A Review of Nadolol for the Treatment of Patients with Congenital Long-QT Syndrome

Medicines Management Programme

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1. Purpose

The purpose of this review is to consider the available evidence on the use of the beta blocker nadolol, for the treatment of congenital long-QT syndrome (LQTS). It is suggested that nadolol is the medication of choice to treat this condition. However it is unlicensed in Ireland and has a very high reimbursement cost in comparison to other licensed beta blockers.[1,2] This review aims to assess if nadolol is the most appropriate choice to treat congenital LQTS, or if there are any other equally effective treatments, which could be recommended as an alternative.

2. Nadolol

Nadolol is indicated for the treatment of arrhythmias, angina, hypertension, migraine and thyrotoxicosis.[3] The dose for cardiac tachyarrhythmia is initially 40mg daily, increased as necessary up to 160 mg daily, although the dose can be reduced to 40mg daily if bradycardia occurs. Elderly patients should be initiated on a low dose and patients with impaired renal or hepatic function should be monitored during treatment.[3]

2.1 Pharmacodynamics and pharmacokinetics of nadolol: Nadolol is a beta-adrenergic receptor blocking agent, with a prolonged duration of action. It is a non-cardioselective beta blocker with no membrane stabilising or intrinsic sympathomimetic activity. Nadolol exerts an antiarrhythmic action by slowing conduction through the AV node, thus reducing the rapid ventricular response that accompanies atrial fibrillation. It can also be used in angina to block the response to catecholamine stimulation, thereby lowering the oxygen requirements of the heart during effort.[3] Oral bioavailability of nadolol is 30%. It is unaffected by food in the gastrointestinal tract. Peak serum concentration occurs after 3-4 hours and 30% is reversibly bound to plasma protein. Nadolol has a half-life of 20-24 hours, it is not metabolised and is excreted principally unchanged by the kidneys.[3]

2.2 Cautions and contraindications of nadolol: Nadolol has contraindications in common with other beta blockers including asthma, cardiogenic shock, hypotension, bradycardia, Prinzmetals angina, second or third degree AV block, metabolic acidosis, phaeochromocytoma, severe peripheral arterial disease, sick sinus syndrome and uncontrolled heart failure.[4] Nadolol should also be used with caution in diabetes, first degree AV block, obstructive airways disease, myasthenia gravis, portal hypertension and psoriasis.[4]

2.3 Adverse-effects of nadolol: The most common adverse effects of nadolol are bradycardia, cardiac failure, rhythm or conduction disturbance, peripheral vascular disease, hypotension, dizziness, fatigue, sleep disturbance, headache, sexual dysfunction and masking the symptoms of hypoglycaemia.[4]

2.4 Interactions with nadolol: Significant interactions may occur when beta blockers are taken with adrenaline, alpha blockers, amiodarone, anti-arrhythmics, clonidine, diltiazem, dobutamine, nifedipine and verapamil (this list is not exhaustive, a full list of drug interactions for nadolol can be found in the British National Formulary).[4]

3. Background: long-QT syndrome

LQTS is an electrical disorder of the heart characterised by prolonged ventricular repolarisation (QT interval), and the occurrence of life threatening cardiac arrhythmias such as torsades de pointes, which may result in sudden death.[5] LQTS can be categorised into two distinct forms: congenital or acquired. There are many different causes of acquired LQTS, including; myocardial ischaemia, cardiomyopathies, hypokalaemia, hypocalcaemia, hypomagnesaemia and drug-induced.[6]

Drug-induced prolongation of the QT interval is often directly related to the dose and plasma concentration of the drug. There may be an additive effect when two drugs that prolong the QT interval are used together.[7] Pharmacokinetic and pharmacodynamic interactions can also cause QT prolongation.[7] There are many classes of drugs which can cause prolongation of the QT interval. Examples include anti-arrhythmics, macrolide antibiotics, antimotility and antiemetic agents, antifungals, antimalarials, antidepressants and antipsychotics.[7*] This review will focus on congenital LQTS.

