ACTA MYOL 2025;XLIV:23-27;
DOI: 10.36185/2532-1900-1026

REVIEW

Pharmacological therapy of non-dystrophic myotonias

Ilaria Saltarella, Paola Iaghetti, Simone Dell'Atti, Concetta Altamura, Jean-François Desaphy

Section of Pharmacology, Department of Precision and Regenerative Medicine and Ionian Area, School of Medicine, University of Bari Aldo Moro, Bari, Italy

Objectives. Non-dystrophic myotonias (NDM) are rare diseases due to mutations in the voltage-gated sodium (Nav1.4) and chloride (ClC-1) channels expressed in skeletal muscle fibers. We provide an up-to-date review of pharmacological treatments available for NDM patients and experimental studies aimed at identifying alternative treatments and at better understanding the mechanisms of actions.
Methods. Literature research was performed using PubMed and ClinicalTrial.gov.
Results. Today, the sodium channel blocker mexiletine is the drug of choice for treatment of NDM. Alternative drugs include other sodium channel blockers and the carbonic anhydrase inhibitor acetazolamide. Preclinical studies suggest that activators of ClC-1 channels or voltage-gated potassium channels may have antimyotonic potential.
Conclusions. An increasing number of antimyotonic drugs would help to design a precision therapy to address personalized treatment of myotonic individuals.

Key words: non-dystrophic myotonia, pharmacological treatment, sodium channel, chloride channel, drug repurposing

Introduction

Non-dystrophic myotonias are rare neurological diseases due to mutations in SCN4A and CLCN1 genes encoding the voltage-gated sodium (Nav1.4) and chloride (ClC-1) channels in skeletal muscle fibers [1]. The Nav1.4 sodium channel is critical for action potential generation and firing. Missense mutations in SCN4A induce a gain of function of Nav1.4 channels, determining sarcolemma hyper-excitability. The ClC-1 chloride channel is open at rest potentials, thereby stabilizing the sarcolemma voltage and dampening excitability. Missense mutations or nucleotide deletions/insertions in CLCN1 reduce ClC-1 activity and favor muscle excitability. The hyper-excitability of sarcolemma slows down muscle relaxation after contraction resulting in muscle stiffness typical of myotonia.
Sodium channel-related myotonic syndromes are all transmitted in an autosomal dominant manner and are subdivided into Paramyotonia Congenita (PMC) and Sodium Channel Myotonia (SCM). PMC is characterized by paradoxical myotonia (worsening with exercise), marked cold sensitivity, and possible episodes of flaccid paralysis [2]. SCM forms a more heterogeneous group characterized by lack of paradoxical myotonia and paralytic attacks; they can display features like warm-up (improvement with exercise) and marked sensitivity to high blood K^+. Some mutations associated with neonatal onset can be very severe and life-threatening due to respiratory difficulties. Chloride channel-related myotonic syndromes are subdivided into the dominantly inherited Thomsen's Myotonia Congenita (TMC) and the recessive Becker's Myotonia Congenita (BMC), which is often more severe. Warm-up is often observed in BMC, as well as transient weakness occurring at movement initiation.

Received: February 3, 2025
Accepted: February 24, 2025

Correspondence
Jean-François Desaphy
E-mail: jeanfrancois.desaphy@uniba.it

How to cite this article: Saltarella I, Iaghetti P, Dell'Atti S, et al. Pharmacological therapy of non-dystrophic myotonias. Acta Myol 2025;44:23-27. https://doi.org/10.36185/2532-1900-1026

While some myotonic patients can manage myotonia by adapting lifestyle and exercise, others require pharmacological treatment to improve quality of life [3]. Empirically, sodium channel blockers indicated for epilepsy or cardiac arrhythmias have long been used off-label for symptomatic treatment of myotonia. By inhibiting sodium channels in a use-dependent manner, these drugs reduce the abnormal action potential firing in the myotonic muscle without altering normal function in healthy skeletal myofibers, cardiomyocytes, and neurons.

