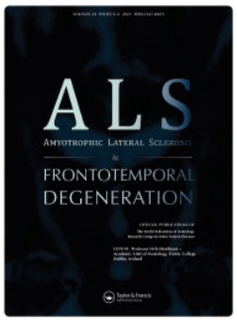

Taylor & Francis
Taylor & Francis Group

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

ALSUntangled #71: Nuedexta

Yuyao Sun, Michael Benatar, Javier Mascías Cadavid, Dave Ennist, Paul Wicks, Kim Staats, Morgan Beauchamp, Sartaj Jhooty, Gary Pattee, Andrew Brown, Tulio Bertorini, Paul Barkhaus, Mark Bromberg, Greg Carter, Richard Bedlack & Xiaoyan Li

To cite this article: Yuyao Sun, Michael Benatar, Javier Mascías Cadavid, Dave Ennist, Paul Wicks, Kim Staats, Morgan Beauchamp, Sartaj Jhooty, Gary Pattee, Andrew Brown, Tulio Bertorini, Paul Barkhaus, Mark Bromberg, Greg Carter, Richard Bedlack & Xiaoyan Li (2023): ALSUntangled #71: Nuedexta, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: 10.1080/21678421.2023.2239292

To link to this article: https://doi.org/10.1080/21678421.2023.2239292

Published online: 26 Jul 2023.

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2023; 0: 1–5

REVIEW ARTICLE

ALSUntangled #71: Nuedexta

YUYAO SUN[1], MICHAEL BENATAR[2], JAVIER MASCÍAS CADAVID[3], DAVE ENNIST[4], PAUL WICKS[5], KIM STAATS[6], MORGAN BEAUCHAMP[7], SARTAJ JHOOTY[8], GARY PATTEE[9], ANDREW BROWN[2], TULIO BERTORINI[10], PAUL BARKHAUS[11], MARK BROMBERG[12], GREG CARTER[13], RICHARD BEDLACK[14] & XIAOYAN LI[14]

[1]Neurology Department, University of Kentucky, Lexington, KY, USA, [2]Department of Neurology, University of Miami, Miami, FL, USA, [3]Neurology Department, Hospital Carlos III-La Paz, Madrid, Spain, [4]Origent Data Sciences Inc, Vienna, VA, USA, [5]Wicks Digital Health, Lichfield, UK, [6]Staats Life Sciences Consulting, Los Angeles, CA, USA, [7]Neuroscience Clinical Trials Unit, UNC Chapel Hill, NC, USA, [8]University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, [9]Department of Neurology, University of Nebraska Medical Center, Omaha, NE, USA, [10]Department of Neurology, University of Tennessee Health Science Center, Memphis, TN, USA, [11]Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA, [12]Department of Neurology, University of Utah, Salt Lake City, UT, USA, [13]St Luke's Rehabilitation Institute, Spokane, WA, USA, and [14]Department of Neurology, Duke University, Durham, NC, USA

Abstract

Nuedexta is a combination of dextromethorphan hydrobromide and quinidine sulfate and was approved by the Food and Drug Administration (FDA) in 2010 to treat pseudobulbar affect (PBA). There have since been anecdotal case reports of bulbar function improvements after Nuedexta treatment. Here, we review the off-label use of Nuedexta for improving bulbar function in people with ALS. Nuedexta has plausible mechanisms for protecting brain stem motor neurons via its effects on S1R and glutamate excitotoxicity. Recent clinical trials support that Nuedexta can improve bulbar function in PALS, with or without PBA. Nuedexta causes mild to moderate side effects. Based on this information, we support considering Nuedexta treatment for bulbar dysfunction in ALS patients with or without PBA.

Keywords: *ALS, Nuedexta, dextromethorphan, N-Methyl-D-Aspartate receptor (NMDAR), sigma-1 receptor (S1R)*

ALSUntangled reviews alternative and off-label treatments on behalf of people living with amyotrophic lateral sclerosis (PALS). Here we review Nuedexta therapy, for which we have had 233 requests (https://www.alsuntangled.com/future-reviews/).

Overview

Bulbar dysfunction manifests as difficulties in speech and swallowing and sialorrhea when cranial nerve motor neurons in the medulla oblongata, i.e. spinal bulb, degenerate in PALS. PBA is characterized by involuntary and uncontrollable laughing or crying, which are out of proportion or incongruent with the patient's emotions. It is thought to be due to corticobulbar tract degeneration.

