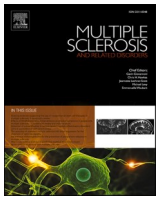
Multiple Sclerosis and Related Disorders 63 (2022) 103925

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



Efficacy of Fluoxetine, Riluzole and Amiloride in treating neuropathic pain associated with secondary progressive multiple sclerosis. Pre-specified analysis of the MS-SMART double-blind randomised placebo-controlled trial

Peter Foley [a,*], Richard A Parker [b], Floriana de Angelis [c], Peter Connick [a], Siddharthan Chandran [a], Carolyn Young [d], Christopher J Weir [b], Jeremy Chataway [c], for the MS-SMART Investigators

[a] Anne Rowling Regenerative Neurology Clinic, Chancellor's Building, University of Edinburgh, 49 Little France Crescent, Edinburgh EH16 4SB, United Kingdom
[b] Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh, Edinburgh, United Kingdom
[c] Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, University College London, London, United Kingdom
[d] Walton Centre NHS Foundation Trust, Lower Lane, Fazakerley, Liverpool L9 7LJ, United Kingdom

ARTICLE INFO

Keywords:
Pain
Neuropathic pain
Multiple sclerosis
Secondary progressive multiple sclerosis
Analgesia
Randomized controlled trial
Serotonin uptake inhibitor

ABSTRACT

Background: Evidence-based treatment of pain in people with MS presents a major unmet need.
Objective: We aimed to establish if use of Fluoxetine, Riluzole or Amiloride improved neuropathic pain outcomes in comparison to placebo, in adults with secondary progressive MS participating in a trial of these putative neuroprotectants.
Methods: In pre-specified secondary analyses of the MS SMART phase-2b double-blind randomised controlled trial (NCT01910259), we analyzed reports of neuropathic pain, overall pain, and pain interference. Multivariate analyses included adjustment for baseline pain severity. Additionally, we explored associations of pain severity with clinical and MRI brain imaging variables.
Results: 445 Participants were recruited from 13 UK neuroscience centres. We found no statistically significant benefit of active intervention on any rating of neuropathic pain, or pain overall. Compared to placebo, adjusted mean difference in pain intensity was 0.38 (positive values favouring placebo, 95%CI -0.30 to 1.07, $p = 0.27$) for Amiloride; 0.52 (-0.17 to 1.22, $p = 0.14$) for Fluoxetine; and 0.40 (-0.30 to 1.10, $p = 0.26$) for Riluzole. Pain severity was positively correlated with depressive symptoms (Spearman correlation 0.19, 95%CI 0.10–0.28) and fatigue (Rho 0.30, 95%CI 0.20–0.39).
Conclusion: Use of Fluoxetine, Riluzole or Amiloride was not associated with improvement in neuropathic pain symptoms, in comparison to placebo.

1. Introduction

Pain is a major priority for people with MS (pwMS) (Heesen et al., 2018) and, in particular, affects approximately 70% of people with Secondary progressive MS (SPMS) (Foley et al., 2013). There is however limited evidence on which to base treatment decisions (Jawahar et al., 2013). Expansion of this evidence base constitutes a major unmet need.

The MS-SMART trial was a phase 2b randomised controlled trial of three putative neuroprotective agents (Amiloride, Fluoxetine and Riluzole) separately tested against placebo, and including 445 adults with SPMS across 13 UK neuroscience centres. The primary outcome measure was percentage brain volume loss over the 96 week duration of treatment (Chataway et al., 2020). Secondary outcomes included clinician-determined and patient-reported outcome measures, specifically including neuropathic pain (Dworkin et al., 2005). Neuropathic pain severity was assessed in the whole trial cohort using the Neuropathic Pain Scale (NPS) (Galer and Jensen, 1997). Because of potential mixed neuropathic and nociceptive pain syndromes in our population

* Corresponding author.
E-mail address: peter.foley@nhslothian.scot.nhs.uk (P. Foley).

https://doi.org/10.1016/j.msard.2022.103925
Received 25 March 2022; Received in revised form 20 May 2022; Accepted 27 May 2022
Available online 28 May 2022

(Foley et al., 2013; Taxonomy, 2011), we additionally measured severity of overall pain (including nociceptive and other pain aetiologies), and pain interference (Cleeland, 1989).

The agents investigated in MS-SMART are widely used and well tolerated (Chataway et al., 2020). They were selected, after systematic review, because of potential neuroprotective actions (Chataway et al., 2020; Vesterinen et al., 2015). Possible analgesic actions have however been suggested for all three agents. Riluzole is known to inactivate voltage-dependant sodium channels and to depress glutamatergic neurotransmission, both of which mechanisms are relevant to neuropathic pain (Galer et al., 2000). A small study of peripheral neuropathic pain disorders in human adults did not demonstrate a significant beneficial effect (Galer et al., 2000), though a previously reported analgesic effect of dextromethorphan/quinidine in pwMS has been attributed to glutamatergic mechanisms (Panitch et al., 2006). Fluoxetine, a selective serotonin reuptake inhibitor widely used for depression, has been found to have beneficial effects on pain in fibromyalgia (Arnold et al., 2002) neuropathy and migraine (Patetsos and Horjales-Araujo, 2016). Amiloride blocks acid-sensing ion channels, which have been implicated in both central and peripheral mechanisms of pain (Wemmie et al., 2013), and has been trialled in human pain conditions including migraine (Holland et al., 2012). Evidence of effective analgesia associated with these agents could expand treatment targets in MS-related neuropathic pain, beyond current commonly-used treatment classes which include anticonvulsant and antidepressant medications (Jawahar et al., 2013).

In addition to investigation of potential analgesic efficacy of the study agents, examination of relationships between pain severity, clinical and MRI imaging variables might improve understanding of pain mechanisms. For instance, despite known associations of pain disorders with brain grey matter volume loss in disorders other than MS (Smallwood et al., 2013), any associations of pain with MS lesions or grey matter volume alterations in pwMS remain unclear (Seixas et al., 2014). Any associations with cognitive performance (Heitmann et al., 2020) or prior disease modifying therapy use (Foley et al., 2013; Seixas et al., 2014) likewise remain unknown.

