Table 1. Key considerations for selecting a second-generation antidepressant in MDD. Antidepressants listed are locally-registered for MDD treatment. Information sourced from international literature[10,16,38,45–55] and local drug information resources[56, 57] (including package inserts). The information in this table is not exhaustive of the subject matter. Refer to package inserts and drug information resources for further details — including contraindications, drug interactions, and medication doses.

Second-generation antidepressant for treating MDD**	Other labelled indications††	Key precautions‡‡		Additional considerations ✚ Advantageous ▬ Disadvantageous ● May be advantageous or disadvantageous, depending on context of individual patient
Selective serotonin reuptake inhibitor				
Escitalopram	GAD, OCD, panic disorder	Risk of bleeding abnormalities with SSRIs; bleeding tendency may be increased if concurrently used with anticoagulants, or medications that affect platelet function (e.g. NSAIDs and aspirin).	Dose-dependent QTc prolongation (higher risk than other SSRIs).	✚ Lower treatment drop-out due to side effects, compared to other antidepressants ● Greater propensity for weight gain compared to other antidepressants
Fluoxetine	Bulimia nervosa, OCD, pre-menstrual dysphoric disorder		Strong inhibitor of CYP2D6.	✚ Lower treatment drop-out due to side effects, compared to other antidepressants ✚ Suitable for patients with poor medication adherence due to a long half-life ✚ Lower risk of discontinuation symptoms compared to other antidepressants ▬ Insomnia very commonly reported ▬ Greater difficulty in switching to another antidepressant due to long half-life ● Activating effect
Fluvoxamine	OCD		Strong inhibitor of CYP1A2, CYP2C19, and CYP3A4.	● Sedating effect
Paroxetine	Pre-menstrual dysphoric disorder, social anxiety disorder		Strong inhibitor of CYP2D6; contraindicated for concurrent use with CYP2D6 substrates that can prolong QT interval.	▬ Greater propensity for anticholinergic effects compared to other antidepressants ▬ Higher risk of discontinuation symptoms compared to other antidepressants ● Greater propensity for weight gain compared to other antidepressants ● Sedating effect
Sertraline	OCD, panic disorder, pre-menstrual dysphoric disorder, PTSD, social anxiety disorder	Risk of bleeding abnormalities with SSRIs; bleeding tendency may be increased if concurrently used with anticoagulants, or medications that affect platelet function (e.g. NSAIDs and aspirin).		✚ Dose adjustment not routinely required in renal insufficiency ▬ Insomnia very commonly reported ● Activating effect
Serotonin–norepinephrine reuptake inhibitor				
Desvenlafaxine	Nil	Risk of bleeding abnormalities with SNRIs; bleeding tendency may be increased if concurrently used with anticoagulants, or medications that affect platelet function (e.g. NSAIDs and aspirin).	May cause increased blood pressure (therefore may not be suitable for patients with uncontrolled hypertension).	▬ Insomnia very commonly reported ▬ Higher risk of discontinuation symptoms compared to other antidepressants
Venlafaxine	GAD, panic disorder, social anxiety disorder			
Duloxetine	Diabetic peripheral neuropathic pain, GAD, pain associated with fibromyalgia		May cause increased blood pressure and is contraindicated in patients with uncontrolled hypertension. Contraindicated if substantial alcohol use is present, if severe renal impairment (creatinine clearance <30 mL/min) is present, or if liver disease is present. Contraindicated for concurrent use with strong CYP1A2 inhibitors (such as ciprofloxacin and fluvoxamine).	▬ Higher risk of discontinuation symptoms compared to other antidepressants

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Second-generation antidepressant for treating MDD**	Other labelled indications††	Key precautions‡‡	Additional considerations ✚ 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.	✚ 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.	✚ 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			
Mirtazapine	Nil	May cause orthostatic hypotension.	✚ 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).	✚ 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).	✚ 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]