Nuedexta contains a fixed-dose combination of two components- dextromethorphan hydrobromide 20 mg and quinidine sulfate 10 mg per capsule. Dextromethorphan is the main effector in reducing PBA, presumably through antagonizing the N-Methyl-D-Aspartate receptor (NMDAR) and activating sigma-1 receptor (S1R) (1,2). However, dextromethorphan demonstrates high first-pass metabolism. In some PALS, dextromethorphan levels are undetectable even after administering

Correspondence: Xiaoyan Li; Richard Bedlack, Neurology Department, Duke University, 932 Morreene Rd, Durham, NC 27705, United States. Email: Xiaoyan.li266@duke.edu, bedla001@mc.duke.edu.

(Received 31 May 2023; revised 28 June 2023; accepted 15 July 2023)

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2023.2239292

750 mg daily (3). To increase the bioavailability, it is co-administered with low-dose quinidine, a potent cytochrome P450 inhibitor.

Nuedexta received approval from FDA in 2010 to treat PBA. Since then, anecdotal reports of improvements in speech, salivation, or swallowing functions emerged. Herein, we review the off-label use of Nuedexta therapy in bulbar function in PALS, both with and without PBA.

Mechanisms

Dextromethorphan can bind to and modulate several neurotransmitter receptors and transporters in the central nervous system (CNS). These include S1R, NMDAR, 5-HT1B/D receptors, serotonin and norepinephrine transporters, and voltage-gated calcium channels (4). It may alleviate PBA by modulating serotonin levels, activating S1R, and inhibiting NMDAR. How dextromethorphan might influence bulbar function is yet to be determined. S1R could be a major mediator as it is highly expressed in brainstem motor nuclei (5,6). Dextromethorphan is also a weak, noncompetitive NMDAR antagonist; however, this function may be less critical in regulating bulbar functions because other NMDA pathway inhibitors, such as Riluzole and ceftriaxone, did not improve bulbar functions of PALS (7).

S1R is a transmembrane chaperone protein that does not have its own intracellular signaling pathway. Instead, it regulates other pathways by interacting with signal molecules and ion channels such as protein kinases and calcium channels. S1R expression is enriched in the endoplasmic reticulum (ER) and mitochondrial membrane and is also found in the nucleus and plasma membrane of neurons and glial cells in the CNS (8). Studies have shown that activation of S1R modulates ER stress and prevents mitochondrial dysfunction (8,9), which could potentially promote motor neuron survival. Additionally, S1R has been found to regulate cell apoptotic pathways and promote cell survival (10). Activation of S1R has also been shown to reduce glutamate release and suppress excessive NMDA responses in various neuronal injury models (11–13). Lastly, several studies suggest that S1R regulates astrocytes and microglia function and prevents secondary neuroinflammatory damage (14,15).

In line with the above, the deletion of S1R in the SOD1 G93A ALS mouse model triggered an earlier disease onset and a shorter lifespan (16). S1R agonists- PRE-084 and SA4503- improved motor neuron function and prolonged survival (14,17).

ALSUntangled assigns a TOE "Mechanism" grade of B (Table 1).

Table 1. Table of Evidence for Nuedexta.

	Grade	Explanation
Mechanism	B	S1R was shown in peer-reviewed publications to act on a relevant ALS mechanism.
Pre-Clinical	U	Dextromethorphan has not been directly studied in ALS pre-clinical models.
Cases	A	One or more peer-reviewed publications reporting benefits with validated diagnosis and benefits.
Trials	C	One peer-reviewed publication reporting benefits in a well-designed, randomized, blinded, placebo-controlled phase 2 trial. A second clinical trial has been completed, and the results were presented at NEALS Annual Meeting in 2022, but the study has not been published.
Risks	C	At least 10% of exposed patients experienced side effects (no hospitalizations or deaths)

Pre-clinical models

We did not find dextromethorphan being directly studied in ALS pre-clinical models. However, abundant reports showed its neuroprotective effects in various neuronal injuries. For instance, dextromethorphan reduced the vulnerability of cultured cortical neurons and retinal ganglion cells to glutamate-induced excitotoxicity, and the protective effects were likely mediated by S1R (1,18). Systemic injection of dextromethorphan in an excitotoxicity-induced brain injury mouse model significantly reduced neuronal cell death and lesion size (17).

Dextromethorphan also demonstrated neuroprotective effects in dopaminergic neurons in cell culture and Parkinson's disease mouse models (19,20).

Since it is unclear whether these models are relevant to PALS, ALSUntangled assigns a TOE "Pre-Clinical Models" grade of U (Table 1).

