National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: May 2018

Mexiletine for the symptomatic treatment of myotonic disorders – first line

NIHRIO (HSRIC) ID: 21701 NICE ID: 9836

LAY SUMMARY

Myotonic disorders comprise both dystrophic myotonia and non-dystrophic myotonia. These conditions are caused by the mutation of specific genes which affect normal muscle function. The common feature that these conditions share is myotonia, during which muscles relax slowly and with difficulty after a voluntary contraction. This can cause stiffness, cramping, or an aching sensation in affected muscles, as well as muscle pain. Dystrophic myotonia is associated with muscle stiffness and systemic complications such as heart abnormalities which may be linked to sudden death, whereas non-dystrophic myotonia is mainly associated with muscle stiffness and muscle pain.

Mexiletine is under registration in Europe for the symptomatic treatment of myotonic disorders. It is administered as an oral capsule and it exerts its action by reducing the rate of contraction in the heart and other muscles. Currently it is used unlicensed in the UK, meaning that it is not currently approved but some healthcare providers consider it to be potentially beneficial based on research or professional experience. There are currently no licensed treatment options available to treat symptoms of myotonia, therefore, if licensed, mexiletine will offer access to an approved treatment option.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Symptomatic treatment of myotonic disorders in adults – first line

TECHNOLOGY

DESCRIPTION

Mexiletine is an antiarrhythmic agent that inhibits the inward sodium current required for the initiation and conduction of impulses, thus reducing the rate of rise of the action potential, Phase 0. It achieves this reduced sodium current by inhibiting sodium channels. Mexiletine decreases the effective refractory period (ERP) in Purkinje fibres in the heart. The decrease in ERP is of lesser magnitude than the decrease in action potential duration (APD), which results in an increase in the ERP/APD ratio. It does not significantly affect resting membrane potential or sinus node automaticity, left ventricular function, systolic arterial blood pressure, atrioventricular (AV) conduction velocity, or QRS or QT intervals.[1] Furthermore, it may have some anticonvulsant properties.[2] Mexiletine (Namuscla) is being developed as an antimyotonia agent.

Mexiletine is in pre-registration in the EU for the symptomatic treatment of myotonic disorders. In the completed phase III clinical trial (NCT02336477), mexiletine is administered as a capsule with a starting dose of 200 mg, which can be increased based on clinical response up to 600 mg daily (3 capsules per day).[3]

The first Marketing Authorisation for mexiletine (Mexitil) was granted in 1975 to Boehringer Ingelheim, as an antiarrhythmic medicinal product. The medicinal product was discontinued in 2008 for commercial reasons. However, to meet requirements from physicians and patients for the myotonia indication, the Marketing Authorisation in France for the treatment for Myotonia was transferred to Assistance Publique – Hôpitaux de Paris (APHP), with the indication being changed by variation. Outside of France, there are currently no licensed pharmacological treatments for the symptoms of myotonia, and even though limited mexiletine is available in the UK from 'special-order' importation companies, these products are not licensed for the myotonia indication but are used off-label for arrhythmias and myotonia treatment.[a]

INNOVATION and/or ADVANTAGES

Currently there are no licensed medicines in the UK for the treatment of myotonic disorders, however, there is some off-label use of "special-order" imported mexiletine, which has been studied extensively for the treatment of myotonia, and has been found to be safe and efficacious.[4]

If licensed, mexiletine will offer access to an approved option for the symptomatic treatment of myotonic disorders.

DEVELOPER

Lupin Atlantis Holdings SA

[a] Information provided by company

AVAILABILITY, LAUNCH or MARKETING

Mexiletine is a designated orphan drug in the EU for the treatment of myotonic disorders.[5]

PATIENT GROUP

BACKGROUND

Myotonic disorders are a heterogeneous group of disorders joined by a common clinical symptom and characteristic electro-diagnostic features. Clinically, myotonia is both a symptom and a sign that occurs in select neuromuscular disorders. Caused by muscle ion channel dysfunction, myotonia may produce stiffness, cramping, or an aching sensation in affected muscles. Patients with myotonia often report ''painless muscle stiffness,'' or an inability to relax a muscle after a voluntary contraction. It occurs in both skeletal and smooth muscle. When present in skeletal muscle, patients may have reduced agility or functional impairment. Myotonia in leg muscles may impair ambulation, whereas hand myotonia may reduce dexterity and occasionally cause social embarrassment when a patient cannot release a handshake. Axial myotonia may impair neck movement, and cranial muscle myotonia may interfere with chewing or eye lid opening.[6]

