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DRUG REACTIONS AND INTERACTIONS

Cardiovascular side effects of non-SSRI antidepressants are of concern in high-risk patients

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Abstract
Depression is a major risk factor for negative health outcomes in patients with cardiovascular disease (CVD), and in high-risk populations such as the elderly. As selective serotonin reuptake inhibitors (SSRIs) have very few CVD risks, they are first line in the management of depression. However, alternatives are required in case of intolerance or lack of efficacy. Non-SSRI antidepressants such as serotonin and norepinephrine reuptake inhibitors and atypical monoaminergic antidepressants are options, but carry cardiovascular adverse effects (e.g. changes in blood pressure, heart rate or electrocardiogram parameters). While some studies are available to clarify these effects, further investigation is required in high-risk populations.

Depression is linked with negative cardiovascular health outcomes

Patients with cardiovascular disease (CVD) or other vulnerable patient populations (e.g. older or hospitalised patients) are at increased risk of depression [1]. For instance, the prevalence of depression in patients with coronary heart disease (CHD) is ≈3–4 times higher than in the general population. Depression is a major risk factor for negative health outcomes in these high-risk patients, contributing to increased cardiovascular (CV) morbidity and mortality [1, 2]. Depression, in the elderly in particular, is now a global public health concern, contributing to the burdens associated with an aging population due to its impact on comorbidities and quality of life [3].

Having second- and third-line antidepressant choices is necessary for proper management

Though psychotherapy has been proven to be very effective in managing depression, selective serotonin reuptake inhibitors (SSRIs) are the first-line pharmacological option when treating depression [1]. Efficacy and safety have been established in numerous randomized controlled trials (RCTs) and observational trials [1]. In patients with depression and CHD, SSRIs did not increase the incidence of CV adverse effects or CV events [1], and a meta-analysis found SSRIs improved depressive symptoms and did not impact the rate of CHD hospitalisations or mortality compared with control [4].

SSRIs may not be appropriate for certain patients due to intolerance or lack of response, and alternative pharmacological treatments may be warranted [1]. There is concern that other antidepressant classes may also result in CV adverse effects, therefore determining the efficacy and CV safety of antidepressants is challenging but crucial for vulnerable groups, such as older patients, hospitalised patients and patients with CVD [1]. For example, evidence suggests tricyclic antidepressants are associated with a higher CV risk than SSRIs [5], and may increase the risk of acute heart disease [2].

With high-risk patient populations such as the elderly, the challenges around managing comorbidities and (usually life-long) medications are made more difficult by a lack of robust literature surrounding antidepressant choice and tolerability profiles [3]. With particular focus on older adults, the mechanisms of action, recommended dosages and CV adverse effects of non-SSRI antidepressants (serotonin and norepinephrine reuptake inhibitors and atypical monoaminergic antidepressants) are summarized in Tables 1 and 2, as reviewed by Behlke et al. [1]. Elucidating the findings in this patient group may prove relevant for other high-risk populations.

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Table 1 Cardiovascular adverse effects of serotonin and norepinephrine reuptake inhibitors in older patients, as reviewed by Behlke et al. [1]

