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TITLE PAGE

Title: A systematic approach to selecting licensed drugs for repurposing in the treatment of progressive multiple sclerosis

Corresponding author:

Nick Cunniffe.

Department of Clinical Neurosciences, Clifford Albutt Building, Level 4, Cambridge Biomedical Campus, Cambridge, CB2 0AH, United Kingdom

Email: ngc26@cam.ac.uk; Tel +441223762016

Authors and institutions (in order)

Nick Cunniffe, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

Khue Anh Vuong, MS Society, London, UK

Debbie Ainslie, Research Network, MS Society, London, UK

David Baker, Blizard Institute, Queen Mary University of London, London, UK

Judy Beveridge, Research Network, MS Society, London, UK

Sorrel Bickley, MS Society, London, UK

Patrick Camilleri, Independent consultant, Stevenage, UK

Matthew Craner, Department of Neurology, University of Oxford, UK

Denise Fitzgerald, Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, UK

Alerie G. de la Fuente, Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, UK

Gavin Giovannoni, Blizard Institute, Queen Mary University of London, London, UK

Emma Gray, MS Society, London, UK

Lorraine Hazlehurst, Research Network, MS Society, London, UK

Raj Kapoor, Faculty of Brain Sciences, Queen Square Institute of Neurology, University College London, London, UK

Ranjit Kaur, Research Network, MS Society, London, UK

David Kozlowski, Research Network, MS Society, London, UK

Brooke Lumicisi, MS Society, London, UK

Don Mahad, Centre for Clinical Brain Sciences, Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, UK

Björn Neumann, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

Alan Palmer, University of Reading, Berkshire, UK

Luca Peruzzotti-Jametti, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

Stefano Pluchino, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

Jennifer Robertson, MS Society, London, UK

Alan Rothaul, Independent consultant, Woodstock, Oxfordshire, UK

Lyndsey Shellard, Research Network, MS Society, London, UK

Kenneth J. Smith, Department of Neuroinflammation, Queen Square Institute of Neurology, University College London, London, UK

Alastair Wilkins, Department of Neurology, University of Bristol, Bristol, UK

Anna Williams, MS Centre, Centre for regenerative medicine, University of Edinburgh, Edinburgh, UK

Alasdair Coles, Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK

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ABSTRACT

Objective: To establish a rigorous, expert-led, evidence-based approach to the evaluation of licensed drugs for repurposing and testing in clinical trials of people with progressive multiple sclerosis (MS).

Methods: We long-listed licensed drugs with evidence of human safety, blood-brain barrier penetrance, and demonstrable efficacy in at least one animal model, or mechanistic target, agreed by a panel of experts and people with MS to be relevant to the pathogenesis of progression. We systematically reviewed the preclinical and clinical literature for each compound, condensed this into a database of summary documents, and short-listed drugs by scoring each one of them. Drugs were evaluated for immediate use in a clinical trial and our selection scrutinised by a final independent expert review.

Results: From a short list of 55 treatments, we recommended four treatments for immediate testing in progressive MS: R-α-lipoic acid, metformin, the combination treatment of R-α-lipoic acid and metformin, and niacin. We also prioritised clemastine, lamotrigine, oxcarbazepine, nimodipine and flunarizine.

Conclusions: We report a standardised approach for the identification of candidate drugs for repurposing in the treatment of progressive MS.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, primarily inflammatory, disorder of the central nervous system (CNS) in which demyelination occurs alongside axonal and neuronal degeneration.[1] There now exists an extensive therapeutic armamentarium for the 85% of patients presenting with episodic neurological dysfunction (relapsing remitting MS; RRMS).[2] However, the expanding repertoire of these anti-inflammatory disease modifying treatments (DMTs) contrasts with a paucity of effective therapies for the 15% of people that present with progressive disability (primary progressive MS; PPMS), and indeed the 80% of RRMS patients who subsequently develop progression (secondary progressive MS; SPMS).[3] While ocrelizumab and siponimod have shown modest benefits in phase III trials,[4,5] most immunotherapies have failed in non-active progressive disease. Finding drugs to treat progression remains the greatest unmet need for people with MS.

The reasons for the lack of an effective therapy for progressive MS are multifaceted. The pathophysiology of progressive MS is poorly understood (reviewed in [6]), and there is no animal model that accurately mimics the entirety of the disease. So, new target and drug discovery are challenging. Drug repurposing is attractive, with fewer hurdles before reaching clinical trials, but the rationale behind drug selection needs to be carefully considered.[7,8]

In 2011 the MS Society sponsored an initiative to choose licensed drugs to be trialled in secondary progressive MS.[9] Only oral treatments with a putative action against neurodegeneration were considered. Highest priority was given to drugs that had been tested in MS, Alzheimer's disease, motor neuron disease / amyotrophic-lateral sclerosis, Parkinson's disease and/or Huntington's disease. Clinical and laboratory data from each drug were brought, in a standard template, to a panel composed of people with MS, and experts in animal models, disease biology, clinical trial design and systematic review. The final panel treatment selection was: riluzole, amiloride, fluoxetine, ibudilast, oxcarbazepine, pirfenidone and agents of the polyunsaturated fatty acid (PUFA) class (including lipoic acid). Of these, both ibudilast and lipoic acid have since shown efficacy in

progressive MS in phase 2 trials.[10,11] The MS-secondary progressive multi-arm randomisation trial (MS SMART) study tested riluzole, amiloride and fluoxetine versus placebo in 445 people with SPMS.[12] Unfortunately, no treatment effect on brain atrophy (percentage brain volume change) was seen over 2 years.[13]

In 2018, the MS Society set up an expert consortium (Figure 1) to select treatments and design a new phase of drug trials in progressive MS utilising a novel adaptive methodology. Working as the treatment selection component of this consortium, we augmented the previous strategy with an expert and mechanism-led approach, which we describe here.