Congenital LQTS is caused by genetic mutations which affect the ion channels in the cardiac cell membrane. QT prolongation is caused by either a decrease in repolarizing potassium currents or an inappropriate late entry of sodium into the cardiac muscle cells.[6] Thirteen types of congenital LQTS have been identified to date. The first three genotypes discovered (LQT1 to LQT3) remain the most common, accounting for over 90% of all genetically proven cases of congenital LQTS.[8]

These three genotypes are affected by different stimuli, which may trigger cardiac events. In LQT1 patients the majority of cardiac events occur during exercise, such as swimming, whereas in LQT3 patients the majority of cardiac events occur during resting or sleep. In LQT2 patients, emotional stress such as may be caused by auditory stimuli, is the main trigger.[9] The three genotypes also show different rates of cardiac arrest and sudden death in the symptomatic cohorts of patients, increasing from 28% of symptomatic patients with the LTQ1 genotype to 40% with the LTQ2 genotype and 49% with the LTQ3 genotype.[9]

* A comprehensive list of drugs which prolong the QT interval can be found in Stockley's Drug Interactions 11th Edition, 2016.

4. Prevalence of congenital LQTS

The prevalence of congenital LQTS amongst Caucasians has been estimated to be 1:2000 live births.[10] The number of patients with congenital LQTS in Ireland is estimated to be between 400 and 1000 patients but may increase to 2000 with cascade screening.

5. Treatment of congenital LQTS

First-line medication in the treatment of congenital LQTS are beta blockers, assuming there are no other contraindications.[5] If the patient remains symptomatic they may require a surgical left cardiac sympathetic nerve denervation (LCSD), if arrhythmias are still occurring despite this an implantable cardioverter defibrillator (ICD) should be considered.[5]

Identification of the genetic mutations causing congenital LQTS has led to an interest in the use of gene specific therapies. Examples of such therapies include oral mexiletine[11], flecainide[12] and ranolazine.[13] These treatments could be used in high risk LQTS patients, who are not responding to beta blockers or who have recurrent events after LCSD and ICD therapies.[8] The LQT3 genotype is associated with sustained inward sodium current during membrane depolarization, these drugs are thought to be beneficial by reducing the late sodium channel current, thus shortening the QT interval.[13] However, as these treatments have limited follow-up experience and are currently unlicensed in Ireland for the treatment of QT syndrome, they cannot be recommended at this time.[8]

5.1 Beta blockers

There are four beta blockers licensed in Ireland for the treatment of cardiac arrhythmias. These are atenolol, metoprolol, propranolol and sotalol.[14-17] As sotalol is contraindicated in the treatment of congenital long QT syndrome and torsades de pointes, it will not be considered in this review. The remaining three beta blockers atenolol, metoprolol and propranolol could potentially be used as alternatives to nadolol in the treatment of congenital LQTS (table 1).[14-16]

Table 1: Beta blockers used in the treatment of cardiac arrhythmias [3, 14-16]

Drug	Cardiovascular Indications	Maintenance dose for arrhythmia	Frequency	Paediatric use
Nadolol	Arrhythmia, angina, HTN	40-160mg	once daily	safety and efficacy not established
Propranolol	Arrhythmia, angina, HTN, post MI	10-40mg	three to four times daily	0.25mg-0.35mg/kg three to four times daily. max 1mg/kg four times daily (total dose not to exceed 160mg daily)
Atenolol	Arrhythmia, angina, HTN	50-100mg	once daily	not recommended
Metoprolol	Arrhythmia, angina, HTN, post MI	50mg	two to three times daily	not recommended