Antidepressant (dosage)	General comments	Summary of evidence of CV adverse effects
Venlafaxine (initially 37.5–75 mg/day, titrated based on response and tolerability)	↑ serotonin at low doses, ↑ norepinephrine at higher doses	Overall low risk of hypertension in older pts but may ↑ risk of orthostatic hypotension; further investigation required
	Once-daily dosing is advantageous for pt adherence	75–150 mg/day ER: significantly ↓ mean BP and HR [6]
		75–225 mg/day ER: no significant ↓ in BP and HR [7, 8]
	Does not affect the metabolism of many other drugs	≤ 300 mg/day venlafaxine: no significant changes from baseline in QTc interval [9]
	Wide dosage range means more input required to titrate to optimal dosage for pts	≤ 300 mg/day ER venlafaxine: significant ↓ in standing diastolic BP, orthostatic hypotension reported in 50% of pts and ↑ in mean HR by 3.5 bpm [10]
		No significant changes in mean BP vs citalopram [11] or incidence of hypertension vs fluoxetine or PL [12]
		↓ risk of heart failure in venlafaxine vs sertraline recipients with history of or new-onset CVD [13]
Desvenlafaxine (50 mg/day, can titrate to 100 mg/day)	Active metabolite of venlafaxine; not metabolised by CYP2D6	Lack of data in vulnerable pts; existing data insufficient to determine CV adverse event profile vs venlafaxine
	Possible ↓ risk of adverse effects related to CYP2D6 metabolism	100–200 mg/day: ↑ BP in 10% of pts, mean resting HR ↑ by 3.1 bpm [14]
Duloxetine (initially 30 mg, titrated to 60–120 mg/day according to response and tolerability)	Serotonin:norepinephrine reuptake inhibition at a relative ratio of 10:1	Overall minimal CV adverse effects but further investigation required in pts with CVD or depression; may be associated with orthostatic hypotension in older pts but does not seem to cause hypertension
	CYP2D6 and CYP2B6 inhibitor (especially at high doses)	80–120 mg/day: no significant changes in BP or ECG parameters, with exception of low standing systolic BP in 5% of pts [15]
		60 mg/day: significant ↓ in orthostatic BP (≈ 3 mmHg) vs PL, no changes in orthostatic hypotension or QTc interval [16]
		60–120 mg/day: no significant changes vs PL at 24 weeks, with exception of statistically significant ($p \leq 0.05$) but minor ↑ in resting HR and orthostatic diastolic BP at 24 weeks [17]
		↑ rate of adverse events vs PL; ↑ risk of falls in elderly [18]
		30–120 mg/day: no clinically significant differences vs PL [19]
		60 mg/day or 120 mg/day: significantly ↑ HR (by 2.75 bpm) vs PL in pts with diabetes mellitus and history of CVD receiving 120 mg/day duloxetine; otherwise well tolerated [20]
Milnacipran (typically 50 mg twice daily, up to maximum of 200 mg/day)	Approximately equal serotonin and norepinephrine reuptake inhibition	75–100 mg/day: more favourable CV risk profile compared with imipramine; ↓ risk of postural hypotension vs imipramine, minor ↓ in systolic BP and ↑ in HR [21]
		Lack of data in pts with CVD; further investigation required, particularly in high-risk populations (e.g. older or hospitalised pts)
Levomilnacipran (40–120 mg once daily)	Active enantiomer of milnacipran	Significantly ↑ systolic and diastolic BP and pulse in healthy adults; ↑ QTc interval statistically but not clinically significant) [22]
		Lack of data in pts with CVD; further investigation required, particularly in high-risk populations (e.g. older or hospitalised pts)

Unless otherwise specified, studies were conducted in pts aged ≥ 60 years. Mention of significance in this table denotes statistical significance

BP blood pressure, *bpm* beats per minute, *CV* cardiovascular, *CVD* CV disease, *CYP* cytochrome P450, *ECG* electrocardiogram, *ER* extended release, *HR* heart rate, *PL* placebo, *pt(s)* patient(s), ↑ increase(s/d), ↓ decrease(s/d)

Take extra care when starting an antidepressant

Antidepressant medications should only be used in patients with or at risk of CVD when absolutely necessary, such as when the diagnosis is clear for depression (major and minor), suicidal ideation or specific anxiety disorders [1]. Depressive symptoms or episodes alone are inadequate to qualify for antidepressants in patients already at high risk of adverse effects [1].

Recommendations to reduce risk of CV adverse effects when initiating an antidepressant, include [1]:

- Initiate at a low dose for 1–2 weeks and then up-titrate; take into consideration the potential for under dosing the patient.
- Avoid drug-drug interactions (particularly in older patients or patients with polypharmacy); consider pharmacokinetics and risk of interactions before initiating.

Table 2 Cardiovascular adverse effects of atypical monoaminergic antidepressants in older adults, as reviewed by Behlke et al. [1]

