Soon after mirtazapine was licensed in Canada, a 2002 Therapeutics Letter concluded that it has “no proven efficacy or safety advantage over other antidepressant therapies”. Mirtazapine was approved for symptomatic relief of depressive illness and marketed as an alternative to selective serotonin reuptake inhibitors (SSRIs) which had dominated the antidepressant market from the late 1980s. As with all antidepressants, mechanism(s) of therapeutic benefit are unknown. Mirtazapine inhibits adrenergic, serotonergic, histaminic and muscarinic type cholinergic receptors, making it distinctive pharmacologically from tricyclics, SSRIs or monoamine oxidase inhibitors. This Letter updates evidence on mirtazapine’s efficacy (both alone and in combination with other antidepressants), dose response, and harms.

Comparative efficacy
A 2018 systematic review and network meta-analysis of 21 antidepressants examined published and unpublished randomized clinical trials (RCTs). The proportion of responders (defined by a 50% reduction in depression symptom severity using a standardised observer-rating scale) was 42% - 53% for active treatments versus 35% for placebo after approximately 8 weeks of treatment. “Response” for mirtazapine was 50%. When all drug-drug comparisons were considered using network meta-analysis, mirtazapine was deemed relatively more efficacious than 3 other antidepressants available in Canada: fluoxetine, fluvoxamine and trazodone (moderate-quality evidence). The authors did not consider the differences in efficacy between antidepressants as clinically meaningful, given that they describe the drug effect compared to placebo as “modest”.

Dose response and safety
A 2019 systematic review and meta-analysis of dose-response in double-blind RCTs for acute treatment of adults with major depression found the proportion of responders to mirtazapine increased slightly up to 30 mg, but decreased at higher doses (see Figure, left graph).

Withdrawals due to adverse events increased steeply with dose (see Figure, right graph). Therefore, exceeding 30 mg per day decreases benefits and markedly increases harms.

The 2019 Beers Criteria update for potentially inappropriate medication use in older adults recommends caution when using mirtazapine (moderate evidence, strong recommendation) as it may exacerbate or cause the syndrome of inappropriate antidiuretic hormone (SIADH) or hyponatremia. Mirtazapine has a long average half-life that is prolonged after age 55 in men from 22 to 32 hours and in women from 38 to 41 hours. Dose should also be lowered with reduced kidney or liver function.

Figure: Dose-outcome relationships for mirtazapine (Furukawa 2019)
Harms
The 2002 Therapeutics Letter cautioned that mirtazapine “has a prominent sedative effect and patients should be warned that it may cause mental or motor impairment”.
1 Somnolence was experienced by about 50% of RCT participants, but insomnia is not a Health Canada approved indication.

7-10 Mirtazapine was found to have one of the highest rates of somnolence (second only to fluvoxamine) and lowest rates of insomnia (only agomelatine was lower) in a meta-analysis of antidepressant harms.

11 A 2018 Cochrane review of antidepressants for insomnia found no eligible trials of mirtazapine for adults with a primary diagnosis of insomnia.

12 Mirtazapine was associated with the greatest adjusted rate ratio of weight gain (1.50, 95% CI 1.45 to 1.56) among 12 antidepressants used by a cohort of patients followed for 10 years.

13 It is also more likely than SSRIs to cause dry mouth and fatigue (reduced physical and mental capacity due to tiredness), but less likely to cause sweating, nausea or vomiting.

Mirtazapine was found to have fewer sexual side effects in 4 reviewed RCTs comparing mirtazapine with SSRIs; OR 0.31 (95% CI 0.13 to 0.74).

10 Other reviewers caution that “the current degree of evidence does not allow a precise estimate of comparative risk of sexual dysfunction associated with a specific antidepressant”.

Adding mirtazapine to another antidepressant not supported
One high-quality primary care trial, reviewed in a 2019 Cochrane review of persistent depressive symptoms after initial antidepressant treatment, compared adding mirtazapine or placebo to SSRI or serotonin–norepinephrine reuptake inhibitors (SNRI) treatment in people who had not adequately responded at 6 weeks.

15,16 There was no clinically significant difference in depressive symptoms at 12 weeks (1.83 difference between mirtazapine and placebo on the Beck Depression Inventory, BDI-II score range 1 to 63). Adding mirtazapine to SSRI or SNRI treatment increased anticholinergic, CNS adverse events, and weight gain.

Conclusions
• Mirtazapine’s efficacy for depression is similar to other commonly-prescribed antidepressants.
• It causes drowsiness, weight gain, and dry mouth.
• Doses above 30 mg daily provide fewer benefits but markedly increase harms.
• Prescribing mirtazapine for insomnia has not been validated by clinical trials.
• Adding mirtazapine to an SSRI or SNRI does not improve efficacy but increases harm.

References

The draft of this Therapeutics Letter was submitted for review to 130 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.