METHODS

Pilot stage of treatment selection

The original treatment selection group included 10 scientific members [specialist multiple sclerosis clinicians, laboratory scientists, people with experience of the pharmaceutical industry] and two people with MS. The latter were selected from the MS Society's Research Network (RN): a group of people living with, or caring for, someone with MS, who are trained and experienced in working with researchers to strengthen the quality and relevance of research by drawing upon their personal experience of MS.

At the first meeting of the treatment selection group in January 2018 the following principles of treatment selection were agreed: the highest priority would be given to safe licensed drugs acting on pathological mechanisms thought to be relevant to progression in multiple sclerosis, including remyelination; to drugs which cross the blood-brain barrier; and those that had demonstrable efficacy in at least one relevant animal model. Experience of the drug's use in MS or any other neurological illnesses was considered but did not weight treatment choice. Immunotherapies, such as B-cell depleting drugs, were excluded, given the considerable industrial investment in this area. The agreed mechanistic areas were: (i) energy, blood flow and mitochondria; (ii) the neuron and axon; (iii) sodium channels; (iv) microglia and astroglia; (v) intrathecal B cells and plasma cells; (vi) demyelination and myelin repair; and (vii) antioxidants. It was also agreed that the process of drug selection should be iterative, using a modified Delphi method, led by expert opinion within treatment selection group, while at each stage independent expert input would be sought.

We then convened an international treatment selection workshop, held in London in April 2018. Leading experts from the research community gave a series of talks in each mechanistic area and were asked to suggest drugs for consideration. We also invited representatives of the Cure Parkinson's Trust, the Alzheimer's Society, Motor Neuron Disease Association, Parkinson's UK, and Medicine Discovery Catapult (MDC), who had undertaken drug repurposing programmes within their

own disease area.[14,15] We agreed to draw up a template (a "drug CV") for each compound based on the Cure Parkinson's Trust linked clinical trials initiative dossier model. These documents included information on pharmacodynamics, pharmacokinetics, mechanism of action, and evidence-base *in vitro*, *in vivo*, and in clinical trials (Table 1). This CV condensed and systematised the literature on each drug into an accessible summary manuscript; a drug CV for each potential treatment would be completed by at least 2 members of the treatment selection group.

Table 1: Information recorded in the drug CV

Summary information

- Drug name
- Regulatory status
- Mechanistic target
- Dose for human use (and appropriateness for MS)
- Key safety concerns
- Intellectual property
- Outstanding critical issues
- Overall evaluation

Absorption, distribution, metabolism, excretion, pharmacokinetics and pharmacodynamics

- Chemical structure
- Molecular target
- Pathway affected
- Human pharmacodynamics
- Human pharmacokinetics
- Blood-brain barrier penetrance
- Route of administration

Licenced indication

Dose for licenced indication

Dose suitability for MS

Known, or anticipated, drug-drug interactions

Scientific rationale

Efficacy in *in vitro* models

Efficacy in *in vivo* models

Efficacy for primary indication

Efficacy in people with MS (if applicable)

Particular subgroups of people with MS likely to benefit (if applicable)

Safety

Animal safety issues

Therapeutic ratio (if known)

Safety record in humans

Safety record in people with MS

Monitoring requirements

Any particular drug-drug interaction that would limit use in MS

Landscape review

Is there active pre-clinical research on the use of this drug in MS? Where?

Has the Progressive MS Alliance prioritized this drug?

Are there any relevant trials listed on clinical trials databases?

There was then a call for suggestions for repurposed drugs to members of the committee, clinicians, experts from the wider MS research community, people with MS, and the public, via a web-based system that was advertised to the MS Society's mailing lists. Contributors were prompted to

describe the scientific rationale for their proposed intervention. After four months, the call was closed, a long list of drugs was compiled, and drug CVs completed for each.

The scientific members of the committee scored each drug CV according to an agreed system prioritising safety and efficacy (Table 2a). Members of the MS Society's research network also scored each drug, for ease of administration, tolerability, safety and monitoring requirements based on the drug CV and the European Medicines Agency's (EMA) patient information leaflets (Table 2b). The scores were collated before a second face-to-face meeting.