Mexiletine, the first choice drug in non-dystrophic myotonias

Since the 1980's, the antiarrhythmic drug mexiletine became the drug of choice in myotonic syndromes (Fig. 1) [4]. A milestone was achieved in 2012 with the results of an international, randomized controlled trial of mexiletine in myotonic patients [5]. This crossover study compared mexiletine to placebo in 59 adult patients carrying sodium or chloride channel mutations. The primary end-point was a patient reported severity score of stiffness, which was improved during four-week mexiletine treatment. Improvement was also reported for needle electromyography and clinical myotonia (handgrip and eyelid). This successful trial supported the designation of mexiletine as orphan drug in myotonia by the European Medicines Agency in 2013, followed by marketing authorization in 2018. Effectiveness of mexiletine was further confirmed in an aggregated N-of-1 trial and an additional crossover study, involving a total of 55 adult patients [6-7].

Importantly, an open-label interventional study has been completed in pediatric myotonic patients (6 to < 18 years of age) to describe the pharmacokinetics, safety, and efficacy of mexiletine (NCT04624750, clinicaltrials.gov), and results are expected soon. Two observational prospective studies are still undergoing to verify the long-term effectiveness and safety of mexiletine in adult and pediatric NDM patients (NCT04622553; NCT04616807). In two retrospective studies of large cohorts, mexiletine appeared relatively safe and efficient in the long term, up to 20 years [8-9]. The most common side effects were gastrointestinal disorders, which may require specific treatment or may lead to mexiletine interruption by a few patients. In addition, expert recommendations have been recently published regarding the cardiac assessment of NMD adult patients treated with mexiletine [10]. A recent French survey recruiting 47 adults NDM patients reported that most patients were taken mexiletine and obtained, at least occasionally, a significant improvement in muscle stiffness and reduction in falls, muscle pain, and anxiety [11]. Yet, it is widely acknowledged that mexiletine may allow little benefits in a number of myotonic patients due to contraindications (mainly cardiac myopathy), side effects (mainly gastrointestinal), unsatisfactory therapeutic response, high costs and/or limited availability in some countries.

Alternative drugs to mexiletine

Besides mexiletine, other sodium channel blockers are prescribed off-label to myotonic patients. Historically, a common alternative was carbamazepine or phenytoin because of consolidated use by neurol-

