A GUIDE TO

deprescribing

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CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

LONG-ACTING NITRATES

KEY POINTS

Long-acting nitrates are effective in reducing the frequency of stable angina episodes and increasing tolerance to physical activity in those who experience stable angina.

Long-acting nitrates have no benefit on the incidence of acute coronary events when used in patients following acute myocardial infarction, but it is possible that their use may alter the nature of subsequent cardiovascular events.

Side effects from long-acting nitrates are relatively common and include headache, dizziness, orthostatic hypotension, rebound angina, dyspepsia, and peripheral oedema.

Physiological changes associated with aging, lifestyle modification, or treatment may reduce the underlying risk of angina and consideration of dose reduction or cessation is often appropriate in these situations.

Older people may be at higher risk of experiencing falls or prescribing cascades due to nitrate induced side effects and studies suggest deprescribing is often well tolerated and safe in this cohort.

CONTEXT

This guide considers the use of long-acting nitrates for the treatment of stable angina.

BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
Main Benefits Reduced angina symptoms	**Increased Benefit** • Severe or persistent angina • Other anti-anginal medications absent or inappropriate • Physically active (increased myocardial oxygen demand)	**Decreased Benefits** • Physical activity has reduced (reduced myocardial oxygen demand) • Coronary artery function has improved (e.g. revascularisation, long term statin therapy, smoking cessation or significant lifestyle change) • Angina due to coronary microvascular dysfunction
Main Harms Dizziness, Lightheadedness and Falls	**Reduced Harm** • Low baseline risk of falls (e.g. younger age, higher BP, preserved mobility)	**Increased Harms** • Orthostatic hypotension (drop in systolic blood pressure ≥ 20mmHg) • Frailty • Comorbid conditions or medication which increase the risk of falls

RECOMMENDED DEPRESCRIBING STRATEGY

Patients prescribed long-acting nitrates who have not experienced angina symptoms or required short acting nitrates for >3 months should be periodically reviewed, with consideration given to their ongoing need for the long-acting nitrate.

If side effects are present which outweigh benefit (e.g. headache, orthostatic hypotension, rebound angina, dyspepsia, peripheral oedema), dose reduction or cessation (if already on lowest dose) should be considered.

Certain factors may reduce the likelihood of angina recurrence. These include situations where myocardial oxygen demand is lower (e.g. frailty, immobility), where lifestyle changes have resulted in improved cardiovascular function (e.g. weight loss, smoking cessation, long term statin therapy), or where there has been intervention to improve epicardial perfusion (e.g. revascularisation). In these situations, dose reduction or cessation may be possible.

Tapering the dose prior to cessation is generally advisable in order to reduce the risk of discontinuation symptoms. Whilst many modified release tablets should not be broken, isosorbide mononitrate 60mg MR tablets are scored and can be halved to facilitate dose tapering.

An Algorithm for deprescribing of long-acting nitrates in the management of angina is shown in **Figure 1**.

BACKGROUND

The nitrates are a group of nitric oxide (NO) producing medications which have been in use for angina since 1876. The biological effects of NO are diverse and include vasodilation (predominately venodilation), impairment of platelet activation, and anti-inflammatory effects.[1] NO induced vasodilation is the main contributor to the therapeutic effectiveness of nitrates in angina, reducing preload and afterload on the heart, left ventricular (LV) wall tension, and subsequently myocardial oxygen demand. Blood flow in the coronary arteries is also improved.[1]

Nitrates are indicated for symptom management in both stable angina and acute coronary syndromes. There is a lack of data demonstrating significant benefit on cardiovascular outcomes. They may also be used in certain oesophageal conditions (eg. achalasia, distal oesophageal spasm) due to their relaxant effect on the lower oesophageal sphincter. Limited evidence suggests combination with hydralazine may be beneficial as add on therapy in certain heart failure patients. They may also be used topically for peripheral vascular disease, certain tendinopathies, and rectally for anal fissure.

Several nitrate preparations are available in Australia for the management of angina (see **Table 1**). Shorter-acting preparations with rapid onset of effect are used for on-demand treatment of stable angina or in the management of acute coronary syndromes. The longer-acting agents, which also have a slower onset of effect, are used for the long-term management of stable angina and are the focus of this guide.

