It Is Too Early to Put Delirium Prophylaxis to Bed: Stronger Evidence Is Needed for Suvorexant

To the Editor: At the intersection of psychiatric and medical disorders, few conditions are as frustrating to prevent or treat as delirium. Aside from addressing underlying causes of delirium, adequate symptomatic treatments do not exist. Previous treatment mainstays, such as antipsychotics, are not uniformly effective in either the short- or longer-term.[1] We enthusiastically support the search for potential interventions for delirium, yet interventions require rigorous support even when there is a paucity of alternatives. Thus, we provide a comment on 2 recent articles published in JCP regarding the use of suvorexant as an effective prophylaxis of delirium.

Suvorexant, which is an orexin receptor antagonist, has been suggested as a potential agent to treat or prevent delirium, guided by the logic that lessening sleep disruptions may reduce delirium symptoms. Meta-analytic findings[2] have not provided a firm basis for clinical use because of their reliance on studies with sample selection issues and small effect sizes. Two recent studies have suggested that suvorexant is effective in preventing and treating delirium: a prospective case-control study by Hatta et al[3] examined a ramelteon/suvorexant combination for delirium prophylaxis, and a retrospective cohort study by Izuhara et al[4] explored suvorexant as a treatment for delirium. While both studies enhance our knowledge of the potential role for suvorexant in treating delirium, we caution that neither study provides sufficient evidence for clinical application.

Both reports employed naturalistic approaches, which is laudable, but unfortunately introduced confounds that restricted the attributions of causality made by the authors. Retrospective cohort studies, as reported by Izuhara et al,[4] are informative but cannot establish causal relations because of non-random group assignment and lack of placebo controls. In Izuhara and colleagues' study, suvorexant was initiated at clinical discretion, which can induce systematic group differences that cannot be corrected by the inclusion of covariates in analyses. Similarly, Hatta et al[3] left the decision to receive ramelteon/suvorexant to the discretion of the clinician and/or patient. The resulting medication selection bias in both studies, which may reflect real-world practice, precluded non-random assignment to treatment group and thus prevents the conclusion that suvorexant, as opposed to other unmeasured factors, resulted in group differences.

Differences between the suvorexant and non-suvorexant treatment groups in both studies (which were noted by the authors) create challenges when interpreting the studies' results. For example, in Izuhara and colleagues' study, patients in the suvorexant group were 1.2–3.5 times more likely to have received dexmedetomidine, haloperidol, risperidone, trazodone, and/or ramelteon prior to the onset of delirium. These medications are used, with varying degrees of success, to prevent[1,5] and/or to treat delirium,[6] which suggests that patients in the suvorexant group may have been treated either preventatively or preemptively for early or prodromal symptoms of delirium prior to receiving suvorexant. Treatment prior to study entry also suggests that early and/or subtle symptoms may have spurred clinical decisions to prescribe suvorexant. Similarly, treatment and non-treatment groups in the study by Hatta et al differed with respect to benzodiazepine and steroid use and whether the hospitalization had been emergent. These and other unknown factors in non-randomized studies can affect the likelihood of delirium through complex interactions and are not readily addressed by their inclusion as simple covariates in a regression.

Collectively, the non-randomized assignment of patients to treatment in both studies does not allow for the definitive conclusion that suvorexant or the combination of ramelteon/suvorexant lessens the symptoms of delirium. That is, patients were provided with the option of taking suvorexant if ramelteon was not sufficiently hypnotic. Although naturalistic studies are helpful in determining the efficacy of suvorexant in delirium prophylaxis, a matched cohort sample may have provided a more readily interpretable relation. Unfortunately, the issue of self-selection or clinician selection of subjects does not provide a sufficient basis for treatment recommendation.

Several aspects of the subject selection process in Hatta and coworkers' ramelteon/suvorexant prophylaxis study further limit the generalizability of the results. For example, although the authors divided subjects into groups with and without delirium, it would appear that *all* patients were in fact delirious at study entry as they exhibited hyperactive delirium, or at the very least sleep/wake cycle dysregulation, prior to study entry. Subjects classified as without delirium may have been in a waning phase. Consequently, this issue presents challenges in considering suvorexant as a "preventative" agent.