We report here a pre-planned analysis of neuropathic pain severity from the entire cohort of people with SPMS enroled in the MS-SMART trial. We hypothesised an effect of one or more of the experimental trial agents on neuropathic pain severity, based on their putative effects on pain pathways. Additionally, we explored associations of overall pain severity with clinical and MRI brain imaging variables at study baseline.

2. Methods

2.1. Summary of trial methodology

The methodology of the MS-SMART trial is described in detail separately (Chataway et al., 2020; Connick et al., 2018). Briefly, adults aged from 25 to 65 with confirmed secondary progressive MS were recruited across 13 neuroscience centres in the UK from December 2014 (first randomisation January 2015) to June 2016, and followed up for 96 weeks. Inclusion criteria included Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) between 4.0 and 6.5 (maximum disability mobile with bilateral aid), clinical evidence of progressive disability within the preceding 2 years, and no use of MS disease-modifying therapies within the last 6–12 months (depending on the agent). Exclusion criteria included moderate-severe depression (Beck Depression Index II score >19) (Beck et al., 1961), epilepsy, recent MS relapse or corticosteroid administration and concurrent treatment with Serotonin Reuptake Inhibitors (SSRIs).

2.2. Randomisation and blinding

Participants were randomised within 30 days of screening for enrolment using a centralised online service provided by the Edinburgh Clinical Trials Unit (Usher Institute, University of Edinburgh, Edinburgh, UK). Group assignation included minimisation by sex, age (<45 years old vs 45 and older), EDSS score (4.0 to 5.5 vs 6.0 to 6.5) and trial site, as well as an additional random element (Chataway et al., 2020). Participants and investigators were unaware of allocated treatments.

2.3. Trial interventions

According to treatment allocations, participant received Fluoxetine 20 mg, Riluzole 50 mg, Amiloride 5 mg or placebo tablets once daily for 4 weeks, and then twice daily until trial completion (week 96). All study agents were over-encapsulated and appeared identical. Compliance was confirmed at each trial visit.

2.4. Sample size

We calculated that a sample size of 110 patients for each of four study arms would provide 90% statistical power in a covariance analysis, to detect 40% reduction in percentage brain volume change in comparison to placebo (allowing for an anticipated drop-out rate of 10%) (Chataway et al., 2020; Connick et al., 2018).

2.5. Data collection and pain measures

The primary endpoint of the MS-SMART study was percentage MRI brain volume change between baseline and 96 weeks. A number of secondary endpoints were additionally collected (Chataway et al., 2020) at baseline (0 weeks), 48 weeks and 96 weeks.

The principal outcome measure for severity of neuropathic pain symptoms was the Neuropathic Pain Scale (NPS) (Galer and Jensen, 1997). The NPS generates eleven items, eight of which quantify severity of particular neuropathic pain qualities (“sharp”, “hot”, “dull”, “cold”, “sensitive”, “Itchy”, “deep intensity” and “surface intensity”). Additional items assess pain intensity overall and unpleasantness. One NPS item (Question 8) records temporal and qualitative accounts of pain characteristics and is not included in the current analysis. The remaining ten items were individually scored from minimum 0 to maximum 10. NPS sum score (Argoff et al., 2004) was generated by adding these scores (range 0–100). For participants where scores for one or more NPS items (excluding Question 8) were missing, NPS sum score was excluded from analysis.

We additionally included a measure of the severity of pain of any aetiology, in the week preceding questionnaire completion. Participants were asked to rate pain on average over the past week (Numerical Rating Scale, anchors at 0 “no pain”, and 10 “pain as bad as you can imagine”) (termed here “overall pain severity”) (Cleeland, 1989; Tan et al., 2004). We also used Brief Pain Inventory items to measure pain interference with general activity, mood, walking ability, work, interpersonal relations, sleep, and enjoyment of life (Numerical Rating Scale, anchors at 0 “does not interfere” to 10 “completely interferes” scored separately for each item). We calculated the mean of these pain interference estimates (range 0–10) as a measure of pain interference overall (Cleeland, 1989; Tan et al., 2004).

2.6. Data analysis

Our principal outcome of interest was Neuropathic Pain Scale data at study completion (96 weeks), analyzed using multiple linear regression models. We analyzed individual questionnaire items rather than any total score, since the items are individually meaningful. Adjusted mean differences and 95% CIs for the individual comparisons between each investigational treatment and placebo were calculated. The multiple regression models included trial arm as an explanatory factor variable (with placebo as the reference category), the baseline value (of the outcome variable being analyzed), and the minimisation variables: age, sex, treatment centre and EDSS at randomisation. Treatment centre was

included as an explanatory factor variable. Pre-specified analyses were applied to the entire trial cohort. In additional post-hoc analyses requested by a peer reviewer, identical multiple linear regression models were repeated in a subgroup excluding participants who reported a pain intensity of zero at trial entry (Neuropathic Pain Scale, Item One). Analyses employed SAS version 9.4 (SAS Institute, Cary, NC, USA) and R v3.6.1 (https://www.R-project.org/). Statistical significance was accepted at the two-sided 5% level. Unadjusted ratings of overall pain severity at baseline and study completion (96 weeks) were presented graphically to allow data visualisation. For clarity, availability of NPS data during follow up was assessed using a single NPS item (question 1, which quantifies pain intensity overall).

2.7. Exploratory analysis of associations with pain severity at baseline visit

In addition, because of limited existing data concerning mechanisms and associations of neuropathic pain in SPMS (Foley et al., 2013; Seixas et al., 2014), we used the nonparametric Wilcoxon Rank Sum Test and Spearman correlation to explore associations between overall pain severity (and NPS sum score Argoff et al., 2004), with demographic, clinical and imaging variables at baseline study visit. We included prior disease modifying therapy (DMT) exposure at any time (binary variable, yes or no). We furthermore dichotomised previous use of Disease Modifying Therapies into higher or lower efficacy treatment, according to whether monoclonal antibody therapy had been used at any time and for any duration (Harding et al., 2019). MRI brain imaging variables (total brain volume, whole brain T2 hyperintense lesion volume, cortical grey matter volume and deep grey matter volume) were calculated as previously described (Chataway et al., 2020; Connick et al., 2018) and expressed as a proportion of intracranial volume in subject space. Additional clinical variables included disease duration (participant-reported time since first demyelinating event), use of neuropathic analgesia at study entry, use of non-neuropathic analgesia at study entry, Symbol Digit Modalities Test (Parmenter et al., 2007), Paced Auditory Serial Addition Test (Fischer et al., 1999), Expanded Disability Status Scale (Kurtzke, 1983), and Neurological Fatigue Index (Mills et al., 2010).

