



Drug information question: Is there a relationship between mirtazapine (Remeron®) dose and sedation?

**Conclusion: The relationship between mirtazapine dose and sedation is unclear but available evidence indicates that the risk of adverse events causing patients to discontinue mirtazapine increases with dose.**

One of the BC Provincial Academic Detailing (PAD) Service's 2020-2021 topics, [Antidepressants: Drug Information](#) offers participants the opportunity to discuss:

- How the efficacy of antidepressants is measured in clinical trials and reported in meta-analyses
- The quality and quantity of evidence that informs conclusions regarding antidepressant comparisons and combinations
- Drug information relevant to the prescribing, deprescribing and monitoring of antidepressants

We frequently receive this question during academic detailing sessions: *Is mirtazapine less sedating at higher doses?*

The [Health Canada](#) prescribing information for mirtazapine states that approximately **50% of patients experience somnolence** which may be due to its potent antihistaminic effects.<sup>1</sup> Common tertiary references report that mirtazapine is more sedating at lower doses (< 30 mg) than it is at higher doses (≥ 30 mg).<sup>2,3</sup> It is speculated to be more noradrenergic at higher doses.<sup>2,3</sup> This may lead to the prescribing of higher doses in an effort to overcome the drug's sedative effects.

[Health Canada](#) advises that a relationship between mirtazapine dose and antidepressant efficacy has not been established but patients not responding to the initial 15 mg dose may have their dose increased up to a maximum of 45 mg per day.<sup>1</sup> A 2019 [dose-response meta-analysis](#) indicated that mirtazapine's antidepressant efficacy increases up to doses of 30 mg per day, but not at doses above 30 mg.<sup>4</sup> **The risk of discontinuing mirtazapine due to an adverse event, however, continues to increase steeply as the dose increases.**<sup>4</sup> Compared to SSRIs, there are few dose-response trials for mirtazapine, contributing some uncertainty to our understanding of the relationship between dose and response.

In 1996 during the [regulatory review of mirtazapine](#), the US Food and Drug Administration (FDA) identified that **somnolence was the most common adverse event causing patients to discontinue mirtazapine.**<sup>5</sup> The review states "One of the most troublesome of the common adverse events associated with mirtazapine use is its somnolent properties. What is unknown from the available data is the dose dependency for this event and whether or not and to what extent there may be adaptation."<sup>5</sup> The FDA requested a postmarketing trial examining the relationship between dose and sedation. Our literature search did not identify a completed, postmarketing dose-response trial fulfilling this requirement.

We contacted the manufacturer of Remeron® requesting relevant information and they provided three publications: a single [case report](#),<sup>6</sup> one [retrospective review](#)<sup>7</sup> and one [pharmacokinetic analysis](#).<sup>8</sup> None of these publications adequately address whether mirtazapine becomes less sedating at higher doses.

<sup>1</sup>Health Canada Drug Product Database; <sup>2</sup>UpToDate® Atypical antidepressants; <sup>3</sup>Clinical Handbook of Psychotropic Drugs 23<sup>rd</sup> edition; <sup>4</sup>FURUKAWA Lancet Psychiatry 2019;6:601-9 (PMID: 31178367); <sup>5</sup>US FDA 1996 Mirtazapine Review; <sup>6</sup>LEONARD Proc UCLA Healthcare 2015 Volume 19; <sup>7</sup>SHUMAN Ment Health Clin 2019;9:41-7 (PMID: 30627503); <sup>8</sup>GRASMADER Pharmacopsychiatry 2005;38:113-7 (PMID 15902580)