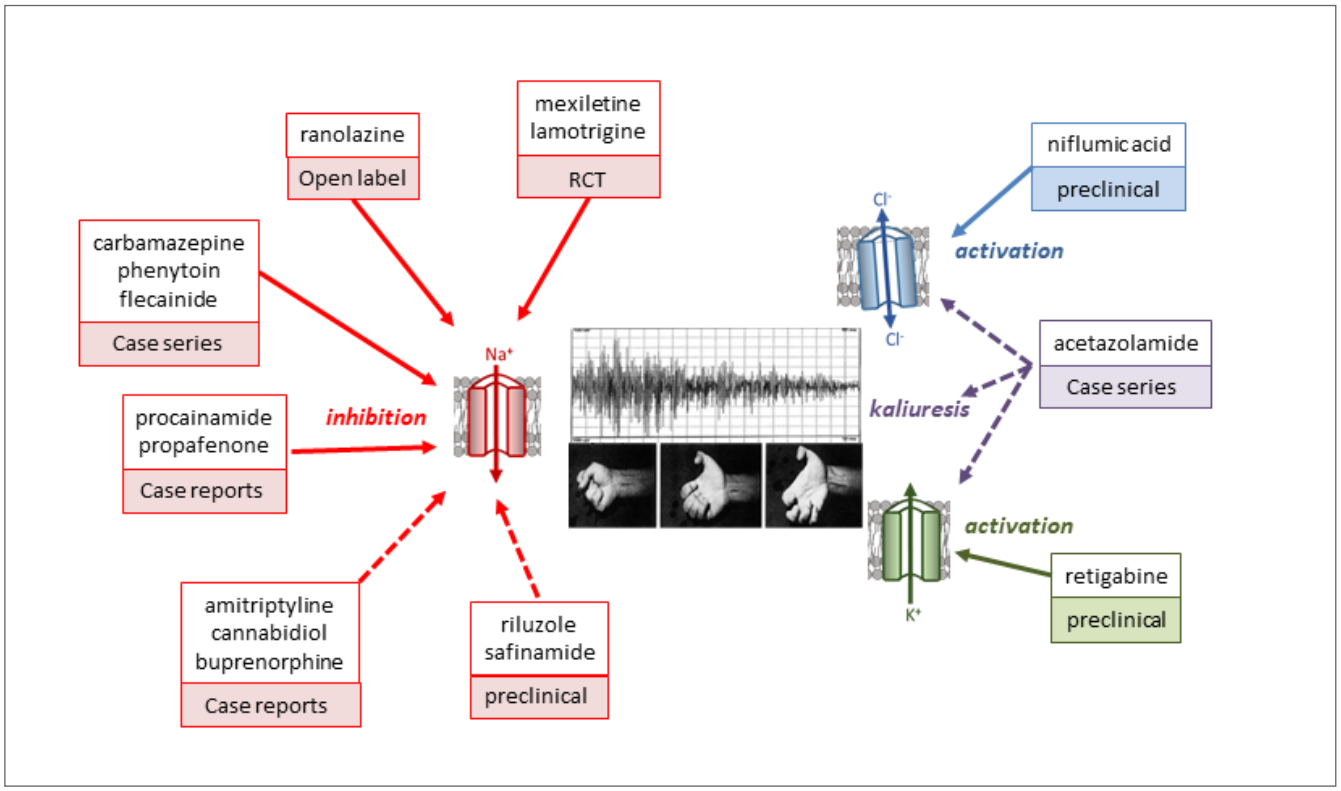

Figure 1. Pharmacological treatments available for NDM or in preclinical studies, with their mechanism of action. Dashed arrows indicate hypothetical mechanisms of action. RCT: Randomized Controlled Trial.

ogists in epilepsy, especially in the pediatric setting [12]. The cardiac antiarrhythmic flecainide proved beneficial in some SCM or PMC patients, who were unsatisfied with mexiletine [13-17]. One possible explanation may be the reduced sensitivity of specific sodium channel mutants to mexiletine [18]. The anti-anginal ranolazine showed benefits in two open-label trials in MC and PMC patients [19-20]. Other sodium channel blockers used occasionally include procainamide and propafenone. However, randomized controlled trials (RCT) to confirm effectiveness of these drugs are lacking.

One exception is the anticonvulsant lamotrigine, which effectiveness in adult NDM patients was demonstrated in a double-blind randomized, placebo-controlled, crossover study [21]. Of the 26 enrolled patients (12 with PMC and 14 with MC), 18 showed myotonia improvement with lamotrigine, 4 reported no effect of treatment, and 4 dropped out (one for treatment related allergy). According to the authors, lamotrigine could be considered first-line therapy because of effectiveness, limited side effects, lower price, and availability, as well as second line in mexiletine-intolerant patients. A recent head-to-head, crossover study in NDM patients confirmed effectiveness of both mexiletine and lamotrigine but failed to demonstrate the non-inferiority of lamotrigine to mexiletine [22]. Nevertheless, half of the participants who took mexiletine before the study changed to lamotrigine after the study, due to reduced side effects, increased efficacy, or better access. In addition, the authors highlighted the huge cost disparity between the two drugs in the UK. Thus, they proposed a personalized treatment algorithm based on symptoms, co-morbidities, patient's preferences, and economical considerations. Another head-to-head trial of lamotrigine versus mexiletine has been announced (NCT05639257).