MI: myocardial infarction; HTN: hypertension

The dose and frequency required to treat arrhythmias varies depending on the beta blocker. Nadolol and atenolol have longer durations of action and therefore only require once daily administration. Once daily dosing is considered advantageous when selecting a drug, as it aids compliance.[18] This is of particular importance in patients with congenital LQTS to prevent the occurrence of life threatening events, such as sudden cardiac death. Evidence has shown that LQT1 patients who administer their beta blocker as prescribed and avoid drugs which prolong the QT interval have an extremely low risk of life-threatening events.[19]

The only beta blocker licensed for use in paediatric arrhythmias is propranolol. Due to the inherited nature of congenital LQTS many patients may commence treatment with beta blockers during childhood. The mean age for the disease to manifest itself is 12 years old.[20] This may be an important factor when choosing a beta blocker for initial treatment.

5.1.1 Beta blockers mechanism of action

Beta blockers have different pharmacokinetic properties. In terms of cardioselectivity, atenolol and metoprolol are cardioselective, whereas propranolol and nadolol are non-cardioselective.[4] Atenolol and nadolol are hydrophilic, whereas propranolol and metoprolol are lipophilic.[4] Hydrophilic beta blockers are less likely to cross the blood brain barrier and are associated with less CNS effects such as sleep disturbance and nightmares.[4] Lipophilic drugs are rapidly absorbed from the gastrointestinal tract and have low oral bioavailability (10-30%), due to high first pass metabolism.[21] Lipophilic drugs can cross the blood brain barrier and may be associated with CNS side effects.[21]

Propranolol has been the most extensively used beta blocker in the treatment of congenital LQTS to date, it has the advantage of good tolerability, however multiple daily dosing due to its rapid metabolism may cause

problems with compliance.[22] A long-acting sustained release version of propranolol is available but it is not licensed for the treatment of cardiac arrhythmias in Ireland. However long-acting propranolol is recommended for the treatment of LQTS in some International Guidelines (table 4).

6. Efficacy data

The main clinical studies and reviews on congenital LQTS are listed (table 2 and 3). Due to the nature of congenital LQTS as an inherited disease, it is not possible to perform randomised controlled trials. Therefore trials are limited to observational studies, often using retrospective analysis from available cohorts, such as data from registries.[23] Care must be taken in generalising about preferred therapies for congenital LQTS, as it represents multiple syndromes with unique characteristics.[24]