2.8. Trial preregistration and ethical consents

This trial was registered at ClinicalTrials.gov (NCT01910259), and was carried out in accordance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines. All participants provided written informed consent. Independent ethics approval was granted (REC 13/SS/0007). A Data Monitoring Committee reviewed participant data at 6 months intervals, and medical monitoring was carried out at each individual site.

3. Results

3.1. Baseline sample characteristics

445 participants with SPMS were recruited into the trial. 112 participants were allocated to placebo, and 111 to each of Fluoxetine, Riluzole and Amiloride. Baseline demographic and clinical characteristics were comparable between study groups (Table 1). At baseline, overall pain intensity over the preceding week (Numerical Rating Scale, anchors at 0 “no pain” and 10 “pain as bad as you can imagine”) was 3.07 (moderate pain severity Alschuler et al., 2012).

Percentage loss to follow-up was 5–9% across study groups. NPS pain intensity rating was available for 442 participants at baseline (99.3% of total; Fluoxetine group 111 participants, Riluzole 109, Amiloride 110 and Placebo 112); and 382 at 96 weeks (85.8% of total; Fluoxetine group 93 participants, Riluzole 94, Amiloride 98 and Placebo 97) (Fig. 1). Full baseline NPS data including ratings of individual sensory symptoms is presented in the online supplement (Supplement).

Table 1
Demographic and Clinical variables at study entry.

	Allocated Treatment				
	Fluoxetine (*n* = 111)	**Riluzole (*n* = 111)**	**Amiloride (*n* = 111)**	**Placebo (*n* = 112)**	**Overall (*n* = 445)**
Age (years)	55.5 (50.7 to 60.2)	55.1 (49.8 to 59.1)	55.2 (49.0 to 60.4)	56.4 (49.2 to 60.4)	55.5 (49.7 to 60.3)
Female Sex	74 (67%)	74 (67%)	75 (68%)	75 (67%)	298 (67%)
Time since first symptoms (years)	21.0 (16.0 to 29.0)	21.0 (16.0 to 26.0)	20.0 (13.5 to 29.5)	19.0 (13.0 to 29.0)	21.0 (15.0 to 29.0)
Expanded Disability Status Scale score	6.0 (5.5 to 6.5)	6.0 (5.8 to 6.5)	6.0 (5.8 to 6.5)	6.0 (5.9 to 6.5)	6.0 (5.5 to 6.5)
Overall pain severity in preceding week	2.0 (0.0 to 4.0)	3.0 (1.0 to 5.0)	3.0 (0.25 to 5.0)	3.0 (1.0 to 5.0)	3.0 (1.0 to 5.0)
NPS pain intensity	2.0 (0.0 to 4.0)	3.0 (1.0 to 6.0)	2.0 (0.0 to 6.0)	2.0 (1.0 to 5.0)	2.0 (0.25 to 5.0)
Neuropathic Analgesia	36 (32.4%)	47 (42.3%)	44 (39.6%)	47 (41.9%)	174 (39.1%)
Non-neuropathic analgesia	52 (46.9%)	48 (43.2%)	48 (43.2%)	48 (42.9%)	196 (44.0%)
Beck Depression Index II score	6.0 (3.0 to 10.0)	7.0 (4.0 to 12.0)	6.0 (4.0 to 9.0)	7.0 (4.0 to 12.0)	6.0 (4.0 to 11.0)
Neurological Fatigue Index Summary score	17.6 (14.6 to 20.8)	18.4 (16.0 to 22.0)	17.6 (15.3 to 20.1)	17.6 (15.3 to 20.1)	17.6 (15.3 to 21.0)
Symbol Digit Modalities Test	46.0 (36.5 to 52.0)	45.0 (35.0 to 53.0)	46.0 (34.0 to 51.0)	46.5 (35.8 to 51.0)	46.0 (35.0 to 52.0)
Paced Auditory Serial Addition Test	36.6 (26.0 to 50.0)	40.0 (26.5 to 50.0)	41.0 (30.0 to 48.5)	44.0 (34.0 to 52.2)	40.5 (29.0 to 50.0)

Data presented are n (%), or median (Interquartile range).
NPS: Neuropathic Pain Scale.

3.2. Overall pain intensity at baseline, and study completion

Unadjusted scores for overall pain severity in the preceding week (Numerical Rating Scale, range 0–10) were visualised by boxplot in the study cohort overall, and each study group individually. Median pain intensity ranged between two and four out of ten in all study groups, both at study baseline and completion (Fig. 2).

In regression analyses of individual NPS items at study completion (96 weeks), no statistically significant benefit in neuropathic pain symptoms was identified in participants receiving Amiloride, Fluoxetine or Riluzole, relative to placebo. Similarly, no statistically significant benefit in overall pain, or pain interference, was identified at study completion in any study group (Table 2).

In identical analyses at 48 weeks (study midpoint), no statistically significant benefit in any pain outcome measure, relative to participants receiving placebo, was identified (Supplement). In 331 participants who reported pain at trial entry (74.9% of participants), post-hoc analyses were congruent with results of the pre-specified analyses (Supplement).