Interestingly, cannabinoids were recently shown to improve myotonia in a small cohort of myotonic patients [23], an effect likely related to inhibition of Nav1.4 channel by cannabidiol [24-25]. Also the tricyclic antidepressant amitriptyline and the opioid analgesic buprenorphine, which both exert Nav1.4 channel inhibition, were reported effective in a few patients [26-27].

Besides sodium channel blockers, the carbonic anhydrase acetazolamide has been used off-label for treating myotonia but no RCT has been performed [28-29]. The mechanism of action of acetazolamide in myotonia may include kaliuresis allowing dampening of skeletal muscle excitability. Direct activation of skeletal muscle Ca^{2+}-activated potassium channels by acetazolamide has been also reported but recent studies suggest that this might be counterproductive in myotonia [30-32]. Acetazolamide-induced acidosis may also modulate various metabolic pathways in muscle fibers. For instance, the drug was shown to increase ClC-1 channel activity through intracellular acidosis, thereby reducing muscle fiber excitability in vitro [33].

Experimental pharmacology

The pharmacological study of ion channels using the patch-clamp technique offers a good opportunity for testing new anti-myotonic drugs. There is the possibility to express recombinant human skeletal muscle sodium or chloride channels in mammalian cell lines, as well as their myotonic mutants. The more promising drugs can be then tested in animal models of myotonia congenita, such as the *adr* mouse carrying a recessive *CLCN1* mutation or the myotonic rat, in which myotonia is induced by pharmacological inhibition of chloride channels [34-36]. Two mouse model of sodium-channel related myotonia are available but have not been used for pharmacological studies [37-38].

Regarding Nav1.4 channels, a rather good correlation was found between *in vitro* inhibition of sodium channels and *in vivo* antimyotonic effects in animal MC models [39]. For instance, a new derivative of tocainide, which was 120-fold more potent in blocking Nav1.4 channels *in vitro*, was 100-fold more potent in inhibiting myotonia in the myotonic rat [40]. Thus, an *in vitro* and *in vivo* screening of clinically-used sodium channel blockers disclosed riluzole and safinamide as promising antimyotonic drugs, but clinical evidences are still lacking [39,41-43]. Nevertheless, translation of preclinical results to humans already proved successful for ranolazine, lamotrigine, and flecainide [14,44-46].

There is currently no selective drug able to increase ClC-1 channel activity. Many myotonic mutations reduce the sarcolemma chloride conductance by altering the voltage-dependence of ClC-1 channels, rendering the channel less prone to opening at physiological voltage [47-48]. In such a case, a "gating corrector" able to restore the normal voltage dependence in ClC-1 channels might be useful. Interestingly, such mechanism might be acted indirectly by acetazolamide [33]. Another common defect induced by ClC-1 mutations is the reduced expression of the channel in the sarcolemma due to altered proteostasis (biogenesis in the ER, trafficking to the sarcolemma, and protein turn-over at the membrane) [49]. A drug of choice for these mutations should act as a pharmacological chaperone, favoring channel trafficking to and stabilization at the membrane. Recently, the non-steroidal anti-inflammatory drug niflumic acid was shown to exert such an effect on heterologously expressed ClC-1 channel mutants [50]. Whether this may occur in skeletal muscle in vitro and in vivo remains to be demonstrated.

In vitro studies on isolated myotonic muscles suggested that activation of voltage-gated potassium (Kv) channels by retigabine may enhance the warm-up phenomena, reducing the duration of myotonia [51-53]. Antimyotonic effect of retigabine was also observed *in vivo* in the adr mouse but motor performance was not improved, maybe due to extra-muscle effects [52]. Yet, these studies suggest that Kv channel openers might broaden the therapeutic arsenal for treating NDM.

Conclusions

The non-dystophic myotonias represent a paradigm for drug repurposing in rare diseases [4]. Today, mexiletine is the sole drug with therapeutic indication for NDM but there is a good consensus for the use of other sodium channel blockers at least in patients unsatisfied with mexiletine, including lamotrigine, carbamazepine, and flecainide. The first two ones present the advantage to have pediatric indication and consolidated use by neurologists in epilepsy, while flecainide showed significant improvement in patients carrying sodium channel mutations "resistant" to mexiletine. A challenge for pharmacological studies in humans will be to demonstrate the non-inferiority of these drugs to mexiletine.