Table 2: Clinical studies in congenital long QT syndrome

Study	Year	Beta blockers	Conclusions
Efficacy of different beta blockers in the treatment of long QT syndrome [23] n=1,530	2014	atenolol propranolol metoprolol nadolol	Primary endpoint was the occurrence of first cardiac event from beta blocker initiation. In LQT1 patients risk reduction was 57% for any beta blocker (p<0.01). There was no difference in efficacy between beta blockers. In LQT2 patients nadolol was significantly better at reducing the risk of cardiac events, compared to other beta blockers (hazard ratio 0.4, p<0.05). In high risk patients, who had a prior cardiac event while taking beta blockers, recurrent cardiac events occurred more frequently in propranolol (48%) than atenolol (33%), nadolol (31%) and metoprolol (27%).
Not all beta blockers are equal in management of long QT syndrome types 1 and 2 [22] n=382	2013	propranolol metoprolol nadolol	The occurrence of breakthrough cardiac events (BCEs) was 29% for patients on metoprolol, 8% for propranolol and 7% for nadolol. Cumulative event free survival was significantly better (p=0.02) for nadolol/propranolol patients (91%) than metoprolol patients (60%). Propranolol had significantly better QTc-shortening effect, particularly in patients with prolonged-QT, compared to metoprolol and nadolol (p=0.01).
Beta blocker efficacy in high-risk patients with the congenital long-QT syndrome types 1 and 2 [25] n=971	2010	atenolol propranolol metoprolol nadolol	Beta blockers should be administered first line to all high risk LQT1 and LQT2 patients. There was a similar risk reduction of cardiac events with beta blockers in LQT1 and LQT2 patients (p<0.001). In LQT1 patients atenolol had the most significant reduction in risk of cardiac events 77% (p=0.008), nadolol did not have a significant risk reduction (p=0.09). In contrast in LQT2 patients nadolol had an 87% reduction in the risk of cardiac events (p<0.001), atenolol had no statistical benefit in this group.
High efficacy of beta blockers in long QT syndrome type 1 [19] n=216	2009	atenolol propranolol metoprolol nadolol	LQT1 patients had a significant reduction in cardiac events after beta blocker initiation (p<0.001). 75% of patients were asymptomatic after treatment. Beta blocker patients who are compliant and not taking QT prolonging drugs have a significantly reduced risk of cardiac arrest and sudden death, than non-compliant patients on QT-prolonging drugs. Reduced from 27.5 % to 0.6% (p<0.001).
Beta blocker therapy failures in symptomatic probands with genotyped long QT syndrome [26] n=28	2004	atenolol propranolol metoprolol nadolol	25% of genotyped LQTS patients experienced a breakthrough cardiac event on beta blocker treatment. 33% of LQT1 patients had a BCE compared to 14% LQT2 patients. Significantly more BCEs occurred in patients taking atenolol, than propranolol (p=0.03). Limitations due to small study size.
Association of long QT syndrome loci and cardiac events among patients treated with beta blockers [27] n=335	2004	beta blocker, drug not specified	Primary endpoint was cardiac events while patients received beta blocker therapy. Cardiac events occurred in 10% LQT1 patients, 23% LQT2 patients and 32% LQT3 patients (p<0.001) while on beta blocker therapy.
Effectiveness and limitations of beta blocker therapy in congenital LQTS [28] n=869	2000	atenolol propranolol metoprolol nadolol	There was a significant reduction in cardiac events in LQTS patients after initiation with beta blockers (p<0.001). 32% of patients with cardiac symptoms before beta blockers will have another cardiac event within 5 years while on beta blockers.

Table 3: Reviews of congenital long QT syndrome

Review	Year	Conclusions
The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy[29]	2013	Not all beta blockers are equally effective. Propranolol and nadolol produce the least LQTS recurrences. Propranolol is the most widely used, especially in infants and children. Metoprolol cannot be recommended in symptomatic patients due to the high risk of recurrences. Atenolol is less effective but evidence is limited.
Pharmacological and non-pharmacological management of the congenital long QT syndrome: the rationale[5]	2011	Beta blockers are first line therapy in congenital LQTS unless contraindicated. Propranolol and nadolol are the most effective treatments. If the patient has an episode of syncope while taking a beta blocker LCSD should be performed and an ICD implant considered.
Long QT syndrome[6]	2008	Beta blockers are first line prophylactic therapy for all intermediate or high risk individuals and considered on an individual basis for low risk patients. Patients who remain symptomatic on beta blockers should be considered for more invasive therapies.

6.1 Evidence for the use of beta blockers in congenital LQTS

Abu-Zeitone et al. (2014) found a significant (57%, $p<0.01$) risk reduction for first cardiac events while taking beta blockers and Vincent et al. (2009) provided evidence of beta blocker efficacy in LQTS1 patients, finding 75% of patients were asymptomatic following beta blocker treatment, with a significant reduction of cardiac events ($p<0.001$).[23,19] Goldenberg et al. (2010) also studied beta blocker efficacy in high risk LQTS1 and LQTS2 patients and found significant reductions in the risk of cardiac events of 54% and 64% respectively.[25]

