SHARED CARE GUIDELINE FOR THE USE OF NADOLOL IN LONG QT SYNDROME

INDICATION

Long QT syndromes are inherited conditions characterized by prolongation of a specific portion of the ECG. This predisposes to ventricular arrhythmia and sudden cardiac death and may present with syncope. Some medicines and conditions can cause acquired long QT syndrome.

Treatment includes lifestyle changes such as avoidance of QT-prolonging drugs and avoidance of strenuous exercise. Beta blockers are the pharmacological treatment of choice for patients who are asymptomatic with a QT interval >470ms and/or symptomatic for syncope or documented ventricular tachycardia / ventricular fibrillation. If beta blockers are not effective, not tolerated or contraindicated then left cardiac denervation surgery is recommended and for those patients surviving a cardiac arrest an implantable cardioverter defibrillator is recommended.

The apparent protective effect of non-cardioselective beta blockers far exceeds the efficacy observed with selective beta blockers. Non-cardioselective beta-blockers are relatively contraindicated in active asthma and COPD and should be used with caution. Long-acting beta-blockers, such as nadolol are advantageous as they can be given once or twice a day with avoidance of wide fluctuations in blood levels.

Nadolol is a little used non-cardioselective beta blocker and has been available for many years. Nadolol is licensed for the treatment of cardiac tachyarrhythmias and is recognized as an alternative to propranolol for patients that are not controlled on conventional therapies (note that propranolol MR and bisoprolol are not licensed for arrythmias). There is a strong experimental preference throughout the world towards the use of nadolol in LQTS and there is strong consensus among LQTS experts that nadolol is the preferred effective drug therapy in the condition.

Nadolol should be initiated by an appropriate cardiologist at the standard dose of 80mg daily with all dose titrations being carried out by the initiating cardiologist. Once stabilized on treatment the prescribing responsibility could be passed to the patient's GP.

AREAS OF RESPONSIBILITY FOR SHARED CARE

Patients should be at the centre of any shared care arrangements. Individual patient information and a record of their preferences should accompany shared care prescribing guidelines, where appropriate. Transfer of clinical responsibility to primary care should only be considered where the person's clinical condition is stable or predictable.

Referral to the GP should only take place once the GP has agreed to this in each individual case, and the hospital or specialist will continue to provide prescriptions until a successful transfer of responsibilities. The GP should confirm the agreement and acceptance of the shared care prescribing

arrangement and that supply arrangements have been finalised. The secondary/tertiary provider must supply an adequate amount of the medication to cover the transition period. The patient should then be informed to obtain further prescriptions from the GP.

When clinical responsibility for prescribing is transferred to general practice, it is important that the GP, or other primary care prescriber, is confident to prescribe the necessary medicines. Shared care agreements play a key role in enabling primary care prescribers to prescribe medicines with which they may not initially be familiar.

Clinical responsibility for prescribing is held by the person signing the prescription, who must also ensure adequate monitoring.

REFERRAL AND INITIATION

Shared Care is only appropriate if it provides the optimum solution for the patient. Patients will only be referred to the GP once the GP has agreed in each individual case.

Specialist Responsibilities	
1	To assess the patient and establish the diagnosis, determine a management strategy and ensure appropriate follow-up in conjunction with the GP.
2	The specialist will: • Initiate and stabilize treatment (including dose titration); • Obtain consent from the patient's GP to continue prescribing once treatment has been stabilized (usually after minimum of 4 weeks) • Monitor the patient and their therapy at six monthly intervals
3	To provide the GP with appropriate prescribing information and any additional information requested.
4	To be available for advice if the patient's condition changes.
5	To ensure that procedures are in place for the rapid re-referral of the patient by the GP.
6	To ensure the patient has given informed consent to their treatment.
7	To liaise with the GP on any suggested changes in prescribed therapy
8	To discontinue treatment if no longer thought to be beneficial after assessment at any point during treatment

General Practitioner Responsibilities	
1	Where appropriate to continue to prescribe nadolol as part of a shared care arrangement, usually at least 4 weeks after treatment has been initiated and the patient is stabilised
2	Deal with general health issues of the patient
3	Monitor concordance with therapy and raise concerns with the specialist team as appropriate
4	Review use of drugs likely to prolong the QT interval
5	To liaise with the specialist on any suggested changes in prescribed therapy

Patient's role (or that of carer)	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Attend appropriate appointments with the GP and specialist
3	Share any concerns in relation to treatment with nadolol with GP or specialist
4	Use written and other information provided with the medication
5	Seek help urgently if suspecting side-effects, or otherwise unwell

SUPPORTING INFORMATION

Dose, route of administration and duration of treatment

The recommended starting dose is 80mg daily; the dose can be increased if necessary up to 160 mg once daily, doses should be increased at weekly intervals; reduced to 40 mg daily if bradycardia occurs.

Adverse effects (incidence, identification, importance and management)

Common (>1 in 10)	Bradycardia (heart rate < 60 BPM); Heart rate < 40 BPM and or symptomatic bradycardia; cardiac failure; rhythm/conduction disturbances; symptoms of peripheral vascular insufficiency usually of the Raynaud type; hypotension; dizziness; fatigue
Uncommon (between 1 in 100 and 1 in 1,000)	Paraesthesias and sedation; headache and slurred speech; change in behaviour; nausea, diarrhoea, abdominal discomfort, constipation, vomiting, indigestion, bloating and flatulence; dry mouth; anorexia; cough and nasal stiffness; bronchospasm; rash, pruritus; dry skin; facial swelling and sweating; weight gain; impotence or decreased libido; dry eyes and blurred vision; tinnitus
Frequency not known	First degree and third-degree heart block (intensification of AV block is a known effect of beta-blockers); light-headedness; cold extremities insomnia hypoglycemia in neonates, infants, children, elderly patients, patients on haemodialysis, patients on concomitant anti-diabetic therapy, patients with prolonged fasting and patients with chronic liver disease has been reported reversible alopecia