Besides clinical studies, preclinical research is still required to 1) identify new sodium channel blockers with antimyotonic potential, 2) better understand the mechanisms of action of acetazolamide in

NDM, 3) identify CIC-1 chloride channel activators, and 4) evaluate the antimyotonic potential of Kv channel activators.
By increasing the arsenal of antimyotonic drugs, the hope is to design a precision therapy to address personalized treatment of myotonic individuals [3].

Acknowledgements

The authors thank the non-profit Italian parents' association, MiA ("Miotonici in Associazione"), for kind support.

Conflict of interest statement

JFD was scientific consultant for Lupin Neuroscience Division, France (2021-2022). The other authors declare no conflict of interest.

Funding

The Research contract for IS was co-financed by the European Union - FSE-REACT-EU, PON Research and Innovation 2014–2020, DM 1062/2021.

Authors' contribution

All the authors contributed to literature search. IS and CA wrote a draft of the manuscript. JFD critically revised the manuscript. All authors read and approved the final version of the manuscript.

Ethical considerations

Not applicable.

References

1 Maggi L, Bonanno S, Altamura C, et al. Ion Channel Gene Mutations Causing Skeletal Muscle Disorders: Pathomechanisms and Opportunities for Therapy. Cells. 2021;10(6):1521. https://doi.org/10.3390/cells10061521.

2 Vivekanandam V, Jayaseelan D, Hanna MG. Muscle channelopathies. Handb Clin Neurol. 2023;195:521-532. https://doi.org/10.1016/B978-0-323-98818-6.00006-6.

3 Desaphy JF, Altamura C, Vicart S, et al. Targeted therapies for skeletal muscle ion channelopathies: systematic review and steps towards precision medicine. J Neuromuscul Dis. 2021;8(3):357-381. https://doi.org/10.3233/JND-200582.

4 Altamura C, Saltarella I, Campanale C, et al. Drug repurposing in skeletal muscle ion channelopathies. Curr Opin Pharmacol. 2023;68:102329. https://doi.org/10.1016/j.coph.2022.102329.

5 Statland JM, Bundy BN, Wang Y, et al. Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia: a randomized controlled trial. JAMA. 2012;308(13):1357-1365. https://doi.org/10.1001/jama.2012.12607.

6 Stunnenberg BC, Raaphorst J, Groenewoud HM, et al. Effect of mexiletine on muscle stiffness in patients with nondystrophic myotonia evaluated using aggregated N-of-1 trials. JAMA. 2018;320(22):2344-2353. https://doi.org/10.1001/jama.2018.18020.

7 Vicart S, Franques J, Bouhour F, et al. Efficacy and safety of mexiletine in non-dystrophic myotonias: A randomised, double-blind, placebo-controlled, cross-over study. Neuromuscul Disord. 2021;31(11):1124-1135. https://doi.org/10.1016/j.nmd.2021.06.010.

8 Suetterlin KJ, Bugiardini E, Kaski JP, et al. Long-term safety and efficacy of mexiletine for patients with skeletal muscle channelopathies. JAMA Neurol. 2015;72(12):1531-3. https://doi.org/10.1001/jamaneurol.2015.2338.

9 Modoni A, D'Amico A, Primiano G, et al. Long-term safety and usefulness of mexiletine in a large cohort of patients affected by non-dystrophic myotonias. Front Neurol. 2020;11:300. https://doi.org/10.3389/fneur.2020.00300.

10 Vicart S, Wahbi K, Duchateau J, et al. Recommendations of an expert group for the cardiac assessment of non-dystrophic myotonia adult patients treated with mexiletine. Neuromuscul Disord. 2024;44:104464. https://doi.org/10.1016/j.nmd.2024.104464.