While similarly effective in reducing incidence and intensity of angina when compared with other antianginals, long-acting nitrates have less robust data supporting their use, a comparably high rate of adverse effects, and are now considered second or even third line agents. Side effects of nitrates include headache, orthostatic hypotension, peripheral oedema, dyspepsia and rebound angina. These side effects, particularly hypotension, may be more pronounced in older people. The STOPP (Screening Tool of Older Person's potentially inappropriate Prescriptions) criteria, a set of recommendations aimed at minimising the use of potentially inappropriate medications in older persons, highlight long-acting nitrates as a group of medications implicated in falls in older people. They suggest review of long-acting nitrates if there is "persistent postural hypotension i.e. recurrent drop in systolic blood pressure ≥ 20mmHg (risk of syncope, falls)."[3]

Furthermore, due to changes associated with aging (e.g. reduced mobility, body weight, dietary intake), older people may have a reduced need for antianginal therapy. Consideration of deprescribing of long-acting nitrates is therefore often reasonable in this cohort.

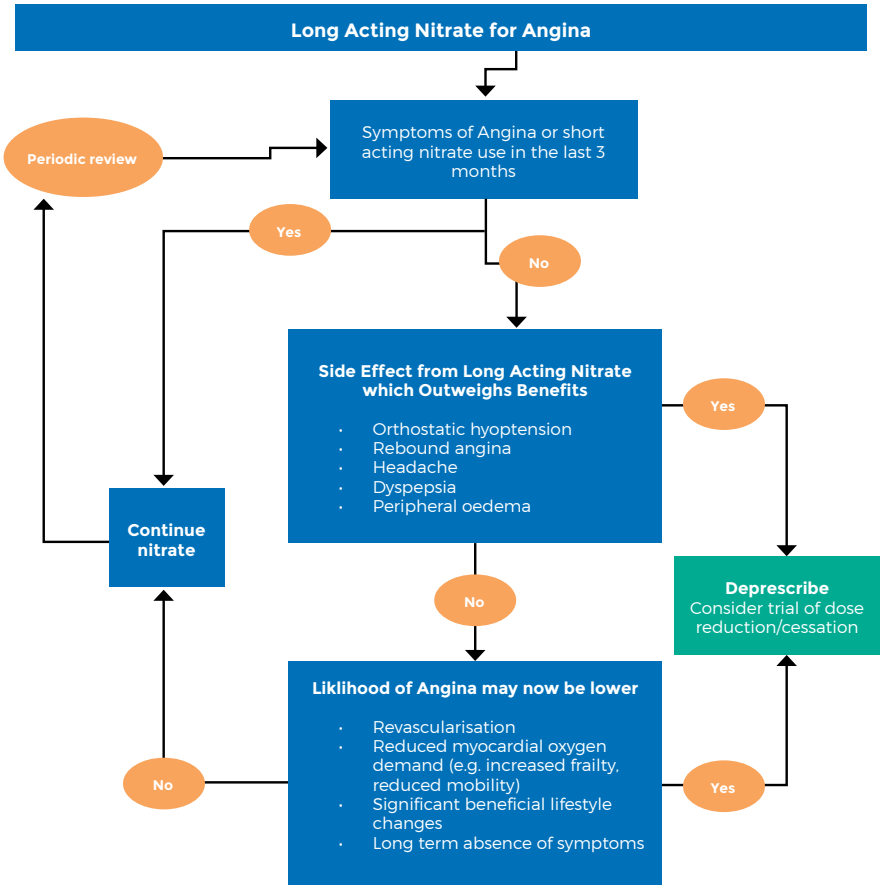

Figure 1: Algorithm for Deprescribing of Long Acting Nitrates for Angina

Nitrate Medication			Speed of onset	Length of effect
Glyceryl trinitrate	Sub-lingual spray	400 mcg/dose	< 5 min	Short
Isosorbide dinitrate	Sublingual tablet	5 mg	< 10 min	Short
Glyceryl trinitrate	Injection	1 mg/mL 5 mg/mL	< 10 min	As per infusion
Glyceryl trinitrate	Transdermal patch	5 mg/24hr 10 mg/24hr 15 mg/24hr	30-60 min	Long
Isosorbide mononitrate	Controlled release tablets	60 mg 120 mg	60-120 min	Long

Table 1: Properties of available nitrate preparations. Long-acting preparations in grey. Adapted from reference 2.

EFFICACY

STABLE ANGINA

Angina is a common condition estimated in 2019 to affect around 227,000 Australians.[4] It is thought that angina occurs as a result of a mismatch between myocardial oxygen supply and demand.[5,6] Several causative pathological processes have been identified including atherosclerosis, epicardial coronary spasm (vasospastic angina), and coronary microvascular dysfunction.[5,7,8]

A large number of studies support the effectiveness of nitrates for the management of acute angina, however, the majority of these are small in size and are of variable quality. A meta-analysis published in 2010 by Wei et al. found long term administration of nitrates reduced the number of angina episodes by 2.45 per week, lengthened exercise duration by 38 seconds, increased time to onset of angina (during exercise) by 52 seconds, and prolonged time to 1mm ST depression (during exercise) by 66 seconds.[9] While effective for symptom management, the most recent studies (conducted in the fibrinolytic era) suggest long-acting nitrates have no benefit on the incidence of acute coronary events when used in patients following acute myocardial infarction.[10,11]