Myotonic disorders can be either classified as dystrophic or as non-dystrophic myotonias.[6] Dystrophic myotonia, or myotonic dystrophy are autosomal dominant, multisystem disorders which are characterized by myotonic myopathy. Two types can be distinguished; myotonic dystrophy type 1 (DM1) caused by an expansion of an unstable CTG trinucleotide repeat in the 3' untranslated region (UTR) of the myotonic dystrophy protein kinase gene (DMPK), and myotonic dystrophy type 2 (DM2) caused by an unstable tetranucleotide repeat expansion, CCTG in intron 1 of the nucleic acid-binding protein (CNBP) gene.[7,8] Those with DM1 or DM2 typically have progressive, fixed muscle weakness and wasting along with dystrophic muscle histology; however, myotonia is often noticed before weakness. Multi-systemic complications of DM1 include increased risk of arrhythmias and sudden death when experienced in adulthood,[9] but symptoms can range from mild features such as cataracts or baldness, to cardiac failure or respiratory distress.[7] DM2 is associated with similar cardiac conduction abnormalities as in DM1, however patients with DM2 additionally have proximal muscle weakness with muscle pain without atrophy,[7] and experience lower rates of respiratory failure.[6]

Patients with non-dystrophic myotonic disorders have ion channel dysfunction.[6] The non-dystrophic myotonias are skeletal muscle ion channel disorders traditionally considered to be distinct from myotonic dystrophy because of the absence of progressive weakness and systemic features. The non-dystrophic myotonias are caused by mutations of key skeletal muscle ion channel genes. According to their genotype and phenotype, they can be further categorised as autosomal dominant and autosomal recessive chloride channel myotonias and sodium channel myotonias, such as paramyotonia congenita and potassium aggravated myotonias, in particular hyperkalaemic periodic paralysis with myotonia.[b] The main clinical manifestations associated with non-dystrophic myotonias are stiffness resulting from myotonia, as well as pain, weakness and fatigue which highlights the non-life threatening extent of the conditions.[10,11] Historically, non-dystrophic myotonias were classified solely on their clinical features and inheritance patterns, however, more recently, genetic testing has further

[b] Information provided by company

defined patients. Although informative, a purely genetic classification for the non-dystrophic myotonias is not ideal, as it excludes patients with non-dystrophic myotonia who lack a previously validated genetic mutation (e.g., mutations without a clear phenotype–genotype correlation). In general, these disorders are much less common than either DM1 or DM2.[6]

CLINICAL NEED and BURDEN OF DISEASE

The clinical onset of symptoms in patients with DM ranges from birth (congenital form of DM1) to late adulthood with phenotypes classified by disease severity and age of disease onset. There is no gender preference due to the mutated gene falling on neither the X nor Y chromosome.[12] The onset of symptoms in non-dystrophic myotonia tend to present between the ages of 4 and 12 years.[13]

The prevalence of dystrophic myotonia can vary greatly across ethnicities, however, many people may go unrecognised or undiagnosed, which makes the determination of the true prevalence of these conditions extremely difficult.[14] A detailed population based study conducted in the North of England found that the prevalence of dystrophic myotonias to be 10.6 per 100,000 people in 2007.[15] Using 2016 mid-year estimates for the population of England and Wales, the prevalence of dystrophic myotonia in adults would be 4,873.[16]

In England between 1997 and 2011, data obtained from the national channelopathy service indicate that 0.75 per 100,000 people were affected by non-dystrophic myotonia.[17] Using 2016 mid-year estimates for England and Wales, the prevalence of non-dystrophic myotonia in adults would be 345.[16]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

There is currently no NICE guidance for the treatment of myotonic disorders.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract For Neurosciences: Specialised Neurology (Adults). D04/S/a.
- NHS England. 2013/14 NHS Standard Contract For Diagnostic Service For Rare Neuromuscular Disorders (All Ages). D04/S(HSS)/a