Moss et al. (2000) also demonstrated that initiation of beta blockers significantly reduced the risk of cardiac events in LQTS patients, however 32% of patients who experienced a cardiac event before treatment were found to experience another event within 5 years, while taking beta blockers.[28] The suggestion that beta blockers may not provide adequate protection for all patients was also investigated by Priori et al. (2004), who found that cardiac events occurred in 10% of LQT1 patients, 23% of LQT2 patients and 32% of LQT3 patients whilst on beta blocker therapy.[27] In a review of LQTS, Schwartz and Ackerman (2013) observed that beta blockers were extremely effective in LQTS1 patients and beta blocker failures were almost exclusively due to non-compliance, or drugs that prolong the QT interval.[29] The review also stated that not all beta blockers are equally effective.[29]

6.2 Selecting a beta blocker

Propranolol and nadolol were found to be similarly effective in a study by Chockalingam et al. (2013) which compared the efficacy of beta blockers in the management of congenital LQTS.[22] The incidence of breakthrough cardiac events in patients who were initiated on propranolol was 8% and nadolol 7%.[22] The 10 year cumulative event free survival for patients taking propranolol or nadolol was 91%, compared to 60% for metoprolol.[22] The effectiveness of propranolol and nadolol in the treatment of symptomatic LQTS was also

stated in reviews into congenital LQTS management by Schwartz (2011) and Schwartz and Ackerman (2013).[5,29]

Nadolol was found to significantly reduce the risk of cardiac events in LQT2 patients (p=0.01), but not LQT1 patients, in a study by Goldenberg et al. (2010).[25] Further evidence of this finding was provided by Abu-Zeitone et al. (2014) which demonstrated that nadolol was the only beta blocker that provided a significant risk reduction of first cardiac events (p=0.04) in LQT2 patients.[23] However all four beta blockers included in the study reduced the risk of first cardiac events by a similar amount in LQT1 patients.[23]

Atenolol has demonstrated less favourable results, although the study by Goldenberg et al. (2010) found it was associated with a 77% reduction in the risk of cardiac events in LQT1 patients, there was no statistical reduction in cardiac events seen in LQTS 2 patients.[25] In contrast Chatrath et al. (2004) found that there were significantly more beta blocker failures (p=0.03) in patients taking atenolol, than propranolol, although the small cohort was a major limitation of this study.[26] The transatlantic review carried out by Schwartz and Ackerman (2013) also stated that atenolol may be a less effective treatment choice, but that data was limited.[29]

Metoprolol is not recommended in patients with congenital LQTS after Chockalingam et al. (2013) found that patients taking metoprolol were four times more likely to experience a baseline cardiac event than patients taking propranolol or nadolol (p=0.02).[22] Goldberg et al. (2010) also found metoprolol did not significantly reduce cardiac events in LQT1 and LQT2 patients, and was the least effective beta blocker when compared to propranolol, nadolol and atenolol.[25] Schwartz and Ackerman (2013) concluded that due to the higher risk of recurrence of cardiac events metoprolol could not be recommended to treat symptomatic patients.[29]

The efficacy of propranolol in the treatment of LQTS has recently been disputed in the study by Abu-Zeitone et al. (2014). This study found that in high risk patients, who had a prior cardiac event while on beta blockers, propranolol was the least effective drug at preventing recurrence of cardiac events.[23] There was found to be a 48% cumulative probability of a cardiac event within 2 years in propranolol patients.[23] One theory is that propranolol may not be as effective in this high risk group. Propranolol was still found to be equally effective to other beta blockers in LQTS1 patients.[23] This study differs from the results for propranolol in the Chockalingam et al. (2013) study.[22] The Abu Zeitone et al. (2014) study contained four times the number of patients with LQTS compared to Chockalingam et al. (2013). Also there were differences in how the symptomatic group was defined between trials. Leading cardiologists have advised caution before attempting to change patients from propranolol as both trials had limitations such as lack of

randomisation and reliability of data.[30] LQTS speciality centres throughout the world have arrived at an experiential preference for nadolol or propranolol to treat LQTS patients.[30] Further analysis will have to be carried out before a decision can be made to change treatment protocols.[30]

7. International Guidelines

There are no national clinical guidelines in Ireland or the UK on the treatment of congenital LQTS or the management of patients with inherited arrhythmias at risk of sudden death. Instead, international guidelines are used to guide the management of these patients (table 4).