Combination therapy with other antianginal agents is common due to the utility of such agents in comorbid conditions (eg. beta blockers in arrythmia and heart failure, and calcium channel blockers in hypertension). A meta-analysis conducted in 2014 by Belsey et al. estimated that the addition of a long-acting nitrate to either a beta blocker or calcium channel blocker improved total exercise duration by 3.9% and reduced angina frequency by 19% when compared to the beta blocker or calcium channel blocker alone.[12] This supports the widespread use of these combinations in practice. The combination of beta blocker and nitrate may be particularly useful given the attenuation of nitrate induced tachycardia by blockade of beta receptors.[13]

Efforts have been made to collate data comparing the effectiveness of long-acting nitrates to other antianginal agents, but this has proven challenging due to a paucity of high quality studies.[6,12,14,15]

Recent literature suggests non-obstructive causes of angina such as coronary microvascular dysfunction may be more common than previously thought, with over 50% of individuals undergoing diagnostic angiography having either unobstructed or minimally obstructed coronary arteries.[16] Nitrates have minimal dilatatory effects on arterial microvasculature and there is some evidence that nitrates may be less effective in the treatment of angina due to microvascular dysfunction.[16]

ISSUES ASSOCIATED WITH USE

TOLERANCE

One of the main limitations to the use of long-acting nitrates in angina is the development of tolerance; a loss of therapeutic effect associated with continual administration. The presence of this phenomenon has been known for decades and the use of oral or transdermal dosage regimens that ensure a nitrate-free period (e.g. once daily administration of tablets or 12-hour limits on transdermal preparations) has long been recommended as a way of managing this issue.[16] The meta-analysis by Wei et al. compared the effects of continual and intermittent regimens and found that when measured 1 - 6 hours post-dose, intermittent administration had a greater effect on exercise duration (by 43 seconds), prolonged time to 1mm ST depression (by 55 seconds), and increased time to onset of angina (by 41 seconds). Interestingly, they also found that in the intermittent administration group at 24 hours post-dose (just before the next dose) exercise duration was actually significantly shorter by 22 seconds than in the placebo group.[9] This deleterious effect on angina symptoms towards the end of the dosing interval with intermittent regimens has been referred to as the 'zero hour' effect and may limit the usefulness of long-acting nitrates in some people. The majority of the data demonstrating this effect involves the use of GTN patches.[9] A similar effect has not been demonstrated with oral nitrates such as isosorbide mononitrate.[17]

It has only been in the last few years that the mechanisms underlying the zero-hour effect and nitrate tolerance have started to be defined. It is thought that in addition to the haemodynamic effects (vasodilation, decreased pre-load etc.), long term nitrates have some negative impacts on the vasculature including increased sympathetic activation, oxidative stress, and endothelial dysfunction.[18] These changes increase arterial sensitivity to endogenous and exogenous vasoconstrictors and tolerance is now thought to occur as a result of the build-up of these vasoconstrictive effects in opposition to the therapeutic vasodilatory effects.[18]

Whether the vascular sensitivity induced by long-acting nitrates impacts on the safety of chronic nitrate therapy is yet to be studied in high quality trials, however, multiple observational studies and at least one prospective study have raised concerns that chronic nitrate use may be associated with an increased risk of cardiovascular events. [19-21] Somewhat counter to these data, another study published in 2009 examining data from the Global Registry of Acute Coronary Events (GRACE), found that nitrate users admitted to hospital for ACS were significantly more likely to be diagnosed with non ST-elevation ACS rather than a ST-elevation MI (STEMI) when compared with nitrate naïve patients (after adjustment OR 1.36; 95% CI 1.26-1.46). The authors suggested that the vascular stress induced by nitrate therapy may provide something of a protective 'preconditioning' effect which reduced the severity of the subsequent ACS.[22] The study also found nitrate use was associated with lower release of cardiac necrosis markers during ACS. Overall, these studies raise more questions than they answer, and the long-term cardiovascular safety of long-acting nitrates remains unclear.