OTHER GUIDANCE

NHS Scotland – Scottish Muscle Network. Scottish guideline for the management of Myotonic Dystrophy in adults. 2017.[18]

Best practice guidelines and recommendations on the molecular diagnosis of myotonic dystrophy types 1 and 2. 2012.[7]

The myotonic dystrophies: diagnosis and management. 2010.[11]

Diagnostics and Therapy of Muscle Channelopathies – Guidelines of the Ulm Muscle Centre. 2008.[19]

CURRENT TREATMENT OPTIONS

Difficulties arise in supplying the optimal care for those with DM1 as it is a multisystem disease, whilst diagnostic challenges emerge in being able to recognise the presence of DM2.[7] Furthermore the treatment strategies in non-dystrophic myotonias are based on selective case reports, clinical experience and theoretical benefit,[3] with pharmacological treatment for conditions such as myotonia congenital severely lacking.[20]

Currently there are no licensed medicines in the UK for the treatment of myotonic disorders, however, mexiletine and other antiarrhythmic and antiepileptic medicines are used off-label.[21]

For those with myotonic disorders, best supportive care is available and due to the lack of licensed pharmacological treatments there is a reliance on alternative management strategies such as physiotherapy, lifestyle adaptations, mobility aids and occupational assistance.[c]

EFFICACY and SAFETY

Trial	MYOMEX, NCT02336477; mexiletine then placebo vs placebo then mexiletine; phase III
Sponsor	Assistance Publique - Hôpitaux de Paris
Status	Completed
Source of Information	Trial registry,[3] UK PharmaScan[21]
Location	France
Design	Randomised multi-centre, double-blind, placebo-controlled, crossover trial
Participants	n=24; aged 18-65 years; genetically definite myotonia congenital or paramyotonia congenital; participants who experience myotonic symptoms severe enough to justify treatment.
Schedule	Randomised to receive either: • Gradual dose of mexiletine (1 x 200 mg capsules). Dosing begins at 200 mg per day (1 capsule pre-prandial) which increases by 200 mg every 3 days to reach a maximum of 600 mg per day (3 capsules daily) in 1 week, followed by placebo. Placebo followed by the gradual dose of mexiletine
Follow-up	Active treatment period is 18 days minimum with a maximum of 22 days.
Primary Outcomes	Score of stiffness severity on a self-assessment scale (100 mm VAS) [Time Frame: 18 days]
Secondary Outcomes	• Standardized electromyography measures after repetitive short exercise test at cold and long exercise test [Time Frame: 18 days]

[c] Company contact

	• Chair test: time needed to stand up from a chair, walk around it and sit down again [Time Frame: 18 days] • Severity and disability scale of myotonia to be validated [Time Frame: 18 days] • Quality of life scale (INQOL) [Time Frame: 18 days] • CGI efficacy (Clinical Global Impression- Efficacy index) [Time Frame: 18 days]
Key Results	-
Adverse effects (AEs)	Not reported
Expected reporting date	Publication scheduled for Q3 2018.[21]

Trial	NCT01406873; mexiletine vs placebo; phase II
Sponsor	University of Rochester
Status	Completed
Source of Information	Trial registry,[22] Publication[23]
Location	USA
Design	Randomised, placebo-controlled trial
Participants	n=52; aged 18-80 years; diagnosis of dystrophy myotonia type 1 (DM1) confirmed by genetic mutation
Schedule	Randomised to receive either: • 150 mg/kg mexiletine capsules taken by mouth, three times daily for 6 months or 150 mg/kg placebo capsules taken by mouth, three times daily for 6 months
Follow-up	Active treatment period is 6 months
Primary Outcomes	• Mean Change From Baseline in Ambulation Using the 6 Minute Walk Distance [Time Frame: Baseline to 6 months]
Secondary Outcomes	• Percentage of Participants That Had a Dose Reduction or a Study Drug Withdrawal or Suspension Over 6 Months [Time Frame: 6 months] • Mean Change From Baseline in Quantitative Measure of Hand Grip Myotonia [Time Frame: Baseline to 6 months] • Mean Change From Baseline in Manual Muscle Testing (MMT) Score [Time Frame: Baseline to 6 months] • Mean Change From Baseline in PR, QRS, and QTc Intervals, and Average Minimum Heart Rate (HR) Via Electrocardiogram (ECG) Monitoring [Time Frame: Baseline to 6 Months] • Mean Change From Baseline in Patient-Reported Disease Burden and Quality of Life [Time Frame: Baseline to 6 months]