Table 2: scoring system for shortlisting drug CVs

a) For scientific members of the panel

Safety – Are the safety data for the treatment satisfactory? To include any regulatory warnings, adverse events, drug-drug interactions, therapeutic index, and safety profile. (Score 0-2)

Efficacy – Do we have sufficient evidence that the treatment is likely to be effective in slowing progression? To include *in vitro* and *in vivo* experimental models, blood-brain barrier penetration, along with human data where available. (Score 0-2)

Overall evaluation - Priority level for the treatment (select one)

a. Licensed drug, ready for a phase 2 trial in MS, high priority

b. Licensed drug, ready for a phase 2 trial in MS, low priority

c. Licensed drug, with critical issues to be resolved before a phase 2 trial in MS

d. Interesting drug, with considerable pre-clinical work to be done

e. Poor scientific rationale: not to be prioritised

b) For research network members (people with MS)

Administration – is the method of taking the drug acceptable? To consider whether it is a tablet, injection or infusion as well as how often it needs to be taken. (Score 0-2)

Side effects and risks – is the safety of the drug acceptable? To consider both the immediate side

effects and risks as well as the long term. (Score 0-2)

Overall evaluation - Priority level (select one)

a. I would take this drug even if it only moderately slowed the progression of my MS.

b. I would take this drug if it stopped the progression of my MS.

c. I would not take this drug even if it stopped the progression of my MS.

At this meeting, in September 2018, the treatment selection group (voting) members were joined by new members of the research community and research network (invited attendees), to provide a fresh perspective on the drug list. Each drug was presented, discussed and given an overall score (between 0 lowest and 5 highest). The results were further reviewed and discussed, before all attendees ranked their top 5 drugs, which resulted in a list of seven prioritised drugs.

In parallel to the pilot stage of treatment selection, the MS Society commissioned Medicines Discovery Catapult (MDC) to independently identify licensed drugs that might impact progressive MS. This was undertaken to scrutinise our long list of drugs which had been compiled through the aforementioned mechanism of drug proposals. MDC searched for all ongoing, or completed, trials in people with MS to identify drugs being tested for any type of MS. They then characterised their molecular targets and sought other compounds that were predicted to impact these targets. The final list was pruned of immunotherapies and symptomatic drugs, as well as those that did not cross the blood-brain barrier, and any not on the original long list were added for consideration during the final stage of treatment selection.

Final stage of treatment selection

The treatment selection group appointed new members, and some original members left, leaving 13 scientific and 6 research network members. A renewed call for drug proposals was opened, and the newly formed group reviewed any new suggested compounds, the original long list of drugs considered during the pilot stage, and those generated by Medicines Discovery Catapult, resulting in

a new long list of 29 drugs. Each of these had a drug CV compiled or updated by a team of four, two with a scientific background and two clinicians. The 13 scientific members of the treatment selection group then scored each drug CV according to a simplified scoring system based on safety, efficacy and an overall assessment of priority (Table 2). Similarly, 6 research network (RN) members of the treatment selection group and an additional 10 invited RN members scored between 5 and 10 of the drug CVs, with additional access to the EMA-approved patient information leaflet, such that at least 5 scores were recorded for each drug. The highest ranked 12 drugs from the collated scores formed the shortlist for a third face-to-face meeting in September 2019 of the treatment selection group, with a new group of invited experts and people with MS. Members of the treatment selection group had the option to rescue a low scoring drug in advance of the meeting by presenting a case for its inclusion and it being accepted by majority vote. For the meeting, each drug was presented by one scientific and one research network member, who focussed on the scientific case and attractiveness to people with MS, respectively. Drugs were then scored out of 5 and the resulting ranking discussed before each attendee individually ranked up to 5 drugs ready for use in a clinical trial.

The drug CVs of the treatments recommended by this meeting, and the two highest scoring drugs in the sodium channel antagonist class, were sent to 4 independent international MS experts outside the UK to achieve a further layer of scrutiny of the decisions and to elicit any information on the drugs that was not publicly available. Their comments were collated and considered alongside the outcome of the final treatment selection meeting by the Treatment Advisory Committee (Figure 1). This committee advised on the final drug selection for the MS Society's Efficient Clinical Trials Platform, which is intended to evaluate repurposed treatments quickly and affordably. This committee comprised 6 scientific members and 3 people affected by MS. They assessed the prioritised list on the basis of scientific evidence, but also in the context of other trials known to be going ahead elsewhere. They also scrutinised drug mechanisms and whether the chosen trial design and outcome measures would allow detection of treatment effects. This facilitated a final decision to be made for the drugs to be tested in a platform trial (Figure 1).

RESULTS

Pilot stage of treatment selection

44 treatments were proposed during the 2018 call for drug suggestions, with at least one believed to act on each of the target mechanisms. 35 were deemed by the treatment selection group to have sufficient scientific rationale for consideration, and drug CVs were completed by its scientific members. Each was then scored, prioritising considerations of efficacy and safety as detailed in Table 2, leading to a shortlist of 19 compounds to be discussed face-to-face in September 2018. At that meeting, each drug was presented and discussed before being scored again, collated separately for the members of the treatment selection group (voting members) and the invited attendees (experts and people affected by MS) (Figure 2). After open discussion of these scores, the treatment selection group members ranked their preferred 7 drugs.

During this pilot stage we learned that the drug CVs were effective, but needed more consistency in authorship to promote comparable levels of detail in each CV, and multiple contributors from different backgrounds to encourage impartiality in the presentation of the literature for each compound. We also reflected on the valuable contributions from people affected by MS, who were in a unique position to weigh the safety and tolerability of each drug and consider the level of benefit they would require to take the proposed treatment for their MS. The group resolved that more research network members should be invited onto the treatment selection group to maximise representation of different viewpoints from within the MS community and to share the burden of scoring CVs and presenting drugs at meetings beyond the 2 original members.