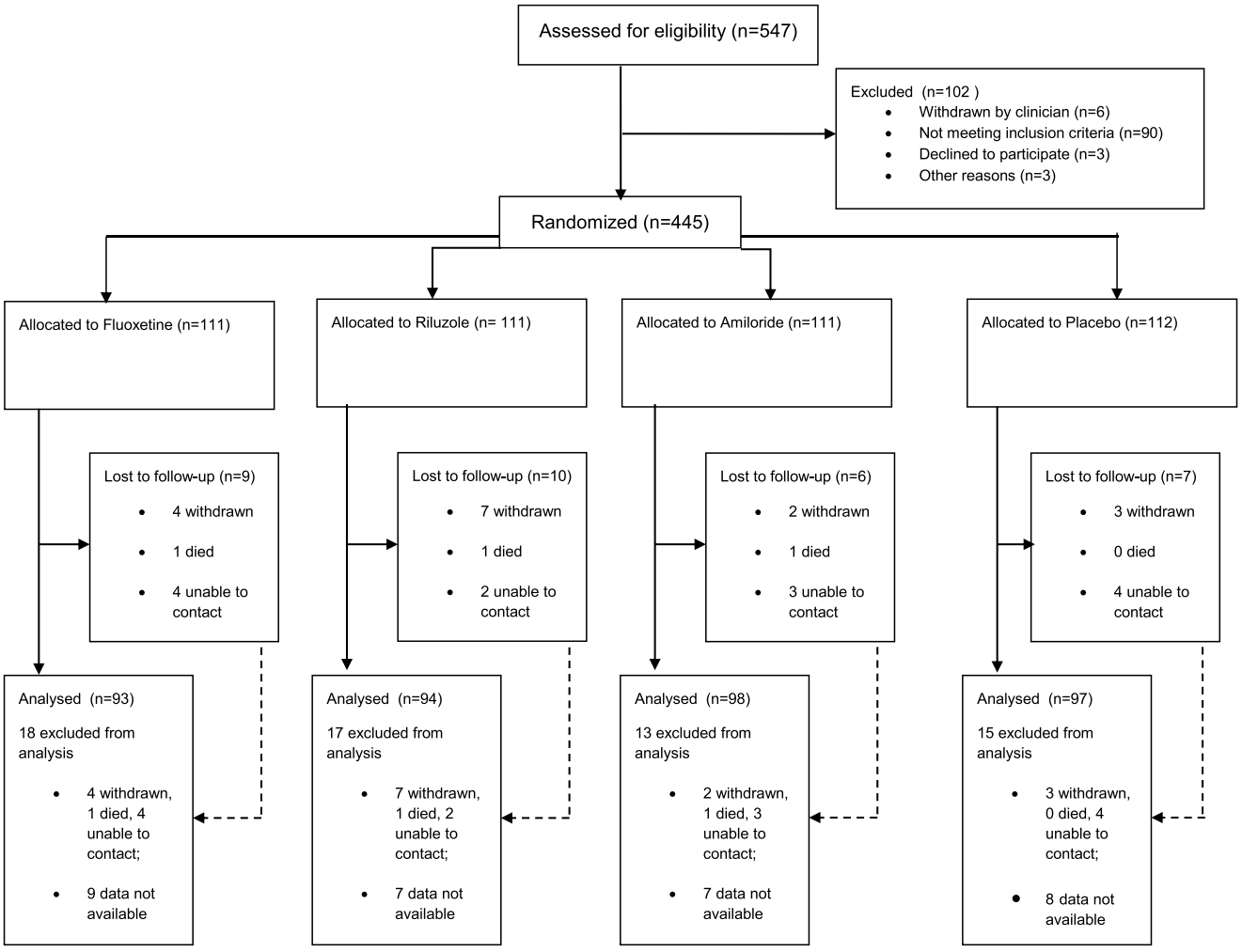


Fig. 1. CONSORT flowchart. For clarity, availability of NPS data during follow up was assessed using a single NPS item (question one, which quantifies pain intensity overall).

3.3. Exploration of associations between overall pain severity, clinical and imaging variables at baseline

Overall pain severity (Cleeland, 1989) did not vary to a statistically significant degree by participant sex (female median 3.0, IQR 1.0–5.0; male median 3.0, IQR 3.2–5.0; Wilcoxon rank sum test $p = 0.33$); by prior DMT use overall (previous use of any DMT median 3.0, IQR 1.0–5.0; never used DMT median 3.0, IQR 1.0–5.0; Wilcoxon rank sum test $p = 0.77$) or by prior use of high-efficacy DMT in comparison to other DMT (previous high-efficacy DMT use median 2.0, IQR 0.0–4.0; previous DMT use without high-efficacy DMT median 3.0, IQR 1.0 to 5.0; Wilcoxon rank sum test $p = 0.27$). Overall pain severity was weakly positively correlated with depressive and fatigue symptoms, to a statistically significant degree. Overall pain severity was not correlated with other clinical or imaging variables examined (Table 3).

In identical analyses examining associations of NPS sum score (Galer and Jensen, 1997), a weak yet statistically significant correlation with depressive and fatigue symptomatology was similarly identified (Supplement).

3.4. Adverse events

A detailed description of adverse events during the study has been presented elsewhere (Chataway et al., 2020). No emergent safety concerns were identified. Three deaths occurred during the study (one each in Amiloride, Fluoxetine and Riluzole trial arms). These were judged by the Data Monitoring Committee to be unrelated to study treatments.

3.5. Participant and investigator blinding

Successful blinding was additionally confirmed by questionnaire at study exit (96 weeks). 51% of participants and 59% of clinicians correctly guessed participants' group membership (active treatment vs placebo).