Key Results	Overall, participants in Patient-Reported Outcome Measure Patient Preferences in Trials Studying Myotonic Dystrophy Type 1 (PROMPTS DM1) favoured the Myotonic Dystrophy Type-1 Health Index (MDHI) over the Individualized Neuromuscular Disease Quality of Life questionnaire and the 36-Item Short Form Health Survey (version 2) (SF-36v2) in multiple areas of perceived relevance, usability, and responsiveness. The MDHI was associated with objective metrics that reflect disease severity in DM1. Specifically, the MDHI was the only instrument that was associated with employment status and Muscle Impairment Rating Scale score and was the instrument with the strongest correlation with muscle strength as measured by the manual muscle test score. PROMPTS DM1 also identified the SF-6D score (total score of SF-36v2) as having the strongest correlation with participant cytosine-thymine-guanine repeat length.
Adverse effects (AEs)	Not reported
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

The proposed average dosing would be 600 mg as a daily maintenance dose and it is expected that up to 25% of patients will receive treatment at peak year.[21]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services as there will not be the administrative burden of importing a special medicine for pharmacy. Improved quality of life is likely to improve patient wellbeing, whilst it is likely there will be a lowering on the reliance on

physiotherapy, lifestyle adaptations, mobility aids and occupational assistance.[d]

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs due to the decreased use of existing services. Additionally, Myotonic Dystrophy type 1 multisystem involvement leads to functional impairment with an increased risk of breaks & falls. 15% of falls attributed to "stiffness"[e]

☒ Other: *there are currently no licensed treatment options for myotonic disorders*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

[1]The Human Metabolome Database. *Mexiletine.* Available from: http://www.hmdb.ca/metabolites/HMDB0014523 [Accessed 09 May 2018]

[2]PubChem. *Mexiletine.* Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Mexiletine [Accessed 09 May 2018]

[3]ClinicalTrials.gov. *Mexiletine and Non Dystrophic Myotonias (MYOMEX).* Available from: https://clinicaltrials.gov/ct2/show/NCT02336477 [Accessed 09 May 2018]

[4]Wood L, Bassez G, van Engelen B, Lochmüller H, Schoser B. 222nd ENMC International Workshop:: Myotonic dystrophy, developing a European consortium for care and therapy, Naarden, The Netherlands, 1-2 July 2016. Neuromuscular disorders: NMD. 2018 Feb 12. Available from: https://doi.org/10.1016/j.nmd.2018.02.003

[5]European Medicines Agency. *Orphan Designation - EU/3/14/1353*. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2015/01/human_orphan_001450.jsp&mid=WC0b01ac058001d12b [Accessed 09 May 2018]