Final stage of treatment selection

MDC identified 320 licensed drugs which had a mechanism similar to a drug that had been tried in multiple sclerosis.[16] Once immunotherapies, drugs which did not cross the blood brain barrier and duplicates were removed, guanabenz and trazodone remained from this list. These were added to the 44 treatments that emerged from the pilot phase. During the renewed call for proposals in 2019, new members of the treatment selection committee and outside experts contributed these new suggestions: domperidone, benztropine, prednisolone, ibudilast, spironolactone, oxcarbazepine, hydroxychloroquine, niacin and the combination of metformin and R- -lipoic acid. This long list of 55 treatments was screened by the new treatment selection group, and 28 drugs and one combination therapy were chosen to have comprehensive drug CVs completed.

12 scientific members of the group scored all 29 drug CVs and 16 research network (RN) members (6 of which were members of the treatment selection group) scored up to 10 of the drug CVs, with additional access to the EMA-approved patient information leaflet, such that 5 research network scores were recorded for each drug. The scientific scores were ranked and 13 drugs and 1 combination treatment (metformin and R- -lipoic acid) were short-listed. If a scientific member disagreed with a drug excluded at this stage, they were able to make a case for its inclusion to the group and add to the shortlist by majority vote. Flunarizine and lamotrigine, which had initially been excluded from the list of 12 at the CV scoring stage, were re-added to the list in this way**.**

The 14 shortlisted treatments were discussed and scored, one by one, at a face-to-face meeting of the treatment selection group and invited attendees. The collated scores (Figure 3) were then discussed and debated before the treatment selection group ranked up to 5 drugs, which were ready for immediate use in a phase 2 clinical trial. The final shortlist list of drugs were, in order of preference: R-α-lipoic acid, metformin, the combination treatment of R-α-lipoic acid and metformin, and clemastine. We considered that niacin, flunarizine, and nimodipine were particularly promising, but the treatment selection group felt they needed more pre-clinical work.

This selection, in addition to the 2 highest scoring sodium channel antagonist drugs (lamotrigine and oxcarbazepine), were sent to 4 independent expert reviewers. They scored each compound on safety and efficacy and ranked the drugs by priority level. They were also asked to provide information on any of these drugs that was not publicly accessible. The results of this procedure were considered by the Treatment Advisory Committee of the MS Society's Efficient Clinical Trials Platform (Figure 1), and a final order of prioritisation was made (Table 3). The top 4 were recommended as the most promising for clinical evaluation. The pathway of each drug through these procedures is summarised in Figure 4.

Final list of drugs for prioritisation	**Mechanism of action**
1. R-α-lipoic acid[a]	**Dietary supplement, approved in Germany for diabetic neuropathy;** anti-oxidant, anti-inflammatory, and neuroprotective[11,34,35]
2. Metformin[b]	**Anti-hyperglycaemic agent used for type 2 diabetes mellitus;** anti-inflammatory[23] and promotes remyelination[25] and neuroprotection[24]
3. R-α-lipoic acid and metformin combination	**Mechanisms as above;** complimentary mechanistic targets and neuroprotective in combination[27]
4. Niacin[c]	**Anti-hypercholesterolaemic drug;** promotes oligodendrocyte proliferation,[29] remyelination,[30] and neuroprotection[28]
5. Clemastine	**Antihistamine used for allergic rhinitis;** off-target anti-muscarinic

	(M1) action which promotes oligodendrocyte progenitor differentiation and remyelination[32,33]
6. Lamotrigine	**Sodium channel antagonist widely used as an anticonvulsant;** neuroprotective effects[36]
7. Oxcarbazepine	**Sodium channel antagonist widely used as an anticonvulsant;**; neuroprotective effects[37]
8. Nimodipine	**Calcium channel antagonist used to treat vasospasm in subarachnoid haemorrhage**; promotes remyelination, neuroprotection,[38] and restores CNS perfusion and oxygenation[39]
9. Flunarizine	**Migraine prophylactic;** neuroprotective effects[40]

Table 3. Final recommendations of repurposed interventions for clinical testing in progressive MS. The top 4 were determined to be the most promising for clinical evaluation. [a]1200 mg/day, [b]1 gram twice daily, starting at 500mg twice daily, [c]750mg twice daily of slow release formulation of Niaspan.

DISCUSSION

The pathogenesis of progressive MS is complex, multifaceted and poorly understood. As with many other neurodegenerative diseases, there are no licensed treatments. This remains the greatest unmet need for the more than 2.3 million people affected by MS globally.[17] Placed in context of the high cost, long time, and high attrition rate from target selection to regulatory approval via conventional pathways, there are compelling reasons to explore opportunities provided by drug repurposing. This nevertheless presents a substantial challenge. The myriad reasons for the prior failure to find an effective treatment remain,[6] and the optimum process for selection of drugs to progress to repurposing clinical trials are not standardised. Procedures for synthesising experimental and clinical trial data to enable rational drug selection are required to maximise the chance of successful clinical development.