Cautions and contra-indications

Cautions

- When discontinuing chronically administered nadolol, the dosage should be gradually reduced over a period of 1-2 weeks, and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, nadolol administration should be re-instituted promptly (at least temporarily), and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognised, it may be prudent not to discontinue nadolol therapy abruptly, even in patients under treatment for hypertension alone.
- Beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase the risks of general anaesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output.
- Patients with bronchospastic diseases should not, in general, receive beta-blockers since they may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta receptors. (Nadolol is contraindicated in asthma).
- Beta-adrenergic blockade may prevent the appearance of warning signs and symptoms (e.g. tachycardia and blood pressure changes) of acute hypoglycaemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycaemia; therefore, it may be necessary to adjust the dose of anti-diabetic drugs.
- There have been reports of skin rashes (including a psoriasiform type) and/or ocular changes (conjunctivitis and ‘dry eye’) associated with the use of beta-adrenergic blocking drugs.
- Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism (e.g. tachycardia). Abrupt withdrawal of nadolol in thyroid patients can precipitate thyroid storm.

- Occasionally, beta-blockade with drugs such as nadolol may produce hypotension and/or marked bradycardia, resulting in vertigo, syncope or orthostatic hypotension.
- Nadolol should be used with caution in patients with impaired renal or hepatic function

Contraindications

- Hypersensitivity to nadolol or excipients (refer to summary of product characteristics)
- Bronchial asthma, or history of asthma (beta-blockers, including those considered to be cardio-selective, should usually be avoided in patients with a history of asthma, bronchospasm or a history of obstructive airways disease)
- Sinus bradycardia
- Cardiogenic shock
- Right ventricular failure secondary to pulmonary hypotension
- Overt cardiac failure
- Second and third degree AV block

Monitoring requirements and responsibilities

Heart rate, blood pressure, signs/symptom of angina exacerbation when discontinued Renal function at baseline and during treatment

Clinically important drug interactions and their management

- **General anaesthetics** - Those which cause myocardial depression such as chloroform, cyclopropane, trichloroethylene and ether should be avoided as the patient may be subject to protracted severe hypotension
- **Myocardial depressants** such as lidocaine and procainamide may subject the patient to protracted severe hypotension.
- **Adrenoceptor Stimulants** - Beta-adrenoceptor stimulants such as isoprenaline and verapamil, or alpha-adrenoceptor stimulants such as noradrenaline and adrenaline, will reverse the hypotensive effects and increase vasoconstrictor activity.
- **Catecholamine Depleting Drugs** - Additive effects may occur with nadolol; monitor closely for evidence of hypotension and/or excessive bradycardia (e.g. vertigo, syncope, postural hypotension).
- A**ntihypertensives** (e.g. neurone-blocking drugs, vasodilators, diuretics) - Additive hypotensive effect.
- **Clonidine** - If nadolol and clonidine are given concurrently, clonidine should not be discontinued until several days after Corgard withdrawal.
- **Antidiabetic drugs** (oral agents and insulin) - Hypoglycaemia or hyperglycaemia; adjust dosage of anti-diabetic drug accordingly
- **Monoamine oxidase inhibitors** (MAOIs) - Isolated cases of bradycardia have occurred during concurrent use of beta blockers and MAOIs.
- **Antimuscarinic agents** - May counteract the bradycardia caused by beta blockers.
- **Calcium-channel blockers** generally potentiate the pharmacologic effects of beta-blockers. Patients taking both agents should be carefully monitored for adverse cardiovascular events.
- **Antimuscarinic agents** – may counteract the bradycardia caused by beta blockers.

- **Diltiazem** – an increased risk of depression has been reported when beta-blockers are co-administered with diltiazem.
- **Other antiarrhythmic agents** - Additive or antagonistic effects may occur with nadolol.
- **Lidocaine, IV** - Significant reduction of lidocaine clearance can occur when a beta blocker is administered concurrently.
- **Non-steroidal anti-inflammatory agents** (NSAIDs) - The antihypertensive effects of beta blockers may be reduced during concurrent administration of indometacin and possibly other NSAIDs.
- **Phenothiazines and other antipsychotic agents** - Additive antihypertensive effects have occurred with other beta blockers when they were given concurrently with phenothiazines or haloperidol.
- **Vasoconstrictor agents** - Effects with nadolol can be additive (e.g. with ergot alkaloids).

Peer-reviewed references for product usage

Summary of product characteristics for Nadolol (Corgard®) tablets available at https://www.medicines.org.uk/emc/product/2224/smpc

Joint Formulary Committee. British National Formulary (online). London: BMJ Group and Pharmaceutical Press; Electronic edition. Accessed on 20/04/2021 via www.medicinescomplete.com/

Beta-blocker therapy for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia: Are all beta-blockers equivalent? Ackerman et al (2016) http://dx.doi.org/10.1016/j.hrthm.2016.09.012

Refer to page 10 of NHS England's guidance on Responsibility for prescribing between Primary & Secondary/Tertiary Care for more information/guidance about taking on prescribing of specialist medicines.

This list is not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Drug costs

	Pack size	Cost
Nadolol 80mg tablets	**28**	**£5.00**

Prices correct as per April 2021 Drug Tariff online.

Written By	Faye Thornton, RBH Cardiology Pharmacist on behalf of the cardiology working group	August 2018
Approved By	Dorset Medicines Advisory Group	January 2019
Reviewed by	Cardiology working group	April 2021
Approved by	Dorset Medicines Advisory Group	July 2021
Date of next review	July 2023 or before, in light of new evidence or information.	