4. Discussion

We describe here a pre-specified secondary analysis of the MS-SMART double-blind randomised controlled trial, including 445 adults with SPMS. Neuropathic pain outcomes were analyzed in the entire trial cohort at baseline and study completion (96 weeks), in three separate intervention arms separately compared to a placebo arm. At baseline, the moderate pain severity (Alschuler et al., 2012) described by our cohort, in keeping with previous studies (Heitmann et al., 2020), underscores the importance of pain in this population. However, administration of Fluoxetine Riluzole or Amiloride was not associated with improvement in neuropathic pain symptoms (Galer and Jensen, 1997), in comparison to placebo. We consider that the 95% confidence intervals described, along with convergent results, appreciable sample size and good data availability, are consistent with a lack of effect. We also found no statistically significant improvement in overall pain scores (Cleeland, 1989), nor in pain interference (Cleeland, 1989). Furthermore,

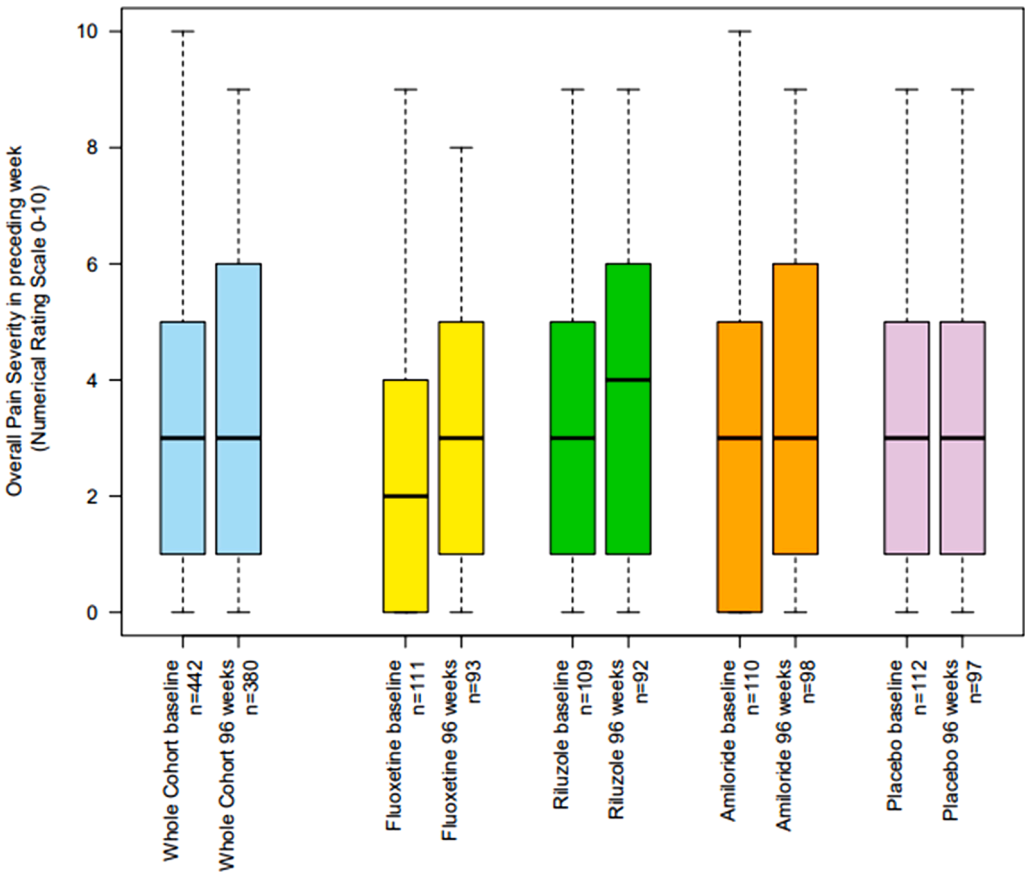


Fig. 2. Average pain severity (unadjusted) over the preceding week, by allocated treatment group, at baseline and study completion. Horizontal lines denote median and interquartile range. Whiskers extend to minimum and maximum values.

additional post-hoc analyses excluding participants reporting no pain at trial entry were congruent with these findings. In exploratory analyses, pain severity at baseline was correlated with depressive and fatigue symptoms, however not with other examined clinical, neuropsychological or MRI imaging variables.

The agents tested in this trial were identified as putative neuroprotective agents on the basis of systematic review evidence (Chataway et al., 2020; Vesterinen et al., 2015) and were not selected specifically for actions on neuropathic pain. They have however been investigated for use in neuropathic pain in preclinical and clinical models based on actions on glutamatergic signalling (riluzole), serotonergic signalling (fluoxetine) and acid-sensing ion channels (amiloride) (Galer et al., 2000; Panitch et al., 2006; Arnold et al., 2002; Patetsos and Horjales-Araujo, 2016; Holland et al., 2012). The present study therefore presents a valuable opportunity to assess the potential analgesic efficacy of these medications in a population commonly affected by neuropathic pain, and to expand understanding of potential treatment targets in MS-related pain disorders (Foley et al., 2013; Jawahar et al., 2013; Rommer et al., 2019).

While chronic neuropathic pain in multiple sclerosis, and in human disease more generally, remains a major unmet need (Heesen et al., 2018), its mechanisms remain incompletely understood, and treatment efficacy is typically modest (Finnerup et al., 2015). In multiple sclerosis specifically, evidence for neuropathic pain treatments is limited. A systematic review identified only a small evidence base on which to base pain treatment decisions, with typically small trial sample sizes in comparison to the current study, and with no previous study recruiting a pure SPMS cohort (Jawahar et al., 2013). Our reported results do not support use of the study agents to treat pain in people with SPMS. However the reported data do add significantly to the limited evidence base available to clinicians treating pwMS who experience neuropathic pain. Further trials of treatments for neuropathic pain in pwMS are needed. Future trials of disease modifying therapies in pwMS may also usefully incorporate pain outcome measures.

Our use of the Neuropathic Pain Scale is not intended to allow dichotomisation of pain aetiologies into neuropathic and non-neuropathic pain, but rather to capture the extent of neuropathic pain symptoms and their modification by trial interventions (Argoff et al., 2004; Rog et al., 2007). Use of a range of patient-reported measures including NPS items, overall pain severity (including pain of any aetiology) and of pain interference (Cleeland, 1989), as well as fatigue, depression and other symptoms (Beck et al., 1961; Mills et al., 2010), furthermore allows assessments of multiple facets of our participants' experience of pain, in keeping with international recommendations (Dworkin et al., 2005) .