The UK MS Society Clinical Trials Network was initiated in 2007 and commissioned key underpinning work including a review of animal and human data on promising drugs. Given the mechanistic overlap between SPMS and other neurodegenerative disorders (namely Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis), their strategy centred on a systematic review and meta-analysis of clinical and preclinical data for agents previously tested in these illnesses.[9] The ensuing list prioritised ibudilast, riluzole, amiloride, fluoxetine, pirfenidone, oxcarbazepine and agents of the polyunsaturated fatty-acid (PUFA) class. Ibudilast and lipoic acid proved successful at phase 2,[10,11] but unfortunately riluzole, amiloride and fluoxetine did not reduce brain atrophy in the MS-SMART study compared to placebo.[12,13]

Here we describe a rigorous, expert-led, evidence-based approach to the selection of licensed compounds for repurposing in clinical trials of people with progressive forms of MS, led by scientific and clinical experts as well as people with MS, involving repeated rounds of assessment, scoring, and independent peer review. We identified key biological mechanisms, performed an exhaustive

literature search on identified drugs, and went through two cycles of shortlisting and prioritisation. We selected this strategy to retain the evidence-based approach of previous mechanisms of drug selection, but with added emphasis on expert opinion and independent expert review which, in our view, would enable our selection to be based on current scientific opinion and more readily identify barriers and knowledge gaps that might affect trials of the proposed compounds. A particular contrast between our strategy and that previously used was that we did not prioritise agents that had previously been subject of clinical trials of people with neurodegenerative illnesses and we required all candidates to have evidence of blood-brain barrier permeability. Other differences are summarised in Table 4.

It is noteworthy that our first ranked drug, lipoic acid, was also prioritised in the 2011 drug selection initiative, despite the contrasting methodologies. Three interventions – R-α-lipoic acid (R-ALA), metformin and niacin – and one combination preparation – of metformin and R-α-lipoic acid – were identified as being priorities for clinical evaluation in cohorts of people with progressive MS, and as having sufficient data to permit immediate entry into a phase 2 trial. Clemastine, lamotrigine, oxcarbazepine, nimodipine and flunarizine were also felt to be promising and ranked in order of priority.

R-α-lipoic acid is the R-enantiomer that makes up 50% of the racemic mixture (R and S) of lipoic acid, a dietary supplement approved in Germany for the treatment of diabetic neuropathies. It has previously been shown to be a potent antioxidant, have anti-inflammatory properties,[18,19] and reduce excitotoxic damage;[20] while the R enantiomer has superior pharmacokinetic, antioxidant and neuroprotective properties than the S enantiomer.[21] When given to 51 people with SPMS, it was shown to have a small benefit to brain atrophy.[22]

Metformin, a biguanide licensed for human use in type 2 diabetes, has previously been demonstrated to reduce inflammation in progressive and relapsing experimental autoimmune encephalomyelitis models,[23] is neuroprotective in models of glucose

deprivation/reoxygenation[24] and, more recently, has been shown to reverse an age-associated barrier to the ability of oligodendrocyte progenitor cells to respond to differentiation factors and facilitate subsequent remyelination.[25] Additionally, it has previously been used in 20 people with MS, and demonstrated a reduction in the number of new or enlarging T2 lesions compared to placebo.[26] The complimentary mechanistic targets of metformin and R-ALA, as well as the potential for synergy,[27] led to the combination of the two featuring on our prioritised list.

Niacin, a nicotinamide adenine dinucleotide (NAD) precursor in use for the treatment of hypercholesterolaemia, has previously been shown to be protective against activated microglial-induced neurotoxicity[28] and to promote oligodendrocyte proliferation *in vitro.*[29] In line with these observations, it reduces axonal degeneration, delays progression, and increases oligodendrocyte proliferation in extrinsic allergic encephalomyelitis.[28,29] While ranked below clemastine by the treatment selection group, data that was unpublished at the time came to light during the treatment advisory committee review: niacin also enhances myelin phagocytosis by microglia, leading to increases in oligodendrocyte progenitor cell numbers and improved remyelination in mice.[30] Niacin has not yet been trialled in people with multiple sclerosis.

Finally, clemastine is a first generation anti-histamine that was identified in two separate screens as being able to stimulate oligodendrocyte progenitor cells to differentiate and carry out the first stages of remyelination.[31,32] This subsequently demonstrated a small, but statistically significant, improvement in the latency of the full-field visual evoked potential of people with relapsing MS and chronic stable optic neuropathy; interpreted as a remyelinating effect in the optical pathway.[33]

A particular strength of our methodology is the multiple layers of revision and review. By undertaking a pilot of treatment selection, we refined the procedures by which we evaluated the literature and assessed each compound to facilitate robust comparisons of agents with disparate mechanistic targets and safety profiles. We also ratified our procedures for drug identification by the work of Medicines Discovery Catapult, which generated a list of drugs of which only 2 had not

previously been identified. Finally, by sending our list of prioritised treatments for external peer review we have better ensured scrutiny of both our methods and our selection.

Table 4. Comparison between the current methodology and that previously used in 2011;[9] MS, multiple sclerosis; AD, Alzheimer's disease; ALS, amyotrophic-lateral sclerosis; PD, Parkinson's disease; HD, Huntington's disease; BBB, blood-brain barrier.