11 Vicart S, Péréon Y, Ghorab K, et al. Self-reported outcomes and quality of life of patients with non-dystrophic myotonia: The French IMPACT 2022 survey. Rev Neurol (Paris). 2024;180(8):791-797. https://doi.org/10.1016/j.neurol.2024.04.007.

12 Öz Tunçer G, Sanri A, Aydin S, et al. Clinical and Genetic Spectrum of Myotonia Congenita in Turkish Children. J Neuromuscul Dis. 2023;10(5):915-924. https://doi.org/10.3233/JND-230046.

13 Desaphy JF, Modoni A, Lomonaco M, et al. Dramatic improvement of myotonia permanens with flecainide: a two-case report of a possible bench-to-bedside pharmacogenetics strategy. Eur J Clin Pharmacol. 2013;69(4):1037-1039. https://doi.org/10.1007/s00228-012-1414-3.

14 Desaphy JF, Carbonara R, D'Amico A, et al. Translational approach to address therapy in myotonia permanens due to a new SCN4A mutation. Neurology. 2016;86(22):2100-2108. https://doi.org/10.1212/WNL.0000000000002721.

15 Portaro S, Rodolico C, Sinicropi S, et al. Flecainide-responsive myotonia permanens with SNEL onset: A new case and literature review. Pediatrics. 2016;137(4):e20153289. https://doi.org/10.1542/peds.2015-3289.

16 Lehmann-Horn F, D'Amico A, Bertini E, et al. Myotonia permanens with Nav1.4-G1306E displays varied phenotypes during course of life. Acta Myol. 2017;36(3):125-134. PMID: 29774303.

17 Terracciano C, Farina O, Esposito T, et al. Successful long-term therapy with flecainide in a family with paramyotonia congenita. J Neurol Neurosurg Psychiatry. 2018;89(11):1232-1234. https://doi.org/10.1136/jnnp-2017-317615.

18 Farinato A, Altamura C, Imbrici P, et al. Pharmacogenetics of myotonic hNav1.4 sodium channel variants situated near the fast inactivation gate. Pharmacol Res. 2019;141:224-235. https://doi.org/10.1016/j.phrs.2019.01.004.

19 Arnold WD, Kline D, Sanderson A, et al. Open-label trial of ranolazine for the treatment of myotonia congenita. Neurology. 2017;89(7):710-713. https://doi.org/10.1212/WNL.0000000000004229.

20 Lorusso S, Kline D, Bartlett A, et al. Open-label trial of ranolazine for the treatment of paramyotonia congenita. Muscle Nerve. 2019;59(2):240-243. https://doi.org/10.1002/mus.26372.

21 Andersen G, Hedermann G, Witting N, et al. The antimyotonic effect of lamotrigine in non-dystrophic myotonias: a double-blind randomized study. Brain. 2017;140(9):2295-2305. https://doi.org/10.1093/brain/awx192.

22 Vivekanandam V, Skorupinska I, Jayaseelan DL, et al. Mexiletine versus lamotrigine in non-dystrophic myotonias: a randomised, double-blind, head-to-head, crossover, non-inferiority, phase 3 trial. Lancet Neurol. 2024;23(10):1004-1012. https://doi.org/10.1016/S1474-4422(24)00320-X.

23 Montagnese F, Stahl K, Wenninger S, et al. A role for cannabinoids in the treatment of myotonia? Report of compassionate use in a small cohort of patients. J Neurol. 2020;267(2):415-421. https://doi.org/10.1007/s00415-019-09593-6.

24 Ghovanloo MR, Choudhury K, Bandaru TS, et al. Cannabidiol inhibits the skeletal muscle Nav1.4 by blocking its pore and by altering membrane elasticity. J Gen Physiol. 2021;153(5):e202012701. https://doi.org/10.1085/jgp.202012701.

25 Huang CW, Lin PC, Chen JL, et al. Cannabidiol selectively binds to the voltage-gated sodium channel Nav1.4 in its slow-Inactivated state and inhibits sodium current. Biomedicines. 2021;9(9):1141. https://doi.org/10.3390/biomedicines9091141.