Hatta et al suggested that ramelteon/suvorexant improved the sleep-wake cycle compared with patients who did not receive the did not receive the medications. In their study, suvorexant was administered as second-line treatment (at clinician and patient discretion) following ramelteon, which is a melatonin receptor type 1 agonist. At baseline, however, patients who took suvorexant/ramelteon had greater sleep-wake cycle disturbance than those patients who did not. This inequality creates a statistical paradox known as "regression toward the mean," in which the patients with more extreme scores are more likely to improve on a subsequent measure than those with less extreme scores. Thus, the improvement in sleep-wake cycle attributed to suvorexant/ramelteon may in part reflect statistical artifact.

Caution should be exercised in several areas when interpreting the results of the Cox regression analysis that Izuhara et al provided, as 84 patients received suvorexant and 615 did not. The stability of the regression model, when incorporating the covariates, unfortunately deteriorates rapidly at 5 days (n = 26/n = 148; suvorexant/nonsuvorexant) and even further by 10 days (n = 8/n = 42) and 30 days (n = 1/n = 3). Thus, the data are sufficient to support an association between suvorexant and decreased rates of delirium during the first 5 days, but not through 30 days.

While there is limited evidence that second-generation antipsychotics are associated with reduced delirium in certain patient profiles,[7] in general prophylactic efforts to subvert delirium are debated.[1] Thus, novel means of delirium prophylaxis are highly important and deserve further study. We suggest that while the data of both Izuhara et al and Hatta et al provide additional evidence of the potential for suvorexant to alter delirium or its course, more definitive data are necessary to establish the use of suvorexant in clinical care.

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Studies Support the Use of Suvorexant for the Prevention of Delirium

To the Editor: In their letter, Brooks and Kruse[1] declare their concerns about the use of suvorexant for delirium prevention. We agree that a cohort study alone cannot provide concrete evidence to support the clinical use of a given remedy. We also agree that our retrospective cohort study could not establish causal relations because of non-random group assignment and lack of placebo controls. Our retrospective cohort study[2] was based on previous randomized controlled trials (RCTs). Hatta et al[3] compared the delirium preventive effect between suvorexant and placebo, whereas Azuma et al[4] compared between suvorexant and standard treatment. Our study aimed to examine whether the results of these RCTs apply to routine clinical practice.[5] For example, patients in these RCTs were asked to provide informed consent; therefore, patients who were comatose, had severe liver failure or respiratory disease, or were using antipsychotics or antidepressants were excluded. RCTs can examine efficacy but not effectiveness. Our retrospective cohort study provided supplementary findings for use of suvorexant to prevent delirium in routine clinical settings. We concluded that the delirium preventive effects observed in the RCTs also apply to our routine clinical practice.

We further agree that initiating suvorexant at clinical discretion can induce systematic group differences that cannot be corrected by the inclusion of covariates in the analyses, which was discussed in our article. In our study, patients in the suvorexant group were more likely to have received dexmedetomidine, haloperidol, risperidone, trazodone, and/or ramelteon before the onset of delirium. The multivariate Cox regression analysis showed no significant effect of these drugs on delirium occurrence. However, as discussed, we could not exclude the possibility that the patients in the suvorexant group may have been treated for early or prodromal symptoms of delirium before receiving suvorexant. We do not claim that our retrospective study proves the effectiveness of suvorexant for delirium prevention. On the basis of previous RCTs, we examined the applicability of the efficacy proved by RCTs to everyday clinical practice. Furthermore, 2 additional cohort studies examined the delirium preventive effects of suvorexant,[6,7] and 3 further cohort studies have examined the effects of suvorexant and/or ramelteon.[8–10] All 5 of these studies showed delirium preventive effects of suvorexant. The results of the RCTs are consistent with these 5 cohort studies as well as our study.

We agree that the number of patients in our study was sufficient to detect an association between suvorexant and decreased rates of delirium during the first 5 days, but not throughout 30 days. In the 2,807 patients included in our study, the median intensive care unit (ICU) stay was 2 days (interquartile range, 1–4 days). Our study covered the majority of patients in ICU; however, studying more patients is necessary to determine the effectiveness of suvorexant for delirium in patients who require ICU stays of more than 5 days.

In conclusion, our study expands on the efficacy of suvorexant for delirium prevention observed in previous RCTs by showing its effectiveness in routine daily clinical practice. However, in line with the concerns of Brooks and Kruse,[1] we must exercise caution regarding our findings until a large randomized controlled study is conducted to determine the effectiveness of suvorexant for delirium prevention, especially for non-insomniac patients.

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