Antidepressant (dosage)	General comments	Summary of evidence of CV adverse effects
Mirtazapine (initially 7.5–15 mg once daily at night, titrated to 30–60 mg/day)	↑ serotonergic and noradrenergic signalling; centrally-acting α-2 antagonist, 5-HT_2 and 5-HT_3 receptor antagonist	15–45 mg/day: no significant differences from baseline and vs paroxetine [23] or vs PL [24]
		9.8–13.5 mg/day (mean dose): no significant changes from baseline in ECG parameters or CV events [25]
	Affects sleep and appetite and can lead to weight gain	Highest odds ratio for all-cause mortality amongst the antidepressants evaluated [26]
		Further investigation required in high-risk populations (e.g. older pts, hospitalised pts or pts with CVD)
Bupropion (initially 150 mg, titrated to 300–450 mg/day for depression)	↓ signalling through inhibition of dopamine and norepinephrine reuptake	350–600 mg/day: significant ↑ in mean supine BP and orthostatic BP (mean ↓ of 4 mmHg when standing); no HR or ECG changes [27]
	Not indicated for anxiety and is a strong CYP2D6 inhibitor	150–300 mg/day: no significant differences vs PL, was well tolerated [28]
	Causes wakefulness and ↓ appetite	Further data required for long-term CV effects of bupropion when used for depression in high-risk pts
	Higher doses can lead to neurotoxic adverse effects (e.g. seizures, falls)	
Vilazodone (initially 10 mg, titrated to ≤ 40 mg/day)	5-HT partial agonist and reuptake inhibitor, ↑ serotoninergic signalling	40 mg/day: no significant changes in BP, HR or ECG parameters [29]
	↑ incidence of nausea vs SSRIs	Lack of data in pts with CVD; further investigation required, particularly in high-risk populations
Vortioxetine (5–20 mg/day)	↑ serotoninergic signalling via action at both presynaptic and postsynaptic 5-HT receptors	5 mg/day: no significant changes in ECG parameters [30]
		Lack of data in pts with CVD; further investigation required, particularly in high-risk populations
Agomelatine (25–50 mg/day)	MT_1 and MT_2 receptor agonist, 5-HT_{2C} and 5-HT_{2B} antagonist; modulates circadian rhythm signalling, ↓ sleep disturbances	Appears to be safe and well tolerated in older pts and pts with CVD; however, further investigation will be helpful
		25 mg/day or 50 mg/day: significant ↓ in BP and HR; pts were coadministered cardiotropic drugs during the trial [31]
	No weight gain, sexual side effects or discontinuation syndrome typically seen with some other antidepressants	25 mg/day or 50 mg/day: no significant changes in BP, HR (and ECG parameters) vs PL [32] or from baseline [33]
Moclobemide (150 mg twice daily, up to 600 mg/day)	Reversible MAOI	400 mg/day: no differences in BP or ECG parameters vs PL, but dosage too low for antidepressant efficacy [34]
		400 mg/day: no differences in BP, HR or ECG parameters vs PL [35]
		Lack of data in pts with CVD, particularly in pts with hypertension at baseline
Ketamine (0.5 mg/kg)	Mechanism of action is unclear, possibly due to N-methyl-d-aspartate receptor antagonism	Transient ↑ (resolved mostly within 90 min) in BP and HR in 23 of 60 studies in a systematic review [36]
	Oral doses of ≈ 2.0–2.5 mg/kg may be required to obtain equivalence to IV ketamine; this may give rise to CV adverse effects not seen with a 0.5 mg/kg oral dose [38]	0.1–0.5 mg/kg subcutaneous injections: transient ↑ in BP [37]
		0.5 mg/kg IV infusions: ↑ BP following infusion, especially in hypertensive pts or pts aged ≥ 60 yrs [39]
		0.5 mg/kg (oral): no changes in BP and no CV events reported [40]
		Lack of data in pts with CVD and depression or evaluating long-term CV effects; further investigation is required
Esketamine	S-enantiomer of ketamine	Esketamine therapy may be associated with ↑ BP in older pts
	Administer under supervision of healthcare professional	28 mg, 56 mg or 84 mg (intranasal spray) twice weekly: transient ↑ in mean BP [41]
	FDA-approved nasal spray	Lack of data in pts with CVD and depression, no evaluation of long-term CV effects; further investigation is required
	Can cause sedation and dissociation	
	Contraindicated in pts with cerebral aneurysms, arteriovenous malformations or history of intracerebral haemorrhage	

Unless otherwise specified, studies were conducted in pts aged ≥ 60 years. Mention of significance in this table denotes statistical significance

5-HT 5-hydroxytryptamine, *BP* blood pressure, *CV* cardiovascular, *CVD* CV disease, CYP cytochrome P450, *ECG* electrocardiogram, *FDA* Food and Drug Administration, *HR* heart rate, *MAOI* monoamine oxidase inhibitor, *MT* melatonin, *pts* patients, *SSRIs* selective serotonin reuptake inhibitors, ↑ increase(s/d), ↓ reduce(s/d)

- Monitor blood pressure before and after initiating antidepressant treatment or when up-titrating; take particular care when administering drugs that can increase blood pressure (e.g. ketamine, esketamine) or cause orthostatic hypotension (e.g. venlafaxine, duloxetine).
- ECG monitoring not necessary before and/or after initiating antidepressant.

Further investigation is required, but may be difficult

Although RCTs are optimal in assessing the CV adverse effects of antidepressants [1, 5], those with higher CVD risk such as elderly patients or patients with comorbidities may often not be eligible for RCTs [1]. This under representation can limit the usefulness of these trials in determining the longer term impact of such drugs, particularly as trial follow-up can be quite short (e.g. due to ethical concerns regarding the administration of placebo in patients with depression) and the inherent variability of smaller sample sizes [1, 5]. Additionally, due to the nature of depression, it may be difficult to determine whether efficacy and safety results from a study can be attributed to antidepressant use or the indication itself (or a combination of both) [1]. Thus, critical evaluation of available evidence and further clinical trial data are key to antidepressant choice in patients with high CVD risk [1, 5].

Take home messages

- Treat depression in patients with or at high risk of CVD (e.g. older patients, hospitalised patients) to improve outcomes.
- Start SSRIs; however, if unable, consider CV adverse effects when choosing second- and third-line options.
- Serotonin and norepinephrine reuptake inhibitors and atypical monoaminergic antidepressants may be safe and effective alternatives in older patients; carefully monitor for adverse events and contraindications.
- Further clinical trial data will be helpful in confirming the CV safety of non-SSRI antidepressants in high-risk patient groups.

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