26 Bissay V, Keymolen K, Lissens W, et al. Late onset painful cold-aggravated myotonia: three families with SCN4A L1436P mutation. Neuromuscul Disord. 2011;21(8):590-593. https://doi.org/10.1016/j.nmd.2011.05.006.

27 Ravaglia S, Maggi L, Zito A, et al. Buprenorphine may be effective for treatment of paramyotonia congenita. Muscle Nerve. 2021;64(1):95-99. https://doi.org/10.1002/mus.27249.

28 Griggs RC, Moxley RT 3rd, Riggs JE, et al. Effects of acetazolamide on myotonia. Ann Neurol. 1978;3(6):531-537. https://doi.org/10.1002/ana.410030614.

29 Markhorst JM, Stunnenberg BC, Ginjaar IB, et al. Clinical experience with long-term acetazolamide treatment in children with nondystrophic myotonias: a three-case report. Pediatr Neurol. 2014;51(4):537-541. https://doi.org/10.1016/j.pediatrneurol.2014.05.027.

30 Tricarico D, Barbieri M, Camerino DC. Acetazolamide opens the muscular KCa2+ channel: a novel mechanism of action that may explain the therapeutic effect of the drug in hypokalemic periodic paralysis. Ann Neurol. 2000;48(3):304–312. PMID: 10976636.

31 Hoppe K, Sartorius T, Chaiklieng S, et al. Paxilline prevents the onset of myotonic stiffness in pharmacologically induced myotonia: A preclinical investigation. Front Physiol. 2020;11:533946. https://doi.org/10.3389/fphys.2020.533946.

32 Dupont C, Blake B, Voss AA, et al. BK channels promote action potential repolarization in skeletal muscle but contribute little to myotonia. Pflugers Arch. 2024;476(11):1693-1702. https://doi.org/10.1007/s00424-024-03005-z.

33 Altamura C, Fonzino A, Tarantino N, et al. Increased sarcolemma chloride conductance as one of the mechanisms of action of carbonic anhydrase inhibitors in muscle excitability disorders. Exp Neurol. 2021;342:113758. https://doi.org/10.1016/j.expneurol.2021.113758.

34 Talon S, De Luca A, De Bellis M, et al. Increased rigidity of the chiral centre of tocainide favours stereoselectivity and use-dependent block of skeletal muscle Na(+) channels enhancing the antimyotonic activity in vivo. Br J Pharmacol. 2001;134(7):1523-1531. https://doi.org/10.1038/sj.bjp.0704366.

35 De Luca A, Pierno S, Liantonio A, et al. New potent mexiletine and tocainide analogues evaluated in vivo and in vitro as antimyotonic agents on the myotonic ADR mouse. Neuromuscul Disord. 2004;14(7):405-16. https://doi.org/10.1016/j.nmd.2004.04.006.

36 Desaphy JF, Costanza T, Carbonara R, et al. In vivo evaluation of antimyotonic efficacy of β-adrenergic drugs in a rat model of myotonia. Neuropharmacology. 2013;65:21-27. https://doi.org/10.1016/j.neuropharm.2012.09.006.

37 Hayward LJ, Kim JS, Lee MY, et al. Targeted mutation of mouse skeletal muscle sodium channel produces myotonia and potassium-sensitive weakness. J Clin Invest. 2008;118(4):1437-1449. https://doi.org/10.1172/JCI32638.

38 Corrochano S, Männikkö R, Joyce PI, et al. Novel mutations in human and mouse SCN4A implicate AMPK in myotonia and periodic paralysis. Brain. 2014;137(Pt 12):3171-85. https://doi.org/10.1093/brain/awu292.

39 Desaphy JF, Carbonara R, Costanza T, et al. Preclinical evaluation of marketed sodium channel blockers in a rat model of myotonia discloses promising antimyotonic drugs. Exp Neurol. 2014;255(100):96-102. https://doi.org/10.1016/j.expneurol.2014.02.023.