Data in PALS

Cases

In one observational study, among 86 PALS who received Nuedexta for PBA, 63 percent experienced an improvement in liquid swallowing rate in 4–8 weeks (21). In contrast, in an open-label study, 21 PALS with bulbar dysfunction were treated with Nuedexta for one year and compared with 20 historical controls (PALS who were not treated with Nuedexta). Nuedexta did not affect the long-term deterioration of bulbar function evaluated with the Norris scale bulbar subscore and ALSFRS-R bulbar subscale or prolong the noninvasive ventilation management phase (22).

In the online community PatientsLikeMe, 112 members report receiving Nuedexta as a treatment for ALS, of whom 45 completed treatment evaluation. Thirteen patients reported slight to major improvements in bulbar functions, but most evaluations did not specify whether the effectiveness was in PBA or bulbar function. We could not validate the ALS diagnosis and the subjective benefits described in these cases.

Because there was one peer-reviewed publication reporting benefits with validated diagnosis and benefits, we assign a TOE "Cases" grade of A (Table 1).

Trials

A phase II multicenter, randomized, double-blind, placebo-controlled cross-over study (NCT01806857) was conducted to assess the effect of Nuedexta on bulbar function in ALS (23). In this study, 60 PALS received either Nuedexta or a placebo for 28 to 30 days, followed by a 10 to 15-day washout period. Subsequently, patients were switched to the opposite treatment arm for the remaining 28 to 30 days. The primary endpoint was the self-reported Center for Neurologic Study Bulbar Function Scale (CNS-BFS) change. CNS-BFS measures functions of speech, swallowing, and salivation- for each domain, patients rate seven questions on a scale of 1 to 5 (least to most affected), allowing a global score from 21 to 112, and a higher score indicates worse bulbar function (24). The Nuedexta treatment group demonstrated statistically significant improvements in the global CNS-BFS score (mean 59.3 vs. 53.5, $p < 0.001$) and in each bulbar domain. This improvement was seen in both PALS with PBA and without PBA. Notably, half of the study patients improved by one or more in the bulbar domain of ALSFRS-R, while the motor and respiratory sub-scores did not change.

A prospective, multicenter pilot study was conducted to evaluate the effect of Nuedexta on bulbar physiology in PALS (NCT03883581). The study assessed multiple outcomes including changes in speech intelligibility, ALSFRS-R bulbar subscale score, patient-reported outcome through CNS-BFS, validated Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) safety and efficiency severity grades, and speech duration of a 60-word reading passage. The preliminary result of this study was presented at the 21st Northeast Amyotrophic Lateral Sclerosis Consortium (NEALS) Annual Meeting in November 2022. Twenty-five patients who were treated with 30-day Nuedexta demonstrated significant improvement in their ALSFRS-R bulbar subscores compared to their baseline (7.47 vs. 8.39, mean difference of 0.92, $p < 0.0004$). The results also showed a longer duration of uninterrupted speech (2.62 vs. 2.96 seconds, $p = 0.035$), but the speech intelligibility did not improve. Furthermore, the quantitative swallowing function measurement revealed reductions in the proportion of unsafe (75% vs. 44%, $p = 0.003$) and inefficient (67% vs. 58%, $p = 0.002$) swallowers after Nuedexta treatment (25).

ALSUntangled assigns a TOE "Trials" grade of C (Table 1).

Dosing, risks, and costs

Nuedexta contains 20 mg dextromethorphan hydrobromide and 10 mg quinidine sulfate per capsule. It is given one capsule daily for the first seven days, followed by one capsule twice daily. The safety profile of Nuedexta was evaluated in a 52-week open-label study of 553 patients with PBA from ALS and other neurological conditions, including MS, stroke and TBI (NCT00056524). 91.8% of patients reported at least one adverse event (AE). The most common AEs were nausea (11.8%), dizziness (10.5%), headache (9.9%), somnolence (7.2%), fatigue (7.1%), diarrhea (6.5%), and dry mouth (5.1%). Most AEs were mild or moderate, occurred early in therapy and were transient (26). The incidence of severe AEs was 22.8% but was largely due to disease progression rather than being treatment related. Though quinidine is known to cause dose-dependent QT prolongation and ventricular arrhythmia, there were no clinically significant arrhythmias reported at 10–30 mg daily dose during Nuedexta clinical trials. Electrocardiography data showed mostly mild QTc interval increases (QTcF 3.2 msec; QTcB 4.6 msec) from baseline. Less than 1% of participants had QTc increase >60 msec and none had QTc >500 msec during the study period. Two patients had QTc > 500 msec during elective treatment extension. Similar AE profiles were found in Nuedexta clinical trials in PALS (23,27,28). Nuedexta is contraindicated in patients with a known history of prolonged QT interval, congenital long QT syndrome, and complete atrioventricular block. When starting Nuedexta in patients at risk of QT prolongation, including left ventricular hypertrophy and dysfunction and concomitant use of QT prolonging drugs, ECG should be evaluated at baseline and 3–4 hours after the first dose. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021879s000lbl.pdf).