	2011	2019
Method of drug identification	Thorough and systematic search of online databases (PubMed, ISI Web of Knowledge, Embase, Clinicaltrials.gov, Cochrane MS group)	Calls for recommendations from academics, clinicians, and people with MS. Systematic search of online databases by medicines discovery catapult
Previous clinical trial use	Previously used in a neurodegenerative disease including progressive MS, PD, HD, AD, and ALS.	Human safety data required only
Mechanistic targets	Excluded immunosuppressant mechanism of action. Combination treatments excluded.	Priority given to candidates targeting several mechanistic targets. Excluded those with *solely* immunosuppressant mechanism. Combination treatments accepted
Method of administration	Oral	Any method of administration
CNS penetration	Reviewed at selection meeting	Evidence of BBB permeability required at study entry
Safety	Excluded those with significant	Excluded those with significant

	adverse effects associated with treatment.	adverse effects associated with treatment.
Method of selection	Systematic evaluation of publications pertaining to each candidate. Systematic review of experimental autoimmune encephalomyelitis (EAE) preclinical data for each candidate. Scrutiny of each drug by an international multi-disciplinary committee	Systematic evaluation of preclinical and clinical publications pertaining to each candidate. Formation of a database of drug CVs. Rating of these by scientific panel. Presentation and decision at international multi-disciplinary meeting
Input from people affected by MS	Patient representatives acting as external advisors	6 members of MS research network on voting panel. Scoring of drug CVs by at least 5 people with, or affected by, MS. Members of MS research network at treatment selection meeting.
Peer review	External advisors with a range of expertise including animal models, disease biology, clinical trial design, systematic review and patient representation.	Methodology and final treatment selection sent for external peer review

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CONTRIBUTORSHIP STATEMENT

Dr Cunniffe and Prof Coles accept full responsibility for the work and conduct of the study, had access to the data, and controlled the decision to publish. *Study concept and design*: NC, KV, DA, DB, JB, SB, PC, MC, DF, AG, GG, EG, LH, R Kapoor, R Kaur, DK, BL, DM, BN, AP, LP, SP, JR, AR, LS, KS, A Wilkins, A Williams, AC. *Members of treatment selection group responsible for analysis or interpretation of data*: NC, KV, DA, DB, JB, SB, PC, MC, DF, AG, GG, EG, LH, R Kapoor, R Kaur, DK, BL, DM, BN, AP, LP, SP, JR, AR, LS, KS, A Wilkins, A Williams, AC. *Drafting of manuscript*: NC, KV, AC. *Critical revision of the manuscript*: NC, KV, DA, DB, JB, SB, PC, MC, DF, AG, GG, EG, LH, R Kapoor, R Kaur, DK, BL, DM, BN, AP, LP, SP, JR, AR, LS, KS, A Wilkins, A Williams, AC.

COMPETING INTERESTS

DB received compensation for consultancy activity from Canbex Therapeutics, Japan Tobacco, Lundbeck, InMune Bio, Merck, Novartis, Roche in the past 3 years. AJC received honoraria and travel support from Genzyme [a Sanofi company] prior to 2017. MC has received honoraria for educational events and/or consultancy from Biogen, Merck, Roche, AbbVie and Novartis. GG has received compensation for serving as a consultant in relation to multiple sclerosis drug development from AbbVie, Actelion, Atara Bio, Biogen, Celgene, EMD Serono, Japanese Tobacco, Sanofi-Genzyme, Genentech, GlaxoSmithKline, GW Pharma, Merck KGa, Novartis, Roche and Teva. LH holds a small number of GSK shares as part of her renumeration when she was an employee, which she left 4 years ago. DM received consultancy fees from Biogen, MedDay and SanofiGenzyme and Novartis. BN holds a patent regarding the treatment of demyelinating diseases including metformin: WO2019/206419 A1, Treatment for demyelinating disease. SP is co-founder, CSO and shareholder

(>5%) of CITC Ltd. and iSTEM Therapeutics, and co-founder and Non-executive Director at asitia Therapeutics. LP is Head of Research at iSTEM Therapeutics. A Williams receives research support from Roche not associated with drug development or use.

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JB received expense payments from Novartis for speaking as patient representative during Siponimod licensing. AJC receives funding from the MRC and MS Society UK. DF is funded by the Wellcome and BBSRC, and has a project with Sangamo. A.G. de la Fuente has been supported by the ECTRIMS postdoctoral fellowship during this period. GG declares current research funding from Merck KGa (CLAD-B study), Roche (ORATORIO-HAND study) and Takeda (SIZOMUS Study). DM received funding previously from Biogen, MedDay and SanofiGenzyme. BN received funding from the Cambridge Centre for Myelin Repair, funded by MS Society UK. SP declares current funding from Italian and US Multiple Sclerosis Societies. LP has been supported by a senior research fellowship FISM - Fondazione Italiana Sclerosi Multipla - cod. 2017/B/5 and financed or co financed with the '5 per mille' public funding, by the Isaac Newton Trust RG 97440 and the Addenbrooke's Charitable Trust RG 97519. KS declares current funding from Fondation Leducq, Multiple Sclerosis Society, Rosetrees Trust. A. Wilkins received a research grant from Sanofy (2018). A. Williams declares funding from MS Society UK, Roche, MRC, Lifearc.

ETHICS APPROVAL

Ethical approval was not required as this study utilised previously published literature and no patient identifiable data are included.

DATA AVAILABILITY

All authors had access to the data in this study and had responsibility for the decision to submit for publication. All data relevant to the study are included in the article or uploaded as supplementary

information. Information recorded in the Drug CV's is available from the MS Society and can be requested via email: research@mssociety.org.uk.

