

| Second-generation antidepressant for treating MDD** | Other labelled indications†† | Key precautions‡‡ | Additional considerations <ul style="list-style-type: none"> ➤ Advantageous ➤ Disadvantageous ● May be advantageous or disadvantageous, depending on context of individual patient |
|--|------------------------------|---|--|
| Melatonergic agonist and serotonergic antagonist | | | |
| Agomelatine | GAD | May cause hepatotoxicity; contraindicated in patients with hepatic impairment or transaminases exceeding 3x upper limit of normal. Concurrent use with strong CYP1A2 inhibitors (such as ciprofloxacin and fluvoxamine) is contraindicated. | <ul style="list-style-type: none"> ➤ Lower treatment drop-out due to side effects, compared to other antidepressants ➤ Lower propensity to cause sexual dysfunction compared to SSRIs and SNRIs ➤ No discontinuation symptoms; no dosage tapering is needed on treatment discontinuation ● Sedating effect |
| Norepinephrine and dopamine reuptake inhibitor | | | |
| Bupropion | Nil | Contraindicated in patients with a seizure disorder or with history of current bulimia or anorexia nervosa. Contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives. | <ul style="list-style-type: none"> ➤ Lower propensity to cause sexual dysfunction compared to SSRIs and SNRIs ➤ Evidence of efficacy for smoking cessation (off-label use) ➤ Insomnia very commonly reported ● Associated with weight loss ● Activating effect |
| Noradrenergic, specific serotonergic antidepressant | | | |
| <u>Mirtazapine</u> | Nil | May cause orthostatic hypotension. | <ul style="list-style-type: none"> ➤ Lower propensity for sexual dysfunction compared to SSRIs and SNRIs ➤ Lower propensity for hyponatraemia compared to SSRIs and SNRIs ➤ Greater propensity for anticholinergic effects compared to other antidepressants ● Greater propensity for weight gain compared to other antidepressants ● Sedating effect |
| Serotonin antagonist and reuptake inhibitor | | | |
| Trazodone | Nil | May cause orthostatic hypotension and QTc prolongation. Risk of bleeding abnormalities; bleeding tendency may be increased if concurrently used with anticoagulants, or medications that affect platelet function (e.g. NSAIDs and aspirin). | <ul style="list-style-type: none"> ➤ Lower risk of discontinuation symptoms compared to other antidepressants ➤ Higher treatment drop-out due to side effects, compared to other antidepressants ● Sedating effect |
| Multimodal serotonergic antidepressant | | | |
| Vortioxetine | Nil | Risk of bleeding abnormalities; bleeding tendency may be increased if concurrently used with anticoagulants, or medications that affect platelet function (e.g. NSAIDs and aspirin). | <ul style="list-style-type: none"> ➤ Lower treatment drop-out due to side effects, compared to other antidepressants ➤ Dose adjustment not routinely required in renal and hepatic insufficiency ➤ Evidence of efficacy for improving cognitive function and memory (off-label use) |

CYP1A2, cytochrome P450 family 1 subfamily A member 2; CYP2C19, cytochrome P450 family 2 subfamily C member 19; CYP2D6, cytochrome P450 family 2 subfamily D member 6; CYP3A4, cytochrome P450 family 3 subfamily A member 4; GAD, generalised anxiety disorder; MDD, major depressive disorder; NSAIDs, non-steroidal anti-inflammatory drugs; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder; QTc, corrected QT interval; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors

** Medications underlined denote availability on government subsidy list at the time of publication. Please refer to the [Ministry of Health website](#) for the latest list of subsidised medications.

†† Typically, an antidepressant may be used to simultaneously treat MDD and other labelled indications. However, note that such scenarios are clinically more complex - dosing and treatment strategy would need to be tailored accordingly, and may require specialist input. Labelled indications are based on available brand-specific package inserts in the [Health Sciences Authority \(HSA\) website](#).

‡‡ Serotonin syndrome may occur with antidepressants, especially in cases of overdose or when an antidepressant is co-administered with other serotonergic medications (including another antidepressant). This is caused by excessive stimulation of serotonin receptors, and mild to severe symptoms may emerge (including neuromuscular abnormalities, autonomic hyperactivity, or altered mental status).⁵⁸ The risk of serotonin syndrome with agomelatine is considered to be low, as it does not increase serotonin levels.⁵⁹