Table 4: International treatment guidelines and expert consensus

Review Body	Guideline	Year	Recommendations
European Society of Cardiology (ESC)[31]	ESC Guidelines on the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death	2015	See combined AHA/ACC/ESC guidelines- no change in beta blocker advice since 2006
American Heart Association/ American College of Cardiology/ European Society of Cardiology (AHA/ACC/ESC)[20]	Guideline for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death	2006	**Beta blockers are recommended:** in patients with a clinical diagnosis of LQTS and for use with LQTS patients with an implantable ICD in patients with a previous cardiac arrest and expectation of survival greater than 1 year **Beta blockers can be effective:** in reducing sudden cardiac death in patients with a LQTS mutation and a normal QT interval **High risk LQT2 and LQT3** patients may be considered for implantation of an ICD and beta blockers to prevent sudden cardiac death
The Cardiac Society of Australia and New Zealand (CSANZ)[32]	Guidelines on the diagnosis and management of familial long QT syndrome	2011	Initiate beta blockers in patients who have had symptoms or a diagnosed long QT interval, in particular pre-adolescent boys, including infants. Long-acting agents are preferred to aid compliance e.g. nadolol or slow release propranolol
Heart Rhythm Society, European Heart Rhythm Association and the Asia Pacific Heart Rhythm Society (HRS/ EHRA/ APHRS)[8]	Expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes	2013	**Beta blockers are recommended:** in LQTS patients who are asymptomatic with QTc ≥470 ms and /or symptomatic for syncope or documented ventricular tachycardia/ventricular fibrillation (VT/VF) **Beta blockers can be useful:** in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤ 470 ms There is no evidence to favour cardioselective or non-cardioselective beta blockers (unless the patient is asthmatic) Long-acting beta-blockers such as nadolol or sustained release propranolol are preferred. Studies do not define the most effective dose, full dose for age and weight should be given if tolerated

In 2006 the European Society of Cardiology (ESC) produced guidelines in collaboration with the American College of Cardiology and the American Heart Association (ACC/AHA) on the management of patients with

ventricular arrhythmias and the prevention of sudden cardiac death.[20] In 2015 the ESC produced its own updated version of these guidelines, with no changes to the recommendations concerning treatment of congenital LQTS.[31] These guidelines recommend beta blockers in the treatment of clinically diagnosed LQTS patients and in LQTS patients with an ICD who have previously experienced a cardiac arrest. These guidelines also consider beta blockers to be a useful treatment option in patients who have been diagnosed with LQTS from genetic testing, but have a normal QT interval.[20,31]

The Cardiac Society of Australia and New Zealand (CSANZ) guidelines state that long acting formulations of beta blocker are preferred, such as nadolol or sustained release propranolol.[32] This advice is repeated in a consensus statement produced by the heart rhythm societies of Europe, Asia and America.[8] In addition, the consensus statement also recommends using the full dose of beta blocker that can be tolerated and states there is no evidence favouring cardioselective beta blockers, unless the patient is asthmatic.[8]

8. Cost

The reimbursement cost of each beta blocker which can be used to treat congenital LQTS was calculated, using data from the Primary Care Reimbursement Service (PCRS), based on a patient taking the required maintenance dose for one month (table 5).[1,2]

Table 5: Monthly reimbursement cost per patient

Drug	Cost per patient per month*
Nadolol‡	€1,348
Propranolol	€6.24
Metoprolol	€4.87
Atenolol	€2.99

*Costs calculated using the maximum maintenance dose per drug for a 30 day supply. Where there was a choice of brands the product with the cheapest reimbursement price was selected. Costs are correct as of December 2016.
‡Nadolol is an unlicensed medication and may be subject to greater price variations than licensed products.