Chronic pain in multiple sclerosis is commonly associated with depressive symptoms (Kalia and O'Connor, 2005; Heitmann et al., 2020) and we further confirmed this association in our cohort. Potential participants with moderate-severe depression (Beck et al., 1988) were however excluded from participation in this study (because their inclusion might have precluded separate, clinically indicated, treatment of depression, including with SSRI medication (Solaro et al., 2018)). We do not consider that exclusion of more-depressed pwMS is likely to influence assessment of analgesic efficacy of the included study agents. In particular, exclusion of participants suffering significant depression may help to distinguish analgesic effects of medication from the well-established effects of SSRIs on mood (Solaro et al., 2018). We did not however assess depressive symptoms longitudinally, therefore are unable to report efficacy of the study agents on depressive symptoms within this trial.

In an exploratory analysis, we found that overall pain severity at study baseline was weakly correlated with depressive (Beck et al., 1961)

Table 2
Analysis of Pain reports at 96 weeks.

Outcome variable		N	Trial agent: Fluoxetine				Trial agent: Riluzole				Trial agent: Amiloride			
			AMD (Fluoxetine–Placebo)	95% Confidence Limits for AMD		P-value	AMD (Riluzole – Placebo)	95% Confidence Limits for AMD		P-value	AMD (Amiloride-Placebo)	95% Confidence Limits for AMD		p-value
Neuropathic Pain Scale (NPS)	Q1: Pain Intensity	379	0.52	−0.17	1.22	0.14	0.40	−0.30	1.10	0.26	0.38	−0.30	1.07	0.27
	Q2: Sharp Pain	384	0.28	−0.46	1.01	0.46	0.39	−0.35	1.13	0.30	0.19	−0.54	0.91	0.61
	Q3: Hot pain	385	0.01	−0.70	0.72	0.98	0.67	−0.03	1.37	0.06	0.33	−0.36	1.02	0.34
	Q4: Dull pain	385	−0.35	−1.12	0.41	0.37	0.32	−0.45	1.08	0.42	−0.19	−0.94	0.56	0.61
	Q5: Cold pain	384	−0.37	−1.08	0.33	0.30	−0.19	−0.89	0.51	0.60	−0.08	−0.77	0.61	0.82
	Q6: Sensitive pain	385	−0.48	−1.16	0.20	0.16	0.50	−0.18	1.19	0.15	−0.14	−0.81	0.53	0.67
	Q7: Itchy pain	385	−0.35	−1.02	0.31	0.29	−0.05	−0.71	0.61	0.89	−0.47	−1.12	0.18	0.16
	Q9: Unpleasant pain	381	−0.26	−0.97	0.45	0.47	0.37	−0.33	1.08	0.30	0.36	−0.33	1.06	0.31
	Q10a: Deep pain intensity	378	0.18	−0.62	0.97	0.67	0.85	0.05	1.66	0.04	0.88	0.09	1.66	0.03
	Q10b: Surface pain intensity	379	−0.45	−1.13	0.22	0.19	0.12	−0.56	0.80	0.73	−0.05	−0.72	0.61	0.88
Overall Pain Severity (preceding week)		374	0.02	−0.58	0.61	0.95	0.14	−0.45	0.73	0.63	0.16	−0.42	0.73	0.60
BPI Pain Interference		388	0.18	−0.44	0.80	0.57	−0.03	−0.65	0.59	0.92	0.42	−0.19	1.02	0.18

AMD: Adjusted mean difference.
Q: Question.
BPI: Brief pain inventory.

and fatigue (Mills et al., 2010) symptoms. These associations have not previously been well defined in people with SPMS specifically (Foley et al., 2013). Our findings are however in keeping with other analyses in pwMS and suggest that further research into shared mechanisms of pain, fatigue and depression is of particular importance (Heitmann et al., 2020). While modulation of serotonergic or glutamatergic signalling, or acid-sensing ion channels, was not associated with analgesia in our study participants, future research into overlapping treatment of pain with depressive and fatigue symptoms (Knowles et al., 2020) may be of interest.

Pain severity was not however associated with a variety of other clinical variables, including age, physical disability (Kurtzke, 1983) or cognitive function (Parmenter et al., 2007; Fischer et al., 1999). We additionally found no association between pain severity and measures of T2 hyperintense lesion volume, cortical or deep grey matter volumes. Although grey matter volume reduction has been repeatedly reported in association with chronic pain states (Smallwood et al., 2013), the association of chronic pain with structural brain MRI variables in pwMS specifically is poorly understood (Seixas et al., 2014). We also describe a lack of association between pain severity, and previous disease modifying therapy use (Harding et al., 2019). Because no therapy is currently known to prevent development of pain in pwMS (Jawahar et al., 2013), future prospective investigation of any long term effect of disease modifying therapies on pain outcomes (Heitmann et al., 2020), including complementary MRI imaging of brain and spine, may be revealing.

We describe results drawn from a large sample, as well as recruitment from a large number of UK neurology centres. In addition, the range of clinical disability present in trial participants (Kurtzke, 1983), and with pain intensity comparable to previous studies of pwMS (Alschuler et al., 2012) suggest that our results may reasonably be generalised to other patients with secondary progressive MS. Further research is needed to confirm if the results apply to people experiencing other MS disease subtypes including primary progressive and relapsing remitting MS.

In conclusion, our results do not support the use of Fluoxetine, Riluzole or Amiloride in management of neuropathic pain associated with secondary progressive MS. From a mechanistic perspective, neither modulation of glutamatergic or serotonergic pathways, nor of acid-sensing ion channels, was associated with analgesia in this population. These results add to a limited yet clinically important evidence base concerning treatment of neuropathic pain in pwMS, and in people with secondary progressive MS in particular.

Data sharing

The MS-SMART study protocol and statistical analysis plan are available on reasonable request to the chief investigator (Prof Jeremy Chataway; j.chataway@ucl.ac.uk). All data requests should be submitted to JC for consideration in the first instance. Access to available fully anonymised data may be granted 12 months after publication, after review by JC and the sponsor (University College London). Requesters will be asked to complete an application form detailing specific requirements, rationale, and proposed use. A data-sharing agreement will need to be signed. Requested data will be made available, along with supporting documentation (eg., data dictionary) on a secure server.