Because at least 10% of exposed patients experienced side effects, ALSUntangled assigns a TOE "Risks" grade of C (Table 1).

The monthly cost of Nuedexta is approximately $1500 in the United States. Most insurance plans only cover Nuedexta for treating PBA.

Conclusion

Nuedexta has plausible mechanisms for improving bulbar function in PALS. Some PALS reported concomitant improvement in bulbar function for at least a short period when taking Nuedexta for PBA. A well-designed phase II trial in PALS demonstrated the efficacy of Nuedexta in patient-reported bulbar function, and the preliminary result of another trial showed improvement in bulbar physiology. However, its long-term effect on bulbar function is unclear, and one open-label study showed a lack of benefit in one year. There is no evidence suggesting Nuedexta slows down ALS progression or prolongs survival. Nuedexta causes mild to moderate side effects, but severe side effects directly caused by Nuedexta have not been reported. It should be avoided in patients with known history of prolonged QT interval. Given all this, we feel there is sufficient evidence to consider Nuedexta treatment for bulbar dysfunction in ALS patients with and without PBA. Financial burden and periodic assessment of its efficacy should be considered for the latter.

Declaration of interest

Richard Bedlack has research support from ALSA, Orion, MediciNova, and the Healey Center, and consulting support from AB Science, Alexion, ALSA, Amylyx, Biogen, Black Swan, Brainstorm Cell, Cytokinetics, Guidepoint, ITF Pharma, Mallinkrodt, New Biotic, Orphazyme, PTC Therapeutics, Projects in Knowledge, Shinkei and Woolsey Pharma.

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Funding

ALSUntangled is sponsored by the ALS Association (Grant 23-SI-622).

ORCID

Michael Benatar http://orcid.org/0000-0003-4241-5135
Paul Wicks http://orcid.org/0000-0002-2293-9284

