the American Academy of Sleep Medicine. Dr Ondo receives grants from Luitpold Pharmaceuticals and payment for lectures including service on speakers bureaus from UCB Pharma. Dr Walters receives grants from Mundipharma, Arbor Pharmaceuticals, National Institutes of Health, UCB Pharma, and Xenoport. Dr Winkel- man receives consultancy fees from Merck and Flex Pharma and grants from Restless Legs Syndrome Foundation, Luitpold Pharmaceuticals, NeuroMetrix, National Institute of Mental Health, and UCB Pharma; he is an employee of Massachusetts General Hospital.

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**ECG changes in the reported cases is unknown and might not relate to the Zika virus—induced cellular pathology, which is generally not reversible.**

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In Reply—
Electrocardiographic Finding in Zika Virus Infection

We thank Yasri and Wiwanitkit for their comments on our work,\textsuperscript{1} which focus on the fact that, as we also stated, there is a lack of literature about cardiovascular manifestations in adult patients with Zika virus (ZIKV) infection. To date, even after a significant number of cases have been reported, particularly in the Americas, during recent outbreaks in countries such as Brazil and Colombia, no observational studies have been conducted to establish that the relative frequency of cardiac compromise in patients infected with ZIKV is “extremely rare.”\textsuperscript{2} Probably, silent asymptomatic or most likely oligosymptomatic cases would present electrocardiographic alterations as found in our study, leading to a lack of reports of such compromise. Moreover, we do not know yet if there would be long-term cardiovascular consequences associated with

To the Editor: We read the article by Villamil-Gómez et al\textsuperscript{1} with great interest. Villamil-Gómez et al reported 2 interesting cases of Zika virus–infected patients with abnormal electrocardiographic (ECG) findings and mentioned that “there is a lack of literature about cardiovascular manifestations in adult patients with ZIKV infection.”\textsuperscript{1,p393} In fact, Zika virus infection might cause cardiac involvement and it is a possibly forgotten clinical presentation.\textsuperscript{2} Nevertheless, the effect on cardiac rhythm is extremely rare. In the present report from an endemic area in tropical Asia, there is no problem of cardiac arrhythmia among the infected cases.\textsuperscript{3} Focusing on the present report by Villamil-Gómez et al, the ECG problem is reversible, which might imply that there might be a reversible cardiac abnormality due to Zika virus infection. The exact underlying pathophysiology of abnormal