REFERENCES

1 Compston A, Coles A. Multiple sclerosis. *The Lancet* 2008;**372**:1502–17. doi:10.1016/S0140-6736(08)61620-7

2 Scolding N, Barnes D, Cader S, *et al.* Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Pract Neurol* 2015;**15**:273. doi:10.1136/practneurol-2015-001139

3 Weinshenker BG, Bass B, Rice GPA, *et al.* The natural history of multiple sclerosis: a geographically based study: I. Clinical course and disability. *Brain* 1989;**112**:133–46. doi:10.1093/brain/112.1.13

4 Montalban X, Hauser SL, Kappos L, *et al.* Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. *N Engl J Med* 2016;**376**:209–20. doi:10.1056/NEJMoa1606468

5 Kappos L, Bar-Or A, Cree BAC, *et al.* Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *The Lancet* 2018;**391**:1263–73. doi:10.1016/S0140-6736(18)30475-6

6 Faissner S, Plemel JR, Gold R, *et al.* Progressive multiple sclerosis: from pathophysiology to therapeutic strategies. *Nature Reviews Drug Discovery* 2019;**18**:905–22. doi:10.1038/s41573-019-0035-2

7 O'Connor KA, Roth BL. Finding New Tricks For Old Drugs: An Efficient Route For Public-Sector Drug Discovery. *Nature Reviews Drug Discovery* 2005;**4**:1005–14. doi:10.1038/nrd1900

8 Pushpakom S, Iorio F, Eyers PA, *et al.* Drug repurposing: progress, challenges and recommendations. *Nature Reviews Drug Discovery* 2019;**18**:41–58. doi:10.1038/nrd.2018.168

9 Vesterinen HM, Connick P, Irvine CMJ, *et al.* Drug Repurposing: A Systematic Approach to Evaluate Candidate Oral Neuroprotective Interventions for Secondary Progressive Multiple Sclerosis. *PLOS ONE* 2015;**10**:e0117705. doi:10.1371/journal.pone.0117705

10 Fox RJ, Coffey CS, Conwit R, *et al.* Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis. *N Engl J Med* 2018;**379**:846–55. doi:10.1056/NEJMoa1803583

11 Spain R, Powers K, Murchison C, *et al.* Lipoic acid in secondary progressive MS. *Neurol Neuroimmunol Neuroinflamm* 2017;**4**:e374. doi:10.1212/NXI.0000000000000374

12 Connick P, De Angelis F, Parker RA, *et al.* 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* 2018;**8**:e021944–e021944. doi:10.1136/bmjopen-2018-021944

13 Chataway J, De Angelis F, Connick P, *et al.* Efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis (MS-SMART): a phase 2b, multiarm, double-blind, randomised placebo-controlled trial. *The Lancet Neurology* doi:10.1016/S1474-4422(19)30485-5

14 Brundin P, Barker RA, Conn PJ, *et al.* Linked Clinical Trials – The Development of New Clinical Learning Studies in Parkinson's Disease Using Screening of Multiple Prospective New Treatments. *Journal of Parkinson's Disease* 2013;**3**:231–9. doi:10.3233/JPD-139000

15 Corbett A, Pickett J, Burns A, *et al.* Drug repositioning for Alzheimer's disease. *Nature Reviews Drug Discovery* 2012;**11**:833–46. doi:10.1038/nrd3869

16 Using a data-driven approach to identify drug candidates for multiple sclerosis | Medicines Discovery Catapult. https://md.catapult.org.uk/case-studies/using-a-data-driven-approach-to-identify-drug-candidates-for-multiple-sclerosis/ (accessed 27 Aug 2020).

17 Browne P, Chandraratna D, Angood C, *et al.* Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology* 2014;**83**:1022. doi:10.1212/WNL.0000000000000768

18 Sook Cho Y, Lee J, Lee T-H, *et al.* α-Lipoic acid inhibits airway inflammation and hyperresponsiveness in a mouse model of asthma. *Journal of Allergy and Clinical Immunology* 2004;**114**:429–35. doi:10.1016/j.jaci.2004.04.004

19 Liu W, Shi L, Li S. The Immunomodulatory Effect of Alpha-Lipoic Acid in Autoimmune Diseases. *BioMed Research International* 2019;**2019**:8086257. doi:10.1155/2019/8086257

20 Park E, Gim J, Kim DK, *et al.* Protective Effects of Alpha-Lipoic Acid on Glutamate-Induced Cytotoxicity in C6 Glioma Cells. *Biological and Pharmaceutical Bulletin* 2019;**42**:94–102. doi:10.1248/bpb.b18-00603

21 Tomassoni D, Amenta F, Amantini C, *et al.* Brain activity of thioctic Acid enantiomers: in vitro and in vivo studies in an animal model of cerebrovascular injury. *Int J Mol Sci* 2013;**14**:4580–95. doi:10.3390/ijms14034580

22 Loy BD, Fling BW, Horak FB, *et al.* Effects of lipoic acid on walking performance, gait, and balance in secondary progressive multiple sclerosis. *Complementary Therapies in Medicine* 2018;**41**:169–74. doi:10.1016/j.ctim.2018.09.006