40 De Bellis M, Carbonara R, Roussel J, et al. Increased sodium channel use-dependent inhibition by a new potent analogue of tocainide greatly enhances in vivo antimyotonic activity. Neuropharmacology. 2017;113(Part A):206-216. https://doi.org/10.1016/j.neuropharm.2016.10.013.

41 Desaphy JF, Farinato A, Altamura C, et al. Safinamide's potential in treating nondystrophic myotonias: Inhibition of skeletal muscle voltage-gated sodium channels and skeletal muscle hyperexcitability in vitro and in vivo. Exp Neurol. 2020;328:113287. https://doi.org/10.1016/j.expneurol.2020.113287.

42 Canfora I, Altamura C, Desaphy JF, et al. Preclinical study of the antimyotonic efficacy of safinamide in the myotonic mouse model. Neurotherapeutics. 2024;21(6):e00455. https://doi.org/10.1016/j.neurot.2024.e00455.

43 Hollingworth D, Thomas F, Page DA, et al. Structural basis for the rescue of hyperexcitable cells by the amyotrophic lateral sclerosis drug Riluzole. Nat Commun. 2024;15(1):8426. https://doi.org/10.1038/s41467-024-52539-4.

44 Desaphy JF, De Luca A, Didonna MP, et al. Different flecainide sensitivity of hNav1.4 channels and myotonic mutants explained by state-dependent block. J Physiol. 2004;554(Pt 2):321-34. https://doi.org/10.1113/jphysiol.2003.046995.

45 Novak KR, Norman J, Mitchell JR, et al. Sodium channel slow inactivation as a therapeutic target for myotonia congenita. Ann Neurol. 2015;77(2):320-32. https://doi.org/10.1002/ana.24331.

46 Skov M, de Paoli FV, Nielsen OB, et al. The anti-convulsants lacosamide, lamotrigine, and rufinamide reduce myotonia in isolated human and rat skeletal muscle. Muscle Nerve. 2017;56(1):136-142. https://doi.org/10.1002/mus.25452.

47 Altamura C, Desaphy JF, Conte D, et al. Skeletal muscle ClC-1 chloride channels in health and diseases. Pflugers Arch. 2020;472(7):961-975. https://doi.org/10.1007/s00424-020-02376-3.

48 Brenes O, Pusch M, Morales F. ClC-1 chloride channel: inputs on the structure-function relationship of myotonia congenita-causing mutations. Biomedicines. 2023;11(10):2622. https://doi.org/10.3390/biomedicines11102622.

49 Jeng CJ, Fu SJ, You CY, et al. Defective gating and proteostasis of human ClC-1 chloride channel: Molecular pathophysiology of myotonia congenita. Front Neurol. 2020;11:76. https://doi.org/10.3389/fneur.2020.00076.

50 Altamura C, Conte E, Campanale C, et al. Chaperone activity of niflumic acid on ClC-1 chloride channel mutants causing myotonia congenita. Front Pharmacol. 2022;13:958196. https://doi.org/10.3389/fphar.2022.958196.

51 Su TR, Zei WS, Su CC, et al. The effects of the KCNQ openers retigabine and flupirtine on myotonia in mammalian skeletal muscle induced by a chloride channel blocker. Evid Based Complement Alternat Med. 2012:803082. https://doi.org/10.1155/2012/803082.

52 Dupont C, Denman KS, Hawash AA, et al. Treatment of myotonia congenita with retigabine in mice. Exp Neurol. 2019;315:52-59. https://doi.org/10.1016/j.expneurol.2019.02.002.

53 Hoppe K, Chaiklieng S, Lehmann-Horn F, et al. Preclinical pharmacological in vitro investigations on low chloride conductance myotonia: effects of potassium regulation. Pflugers Arch. 2020;472(10):1481-1494. https://doi.org/10.1007/s00424-020-02410-4.