Funding

Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership, UK Multiple Sclerosis Society, and US National Multiple Sclerosis Society. CJW and RAP were also supported in this

Table 3
Correlations of overall pain severity, with clinical and imaging variables at baseline.

		Spearman's Rho (95% CI)	P value
Clinical variables	Age	0.05 (−0.05 to 0.14)	0.34
	Disease Duration	−0.04 (−0.13 to 0.06)	0.44
	Depression (BDI)	0.19 (0.10 to 0.28)	<0.001 *
	Physical disability (EDSS)	0.06 (−0.09 to 0.10)	0.90
	Fatigue (NFI)	0.30 (0.20 to 0.39)	<0.001 *
	PASAT	−0.004 (−0.10 to 0.09)	0.93
	SDMT	0.01 (−0.09 to 0.11)	0.82
Imaging variables	TBV	0.06 (−0.04 to 0.16)	0.20
	T2LV	−0.07 (−0.16 to 0.03)	0.16
	cGM	0.04 (−0.06 to 0.13)	0.45
	dGM	0.04 (−0.05 to 0.13)	0.39

Asterisk denotes statistical significance at 5% level (Exploratory analyses).
BDI: Beck Depression Inventory.
EDSS: Expanded Disability Status Scale.
NFI: Neurological Fatigue Index sum score.
PASAT: Paced Auditory Serial Addition Test.
TBV: whole brain volume.
T2LV: whole brain T2 hyperintense lesion volume.
cGM: whole brain cortical grey matter volume.
dGM: total brain deep grey matter volume.
All brain imaging volumes expressed as proportion of intracranial volume.

work by NHS Lothian via the Edinburgh Clinical Trials Unit.

Role of the funders

The funding sources had no role in study design, data collection, analysis or interpretation of data, writing of the report, or in the decision to submit the article for publication.

*MS-SMART investigators

Jeremy Chataway, Claudia A M Gandini Wheeler-Kingshott, Floriana De Angelis, Domenico Plantone, Anisha Doshi, Nevin John, Thomas Williams, Jonathan Stutters, Ferran Prados Carrasco, David MacManus, Frederik Barkhof, Sebastien Ourselin, Marie Braisher, Tiggy Beyene, Vanessa Bassan, Alvin Zapata (Queen Square Multiple Sclerosis Centre, University College London and University College London Hospitals NHS Foundation Trust, London, UK); Siddharthan Chandran, Peter Connick, Dawn Lyle, James Cameron, Daisy Mollison, Shuna Colville, Baljean Dhillon (Anne Rowling Regenerative Neurology Clinic, The University of Edinburgh, Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh, UK); Christopher J Weir, Richard A Parker, Moira Ross, Gina Cranswick, Allan Walker, Lorraine Smith (Edinburgh Clinical Trials Unit [ECTU], Usher Institute, University of Edinburgh, Edinburgh, UK); Gavin Giovannoni, Sharmilee Gnanapavan (Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University, Barts Health NHS Trust, London, UK); Richard Nicholas (Imperial College Healthcare NHS Trust, London, UK); Waqar Rashid, Julia Aram (Brighton and Sussex University Hospitals NHS Trust, Brighton, UK); Helen Ford (Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, Leeds, UK); Sue H Pavitt (Dental Translational and Clinical Research Unit, University of Leeds, Leeds, UK); James Overell (The Queen Elizabeth University Hospital Glasgow, NHS Greater Glasgow and Clyde, Glasgow, UK); Carolyn Young, Heinke Arndt (The Walton Centre NHS Foundation Trust, Liverpool, UK); Martin Duddy, Joe Guadagno (Royal Victoria Infirmary, The Newcastle upon Tyne Hospital NHS Foundation Trust, Newcastle, UK); Nikolaos Evangelou (Queens Medical Centre, Nottingham University Hospital NHS Trust, Nottingham, UK); Matthew Craner, Jacqueline Palace (John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK); Jeremy Hobart (Derriford Hospital, University Hospitals Plymouth NHS Trust, Plymouth, UK); Basil Sharrack, David Paling (Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK); Clive Hawkins, Seema Kalra (Royal Stoke University Hospital, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK); Brendan McLean (Royal Cornwall Hospitals NHS Trust, Truro, UK); Nigel Stallard (Statistics and Epidemiology, Division of Health Sciences, Warwick Medical School, University of Warwick, Coventry, UK); and Roger Bastow (patient representative).

CRediT authorship contribution statement

Peter Foley: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Richard A Parker:** Conceptualization, Formal analysis, Data curation, Writing – review & editing. **Floriana de Angelis:** Investigation, Data curation, Writing – review & editing. **Peter Connick:** Investigation, Writing – review & editing. **Siddharthan Chandran:** Conceptualization, Investigation, Writing – review & editing. **Carolyn Young:** Investigation, Writing – review & editing. **Christopher J Weir:** Conceptualization, Formal analysis, Writing – review & editing. **Jeremy Chataway:** Conceptualization, Investigation, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare no relevant conflicts of interest.

Acknowledgment

We thank those people with multiple sclerosis who took part in this trial. MS-SMART is an investigator-led project sponsored by University College London (UCL), and registered at ClinicalTrials.gov. (NCT01910259). This project (reference 11/30/11) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, a Medical Research (MRC) and National Institute for Health Research (NIHR) partnership. The views expressed in this publication are those of the authors and not necessarily those of the MRC, NIHR or the Department of Health and Social Care. This research was also funded by the UK Multiple Sclerosis (MS) Society and the US National MS Society. Additional support came from the University of Edinburgh, the NIHR-UCL Hospitals Biomedical Research Centre and UCL; and the NIHR Leeds Clinical Research Facility (Dental Translation and Clinical Research Unit). Riluzole was provided without charge by Sanofi, who were not involved in either the trial design, running of the trial or analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.103925.

References

Alschuler, K., Jensen, M., Ehde, D., 2012. Defining mild, moderate and severe pain in persons with multiple sclerosis. Pain Med. 13 (10), 1358–1365.
Argoff, C.E., Galer, B.S., Jensen, M.P., et al., 2004. Effectiveness of the lidocaine patch 5% on pain qualities in three chronic pain states: assessment with the Neuropathic Pain Scale. Curr. Med. Res. Opin. 20, S21–S28.
Arnold, L.M., Hess, E.V., Hudson, J.I., et al., 2002. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am. J. Med. 112, 191–197.

