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LETTERS TO THE EDITOR

Efficacy and safety of esmirtazapine in adult insomnia: unsupported statements about residual daytime effects

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Confirmation that 5-hydroxytryptamine receptor 2A/2C antagonists such as esmirtazapine work for insomnia, based on 2009–2010 trials, is welcome news.[1] Research has shown that 5-hydroxytryptamine receptor 2A/2C antagonists such as mirtazapine and trazodone have a long history of use for insomnia,[2–4] but large double-blind insomnia studies have been lacking. Ivgy-May et al[1] do make some assertions that require caveats.

The authors state without supporting data or references that esmirtazapine has a shorter half-life than the racemic mixture. The half-life of mirtazapine ranges from 20–40 hours; *R*-mirtazapine has a half-life of approximately 18 hours and *S*-mirtazapine has a half-life of approximately 10 hours.[5] Esmirtazapine is subject to *CYP2D6* polymorphism, with poor metabolizers having a 79% larger concentration-time curve. Interestingly, trazodone's half-life is even shorter (4.4 hours).[6]

Ivgy-May et al[1] further state that esmirtazapine's shorter half-life could be associated with a reduced risk of next-day residual sedative effects. This speculation seems reasonable but requires a study comparing the next-day residual sedative effects of esmirtazapine and racemic mirtazapine. If future data show this to be true, then that would be a desirable attribute.

In addition, the authors state that they did not find evidence of any residual effects on daytime functioning or alertness in patients treated using esmirtazapine based on visual analog scales, citing their Figure S2. However, Figure S2 in their article is about rebound sleep parameters after esmirtazapine discontinuation, not about residual daytime effects. Their Table 4 shows that 14.9% of patients treated using esmirtazapine had an adverse event of somnolence compared to 3.5% of those on placebo, which is not consistent with the authors' assertion.

Regardless, the efficacy data for esmirtazapine are strong, with a 48.7-minute treatment effect in total sleep time for esmirtazapine compared to 20–25 minutes for eszopiclone[7] and 27–34 minutes for suvorexant.[8] These findings should lead to a potentially favorable re-evaluation of the mechanism of 5-hydroxytryptamine receptor 2 antagonism for the treatment of insomnia.

CITATION

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