[d] Information provided by company

[e] Information provided by company

[6]Heatwole CR, Statland JM, Logigian EL. The diagnosis and treatment of myotonic disorders. *Muscle & nerve*. 2013 May 1;47(5):632-48. Available from: https://doi.org/10.1002/mus.23683
[7]Kamsteeg EJ, Kress W, Catalli C, Hertz JM, Witsch-Baumgartner M, Buckley MF, Van Engelen BG, Schwartz M, Scheffer H. Best practice guidelines and recommendations on the molecular diagnosis of myotonic dystrophy types 1 and 2. *European Journal of Human Genetics.* 2012 Dec;20(12):1203. Available from: https://doi.org/10.1038/ejhg.2012.108
[8]Meola G, Cardani R. Myotonic dystrophies: an update on clinical aspects, genetic, pathology, and molecular pathomechanisms. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*. 2015 Apr 1;1852(4):594-606. Available from: https://doi.org/10.1016/j.bbadis.2014.05.019
[9]Groh WJ, Groh MR, Saha C, Kincaid JC, Simmons Z, Ciafaloni E, Pourmand R, Otten RF, Bhakta D, Nair GV, Marashdeh MM. Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. *New England Journal of Medicine*. 2008 Jun 19;358(25):2688-97. Available from: https://doi.org/10.1056/NEJMoa062800
[10]Matthews E, Fialho D, Tan SV, Venance SL, Cannon SC, Sternberg D, Fontaine B, Amato AA, Barohn RJ, Griggs RC, Hanna MG. The non-dystrophic myotonias: molecular pathogenesis, diagnosis and treatment. *Brain*. 2009 Nov 16;133(1):9-22. Available from: https://doi.org/10.1093/brain/awp294
[11]Statland JM, Barohn RJ. Muscle channelopathies: the nondystrophic myotonias and periodic paralyses. *CONTINUUM: Lifelong Learning in Neurology*. 2013 Dec;19(6):1598. Available from: https://dx.doi.org/10.1212%2F01.CON.0000440661.49298.c8
[12]Myotonic Dystrophy Foundation. *Myotonic Dystrophy Facts.* Available from: http://myotonic.org/sites/default/files/DM%20fact%20sheet%20RDD.pdf [Accessed 09 May 2018]
[13]CheckOrphan. *Nondystrophic myotonia.* Available from: http://www.checkorphan.org/diseases/nondystrophic-myotonia [Accessed 09 May 2018]
[14]National Organisation for Rare Disorders. *Myotonic Dystrophy.* Available from: https://rarediseases.org/rare-diseases/dystrophy-myotonic/ [Accessed 09 May 2018]
[15]Norwood FL, Harling C, Chinnery PF, Eagle M, Bushby K, Straub V. Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population. *Brain*. 2009 Sep 18;132(11):3175-86. Available from: https://doi.org/10.1093/brain/awp236
[16]Office for National Statistics. Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2016. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2016#main-points [Accessed 09 May 2018]
[17]Horga A, Rayan DL, Matthews E, Sud R, Fialho D, Durran SC, Burge JA, Portaro S, Davis MB, Haworth A, Hanna MG. Prevalence study of genetically defined skeletal muscle channelopathies in England. *Neurology.* 2013 Apr 16;80(16):1472-5. Available from: https://doi.org/10.1212/WNL.0b013e31828cf8d0
[18]NHS Scotland – Scottish Muscle Network. *Scottish guideline for the management of Myotonic dystrophy in adults.* Available from: http://www.smn.scot.nhs.uk/wp-content/uploads/sites/5/2017/12/Mgt-of-Myotonic-Dystrophy-in-adults.pdf [Accessed 09 May 2018]
[19]Lehmann-Horn F, Jurkat-Rott K, Rüdel R. Diagnostics and therapy of muscle channelopathies–Guidelines of the Ulm Muscle Centre. Acta Myologica. 2008 Dec;27(3):98.
[20]Imbrici P, Liantonio A, Camerino GM, De Bellis M, Camerino C, Mele A, Giustino A, Pierno S, De Luca A, Tricarico D, Desaphy JF. Therapeutic approaches to genetic ion channelopathies and perspectives in drug discovery. *Frontiers in pharmacology*. 2016 May 10;7:121. Available from: https://doi.org/10.3389/fphar.2016.00121
[21]UK PharmaScan. *Technology Summary – 648097.* Available from: https://www.ukpharmascan.org.uk/HS/technology/648097 [Accessed 09 May 2018] [Login required]
[22]ClinicalTrials.gov. *Clinical Efficacy Trial of Mexiletine for Myotonic Dystrophy Type 1*. Available from: https://clinicaltrials.gov/ct2/show/NCT01406873 [Accessed 18 May 2018]
[23]Heatwole C, Johnson N, Dekdebrun J, Dilek N, Eichinger K, Hilbert J, Luebbe E, Martens W, McDermott MP, Thornton C, Moxley R. Myotonic Dystrophy Patient Preferences in Patient-Reported Outcome Measures. *Muscle & nerve*. 2018 Jan 12. Available from: https://doi.org/10.1002/mus.26066