There is a marked cost differential between nadolol and other beta blockers that may be used to treat congenital LQTS. A supply of nadolol for one patient is €1,348 per month, which is significantly more expensive than any other beta blocker available for the treatment of arrhythmia. Atenolol has the lowest reimbursement cost of €2.99 per month.

9. Budget Impact

The choice of beta blocker to treat congenital LQTS will have a significant impact on drug expenditure for this condition (table 6). Nadolol has a very high budget impact in comparison to any other beta blocker used to treat LQTS. If 1000 patients per year with LQTS were treated with nadolol the reimbursement cost would be over €16 million per year, compared to €74,880 for propranolol. Atenolol has the lowest reimbursement cost of €35,880 per 1000 patients per year.

Table 6: Budget impact of beta blockers to treat congenital LQTS in Ireland*

Patients	Nadolol (€)	Propranolol (€)	Metoprolol (€)	Atenolol (€)
250 patients/year	4,042,800	18,720	14,610	8,970
500 patients/year	8,085,600	37,440	29,220	17,940
700 patients/year	11,319,840	52,416	40,908	25,116
1000 patients/year	16,171,200	74,880	58,440	35,880

*Costs are correct as of December 2016 [1,2]

10. Summary

Clinical efficacy data has demonstrated the effectiveness of beta blockers in reducing the risk of cardiac events in patients with congenital LQTS.[19,23,25,28,29] International clinical guidelines recommend beta blockers as first choice in the treatment of congenital LQTS.[31,20,32] Some patients may still experience breakthrough cardiac events while taking beta blockers, these patients should be treated with more invasive therapies such as LCSD or ICD.[5,6] Beta blockers are not equally effective in treating congenital LQTS.[29,23,22,25] Metoprolol is not recommended and atenolol has conflicting evidence of efficacy which requires further research.[22,25,26] Propranolol and nadolol are the preferred choices of beta blocker to treat congenital LQTS.[5,29,8,22,32] Nadolol has the advantages of once daily dosing, which improves compliance and hydrophilicity, which may reduce CNS side effects.[3,18] Disadvantages are that it is unlicensed in Ireland, it has an extremely high reimbursement cost and there is not enough evidence to conclude definitively the role of nadolol for the treatment of LQTS in children specifically.[2,3] Propranolol has a much lower reimbursement cost, good tolerability, it is licensed for use in children, and its lipophilicity means it can cross the blood brain barrier (although this may cause more CNS side effects).[22] The main disadvantage is that it requires multiple daily dosing, as the sustained release formulation is not licensed for arrhythmia in Ireland.[16] Recent evidence has disputed the benefits of propranolol in the treatment of high risk LQTS patients, although this study had limitations and propranolol is still being used in LQTS treatment centres globally.[23,30] Nadolol may be a more appropriate choice in this high risk group.

11. Conclusions

- Propranolol appears a reasonable therapeutic option for the treatment of congenital LQT syndrome. However the available evidence suggests that nadolol may be a more appropriate therapy for patients with LQT2.

- To aid the decision making process in this therapeutic area a strategy for the genotyping of patients with congenital LQT syndrome should be considered.

- Approximately one third of the 800-1000 patients with prolonged QT syndrome will have LQT2, which could result in a budget impact exceeding €4 million per annum should nadolol be used in such patients.

- The HSE Medicines Management Programme recommends propranolol for the treatment of LQT1 and LQT3. Nadolol is appropriate for treatment of patients with confirmed LQT2.

List of abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
APHRS	Asia Pacific Heart Rhythm Society
BCE	Breakthrough cardiac event
CSANZ	Cardiac Society of Australia and New Zealand
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
HTN	Hypertension
HRS	Heart Rhythm Society
ICD	implantable cardioverter defibrillator
LQTS	long QT syndrome
MI	Myocardial Infarction
QTc	corrected QT interval
LCSD	left cardiac sympathetic nerve denervation

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