SIDE EFFECTS

HEADACHE

Headache is the most common adverse effect associated with nitrate therapy, reported in up to 82% of people using GTN patches (vs 56% in placebo group) and 38-57% of people using isosorbide mononitrate (vs 15% in placebo group).[17] Tolerance to this effect usually develops within days and only 5-8% of people require cessation of therapy due to headache.[17]

DIZZINESS, LIGHT HEADEDNESS, AND FALLS

Dizziness and light-headedness may occur as a result of nitrate induced vasodilation and hypotension, though compensatory mechanisms (e.g. tachycardia) may help to mitigate drop in blood pressure. Studies suggest dizziness occurs in 26-30% of people using GTN patches (vs 23% in placebo group) and 8-11% of people using isosorbide mononitrate (vs 4% in placebo group).[17] When used in combination with other BP-lowering medications such as ACE inhibitors, the incidence of hypotension is increased.[23] Older people are also more likely to experience these adverse effects due to age associated vascular changes and a pharmacokinetic mediated increased sensitivity to nitrates.[24]

A 2018 meta-analysis examining the risk of falls associated with cardiac medications included five studies of people taking nitrates (n=1966). Despite a trend towards an increased risk of fall, statistical significance was not achieved.[25] Another study from 2018 (n=846) investigated whether certain antihypertensives were associated with an increased risk of orthostatic related syncope in people with dementia. While an increased relative risk similar to that of alpha blockers was identified with nitrates, after multivariate analysis this effect was not statistically significant.[26] While inconclusive, these studies were small and of variable quality, the trend towards an increased falls risk associated with nitrates should therefore not be ignored, particularly in those at highest risk of orthostatic hypotension and falls such as the very old, or in those with comorbid conditions/medications that contribute to falls risk.

REBOUND ANGINA

An increase in the incidence of angina during nitrate free periods (often night time and early morning) has been identified in around 10% of people using GTN patches in one particular trial.[27] This rebound phenomenon which usually occurs just prior to the next dose seems to be less likely or even absent with isosorbide mononitrate;[17,28] switching patients who experience this issue with GTN patches to isosorbide mononitrate may therefore be a reasonable strategy.

OTHER SIDE EFFECTS

Peripheral oedema is a common adverse effect of long-acting nitrate therapy.[2] Dyspepsia due to relaxation of the lower oesophageal sphincter is anecdotally quite common, though it is not well documented in the literature.

FACTORS TO CONSIDER

Long-acting nitrates are useful for symptom management only and do not benefit CV event rates. The decision to continue or discontinue is therefore limited to direct comparison of effect on angina symptoms (benefit), and presence or likelihood of adverse effects (risks).

IN FAVOUR OF DEPRESCRIBING

Most side effects of long-acting nitrates are mild and, in the case of headache, transient. In certain situations, however, side effects such as hypotension may pose significant risk and outweigh the benefit of continuing therapy. Mild peripheral oedema or dyspepsia as a result of nitrate therapy may result in prescribing cascades and favour review of the nitrate.

Certain physiological or behavioural changes, or medical procedures (e.g. revascularisation) may reduce the underlying risk of angina and facilitate dose reduction/cessation.

Commencement of other medications with anti-anginal effects may result in a reduced need for a pre-existing long-acting nitrate (e.g. CCB started for hypertension or a beta blocker for AF).

Patients with a history of milder anginal symptoms are more likely to tolerate reduction/cessation of nitrates.

AGAINST DEPRESCRIBING

Ongoing frequent or serious anginal episodes would generally favour continuation of nitrate therapy.

Recent CV events or a lack of appreciable physiological or behavioural changes since nitrate initiation would suggest cessation is less likely to be tolerated.

DISCONTINUATION SYNDROMES

There are historical case reports detailing a high incidence of cardiovascular events occurring over the weekend in munitions workers exposed to GTN throughout the work week. Coronary vasospasm was implicated and persisted in at least one of the cases for 4-5 days following GTN withdrawal. It was hypothesised that increased vascular sensitivity unopposed by the more transient vasodilatory effects was responsible for the increase in CV risk.[22=9]

These results have not been replicated in the modern era though questions have been raised regarding the cardiovascular safety of chronic nitrate therapy itself. Current guidelines pragmatically suggest withdrawal and cessation should be gradual in nature in order to avoid triggering any rebound effects.[13]

At least two small trials (n=80 and 22) support the safety of withdrawal, with no cardiovascular issues reported in either study following nitrate cessation. Candidates for deprescribing were selected due to clinical stability or reduced need for ongoing therapy (assessed by the authors). Reported successful cessation rates were 90% and 100% respectively.[30,31]

A randomised controlled trial published in 2013 demonstrated no clinically relevant changes in health-related quality of life following long-acting nitrate discontinuation in patients with stable angina (n=50). More specifically, measures of angina stability and angina frequency were unchanged in the cessation group.[32]

When considered together these studies suggest cessation is safe and frequently successful.

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AUTHORSHIP

This guide was prepared for Primary Health Tasmania by Stewart Mearns and reviewed by Dr David Dunbabin, Geriatrician, Angus Thompson, Pharmacist Clinical Editor, Primary Health Tasmania and the Deprescribing Project Advisory Group.

DEPRESCRIBING PROJECT ADVISORY GROUP

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