Beck, A.T., Steer, R.A., Carbin, M.G., 1988. Psychometric properties of the beck depression inventory: twenty-five years of evaluation. Clin. Psychol. Rev. 8, 77–100.
Beck, A.T., Ward, C.H., Mendelson, M., et al., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 561–571.
Chataway, J., De Angelis, F., Connick, P., et al., 2020. Efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis (MS-SMART): a phase 2b, multiarm, double-blind, randomised placebo-controlled trial. Lancet Neurol. 19, 214–225.
Cleeland, C.S., 1989. Measurement of pain by subjective report. Adv. Pain Res. Ther. 12, 391–403.
Connick, P., De Angelis, F., Parker, R.A., et al., 2018. Multiple sclerosis-secondary progressive multi-arm randomisation trial (MS-SMART): a multiarm phase IIb randomised, double-blind, placebo-controlled clinical trial comparing the efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis. BMJ Open 8, e021944.
Dworkin, R.H., Turk, D.C., Farrar, J.T., et al., 2005. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 113, 9–19.
Finnerup, N.B., Attal, N., Haroutounian, S., et al., 2015. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 14, 162–173.
Fischer, J., Rudick, R., Cutter, G., et al., 1999. The multiple sclerosis functional composite measure (MSFC): an integrated approach to MS clinical outcome assessement. Mult. Scler. J. 5 (4), 244–250.
Foley, P.L., Vesterinen, H.M., Laird, B.J., et al., 2013. Prevalence and natural history of pain in adults with multiple sclerosis: systematic review and meta-analysis. Pain 154, 632–642.
Galer, B.S., Jensen, M.P., 1997. Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. Neurology 48, 332–338.
Galer, B.S., Twilling, L.L., Harle, J., et al., 2000. Lack of efficacy of riluzole in the treatment of peripheral neuropathic pain conditions. Neurology 55, 971–975.
Harding, K., Williams, O., Willis, M., et al., 2019. Clinical outcomes of escalation vs early intensive disease-modifying therapy in patients with multiple sclerosis. JAMA Neurol. 76, 536–541.
Heesen, C., Haase, R., Melzig, S., et al., 2018. Perceptions on the value of bodily functions in multiple sclerosis. Acta Neurol. Scand. 137, 356–362.
Heitmann, H., Haller, B., Tiemann, L., et al., 2020. Longitudinal prevalence and determinants of pain in multiple sclerosis: results from the German National Multiple Sclerosis Cohort study. Pain 161, 787–796.
Holland, P.R., Akerman, S., Andreou, A.P., et al., 2012. Acid-sensing ion channel 1: a novel therapeutic target for migraine with aura. Ann. Neurol. 72, 559–563.
IASP Taxonomy, https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698#Neuropathicpain (2012).
Jawahar, R., Oh, U., Yang, S., et al., 2013. A systematic review of pharmacological pain management in multiple sclerosis. Drugs 73, 1711–1722.
Kalia, L.V., O'Connor, P.W, 2005. Severity of chronic pain and its relationship to quality of life in multiple sclerosis. Mult. Scler. 11, 322–327.
Knowles, L.M., Arewasikporn, A., Kratz, A.L., et al., 2020. Early treatment improvements in depression are associated with overall improvements in fatigue impact and pain interference in adults with multiple sclerosis. Ann. Behav. Med. 55 (9), 833–843.
Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis. an expanded disability status scale (EDSS). Neurology 33, 1444–1452.
Mills, R.J., Young, C.A., Pallant, J.F., et al., 2010. Development of a patient reported outcome scale for fatigue in multiple sclerosis: the neurological fatigue index (NFI-MS). Health Qual. Life Outcomes 8 (22), 782.
Panitch, H.S., Thisted, R.A., Smith, R.A., et al., 2006. Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis. Ann. Neurol. 59, 780–787.
Parmenter, B.A., Weinstock-Guttman, B., Garg, N., et al., 2007. Screening for cognitive impairment in multiple sclerosis using the symbol digit modalities Test. Mult. Scler. J. 13, 52–57.
Patetsos, E., Horjales-Araujo, E., 2016. Treating chronic pain with SSRIs: what do we know? Pain Res. Manag. 2016, 1–17. https://doi.org/10.1155/2016/2020915.
Rog, D.J., Nurmikko, T.J., Friede, T., et al., 2007. Validation and reliability of the Neuropathic Pain Scale (NPS) in multiple sclerosis. Clin. J. Pain 23 (473), 782–481.
Rommer, P.S., Eichstädt, K., Ellenberger, D., et al., 2019. Symptomatology and symptomatic treatment in multiple sclerosis: results from a nationwide MS registry. Mult. Scler. J. 25, 1641–1652.
Seixas, D., Foley, P., Palace, J., et al., 2014. Pain in multiple sclerosis: a systematic review of neuroimaging studies. NeuroImage Clin. 5, 322–331.
Smallwood, R.F., Laird, A.R., Ramage, A.E., et al., 2013. Structural brain anomalies and chronic pain: a quantitative meta-analysis of gray matter volume. J. Pain 14, 663–675.
Solaro, C., Gamberini, G., Masuccio, F.G., 2018. Depression in multiple sclerosis: epidemiology, aetiology, diagnosis and treatment. CNS Drugs 32, 117–133.
Tan, G., Jensen, M., Thornby, J., et al., 2004. Validation of the brief pain inventory for chronic nonmalignant pain. J. Pain 5 (2), 133–137.
Vesterinen, H.M., Connick, P., Irvine, C.M., et al., 2015. Drug repurposing: a systematic approach to evaluate candidate oral neuroprotective interventions for secondary progressive multiple sclerosis. PLoS One 10, e0117705.
Wemmie, J.A., Taugher, R.J., Kreple, C.J., 2013. Acid-sensing ion channels in pain and disease. Nat. Rev. Neurosci. 14, 461–471.