References

1. Choi DW. Dextrorphan and dextromethorphan attenuate glutamate neurotoxicity. Brain Res. 1987; 403:333–6.
2. Musacchio JM, Klein M, Paturzo JJ. Effects of dextromethorphan site ligands and allosteric modifiers on the binding of (+)-[3H]3-(-3-hydroxyphenyl)-N-(1-propyl)piperidine. Mol Pharmacol. 1989; 35 :1–5.
3. Zhang Y, Britto MR, Valderhaug KL, Wedlund PJ, Smith RA. Dextromethorphan: enhancing its systemic availability by way of low-dose quinidine-mediated inhibition of cytochrome P4502D6. Clin Pharmacol Ther. 1992; 51: 647–55.
4. Nguyen L, Thomas KL, Lucke-Wold BP, Cavendish JZ, Crowe MS, Matsumoto RR, et al. Dextromethorphan: an update on its utility for neurological and neuropsychiatric disorders. Pharmacol Ther. 2016; 159:1–22.
5. Gundlach AL, Largent BL, Snyder SH. Autoradiographic localization of sigma receptor binding sites in guinea pig and rat central nervous system with (+)3H-3-(3-hydroxyphenyl)-N-(1-propyl)piperidine. J Neurosci. 1986; 6:1757–70.
6. Mavlyutov TA, Epstein ML, Andersen KA, Ziskind-Conhaim L, Ruoho AE. The sigma-1 receptor is enriched in postsynaptic sites of C-terminals in mouse motoneurons. An anatomical and behavioral study. Neuroscience 2010; 167:247–55.
7. Berry JD, Shefner JM, Conwit R, Schoenfeld D, Keroack M, Felsenstein D, et al. Design and initial results of a multi-phase randomized trial of ceftriaxone in amyotrophic lateral sclerosis. PLOS One. 2013; 8:e61177.
8. Hayashi T, Su TP. Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca(2+) signaling and cell survival. Cell 2007; 131: 596–610.
9. Ha Y, Dun Y, Thangaraju M, Duplantier J, Dong Z, Liu K, et al. Sigma receptor 1 modulates endoplasmic reticulum stress in retinal neurons. Invest Ophthalmol Vis Sci. 2011; 52: 527–40.
10. Meunier J, Hayashi T. Sigma-1 receptors regulate Bcl-2 expression by reactive oxygen species-dependent transcriptional regulation of nuclear factor kappaB. J Pharmacol Exp Ther. 2010; 332: 388–97.
11. Lobner D, Lipton P. Sigma-ligands and non-competitive NMDA antagonists inhibit glutamate release during cerebral ischemia. Neurosci Lett. 1990; 117:169–74.
12. Balasuriya D, Stewart AP, Edwardson JM. The σ-1 receptor interacts directly with GluN1 but not GluN2A in the GluN1/GluN2A NMDA receptor. J Neurosci. 2013; 33:18219–24.
13. Zhang X-J, Liu L-L, Jiang S-X, Zhong Y-M, Yang X-L. Activation of the ζ receptor 1 suppresses NMDA responses in rat retinal ganglion cells. Neuroscience 2011; 177:12–22.
14. Mancuso R, Oliván S, Rando A, Casas C, Osta R, Navarro X, et al. Sigma-1R agonist improves motor function and motoneuron survival in ALS mice. Neurotherapeutics. 2012; 9:814–26.
15. Peviani M, Salvaneschi E, Bontempi L, Petese A, Manzo A, Rossi D, et al. Neuroprotective effects of the Sigma-1 receptor (S1R) agonist PRE-084, in a mouse model of motor neuron disease not linked to SOD1 mutation. Neurobiol Dis. 2014; 62:218–32.
16. Mavlyutov TA, Guo L-W, Epstein ML, Ruoho AE. Role of the Sigma-1 receptor in amyotrophic lateral sclerosis (ALS). J Pharmacol Sci. 2015; 127:10–6.
17. Ono Y, Tanaka H, Takata M, Nagahara Y, Noda Y, Tsuruma K, et al. SA4503, a sigma-1 receptor agonist, suppresses motor neuron damage in in vitro and in vivo amyotrophic lateral sclerosis models. Neurosci Lett. 2014; 559:174–8.
18. DeCoster MA, Klette KL, Knight ES, Tortella FC. Sigma receptor-mediated neuroprotection against glutamate toxicity in primary rat neuronal cultures. Brain Res. 1995; 671:45–53.
19. Liu Y, Qin L, Li G, Zhang W, An L, Liu B, et al. Dextromethorphan protects dopaminergic neurons against inflammation-mediated degeneration through inhibition of microglial activation. J Pharmacol Exp Ther. 2003; 305: 212–8.
20. Zhang W, Wang T, Qin L, Gao H-M, Wilson B, Ali SF, et al. Neuroprotective effect of dextromethorphan in the

MPTP Parkinson's disease model: role of NADPH oxidase. Faseb J. 2004; 18: 589–91.
21. Shah NS, et al. Dextromethorphan-Quinidine (Nuedexta) improves swallowing in Bulbar onset ALS patients with pseudobulbar affect - pre-post observational study in 86 ALS patients (P4.4-019). Neurology 2019; 92:P4.4–019.
22. Sancho J, Ferrer S, Burés E, Luis Díaz J, Torrecilla T, Signes-Costa J, et al. Effect of one-year dextromethorphan/quinidine treatment on management of respiratory impairment in amyotrophic lateral sclerosis. Respir Med. 2021; 186:106536.
23. Smith R, Pioro E, Myers K, Sirdofsky M, Goslin K, Meekins G, et al. Enhanced bulbar function in amyotrophic lateral sclerosis: the nuedexta treatment trial. Neurotherapeutics. 2017; 14:762–72.
24. Smith RA, Macklin EA, Myers KJ, Pattee GL, Goslin KL, Meekins GD, et al. Assessment of bulbar function in amyotrophic lateral sclerosis: validation of a self-report scale (center for neurologic study bulbar function scale). Eur J Neurol. 2018; 25:907–e66.
25. Proceedings of the 21st Annual Meeting of the Northeast ALS Consortium. Muscle & Nerve, 2022; 66(S2): S1–S63.
26. Pattee GL, Wymer JP, Lomen-Hoerth C, Appel SH, Formella AE, Pope LE, et al. An open-label multicenter study to assess the safety of dextromethorphan/quinidine in patients with pseudobulbar affect associated with a range of underlying neurological conditions. Curr Med Res Opin. 2014; 30:255–65.
27. Brooks BR, Thisted RA, Appel SH, Bradley WG, Olney RK, Berg JE, et al. Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine: a randomized trial. Neurology 2004; 63:1364–70.
28. Pioro EP, Brooks BR, Cummings J, Schiffer R, Thisted RA, Wynn D, et al. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. Ann Neurol. 2010; 68:693–702.