23 Nath N, Khan M, Paintlia MK, *et al.* Metformin Attenuated the Autoimmune Disease of the Central Nervous System in Animal Models of Multiple Sclerosis. *J Immunol* 2009;**182**:8005. doi:10.4049/jimmunol.0803563

24 Meng X, Chu G, Yang Z, *et al.* Metformin Protects Neurons against Oxygen-Glucose Deprivation/Reoxygenation -Induced Injury by Down-Regulating MAD2B. *Cellular Physiology and Biochemistry* 2016;**40**:477–85. doi:10.1159/000452562

25 Neumann B, Baror R, Zhao C, *et al.* Metformin Restores CNS Remyelination Capacity by Rejuvenating Aged Stem Cells. *Cell Stem Cell* 2019;**25**:473-485.e8. doi:10.1016/j.stem.2019.08.015

26 Negrotto L, Farez MF, Correale J. Immunologic Effects of Metformin and Pioglitazone Treatment on Metabolic Syndrome and Multiple Sclerosis. *JAMA Neurology* 2016;**73**:520–8. doi:10.1001/jamaneurol.2015.4807

27 Ahuja S, Uniyal A, Akhtar A, *et al.* Alpha lipoic acid and metformin alleviates experimentally induced insulin resistance and cognitive deficit by modulation of TLR2 signalling. *Pharmacological Reports* 2019;**71**:614–23. doi:10.1016/j.pharep.2019.02.016

28 Kaneko S, Wang J, Kaneko M, *et al.* Protecting Axonal Degeneration by Increasing Nicotinamide Adenine Dinucleotide Levels in Experimental Autoimmune Encephalomyelitis Models. *J Neurosci* 2006;**26**:9794. doi:10.1523/JNEUROSCI.2116-06.2006

29 Zhang J, Chen J, Li Y, *et al.* Niaspan treatment improves neurological functional recovery in experimental autoimmune encephalomyelitis mice. *Neurobiology of Disease* 2008;**32**:273–80. doi:10.1016/j.nbd.2008.07.011

30 Rawji KS, Young AMH, Ghosh T, *et al.* Niacin-mediated rejuvenation of macrophage/microglia enhances remyelination of the aging central nervous system. *Acta Neuropathologica* Published Online First: 6 February 2020. doi:10.1007/s00401-020-02129-7

31 Deshmukh VA, Tardif V, Lyssiotis CA, *et al.* A regenerative approach to the treatment of multiple sclerosis. *Nature* 2013;**502**:327–32. doi:10.1038/nature12647

32 Mei F, Fancy SPJ, Shen Y-AA, *et al.* Micropillar arrays as a high-throughput screening platform for therapeutics in multiple sclerosis. *Nature medicine* 2014;**20**:954–60. doi:10.1038/nm.3618

33 Green AJ, Gelfand JM, Cree BA, *et al.* Clemastine fumarate as a remyelinating therapy for multiple sclerosis (ReBUILD): a randomised, controlled, double-blind, crossover trial. *The Lancet* 2017;**390**:2481–9. doi:10.1016/S0140-6736(17)32346-2

34 Marracci GH, Jones RE, McKeon GP, *et al.* Alpha lipoic acid inhibits T cell migration into the spinal cord and suppresses and treats experimental autoimmune encephalomyelitis. *Journal of Neuroimmunology* 2002;**131**:104–14. doi:10.1016/S0165-5728(02)00269-2

35 Morini M, Roccatagliata L, Dell'Eva R, *et al.* α-Lipoic acid is effective in prevention and treatment of experimental autoimmune encephalomyelitis. *Journal of Neuroimmunology* 2004;**148**:146–53. doi:10.1016/j.jneuroim.2003.11.021

36 Bechtold DA, Miller SJ, Dawson AC, *et al.* Axonal protection achieved in a model of multiple sclerosis using lamotrigine. *Journal of Neurology* 2006;**253**:1542–51. doi:10.1007/s00415-006-0204-1

37 Al-Izki S, Pryce G, Hankey DJR, *et al.* Lesional-targeting of neuroprotection to the inflammatory penumbra in experimental multiple sclerosis. *Brain* 2013;**137**:92–108. doi:10.1093/brain/awt324

38 Schampel A, Volovitch O, Koeniger T, *et al.* Nimodipine fosters remyelination in a mouse model of multiple sclerosis and induces microglia-specific apoptosis. *Proc Natl Acad Sci USA* 2017;**114**:E3295. doi:10.1073/pnas.1620052114

39 Desai RA, Davies AL, Del Rossi N, *et al.* Nimodipine reduces dysfunction and demyelination in models of multiple sclerosis. *Annals of Neurology* 2020;**n/a**. doi:10.1002/ana.25749

40 Bostanci MÖ, Bağirici F, Canan S. A calcium channel blocker flunarizine attenuates the neurotoxic effects of iron. *Cell Biology and Toxicology* 2006;**22**:119–25. doi:10.1007/s10565-006-0037-9

FIGURE LEGENDS

Figure 1. ***Above*** **Summary of the UK MS Society's expert consortium for progressive MS clinical trials, which has been set up to test treatments in an adaptive platform trial, termed the efficient clinical trials platform. The treatment selection group and treatment advisory committee were responsible for formulating the prioritised list of drugs to enter the clinical trial.** ***Below*** **Flow chart of the procedures undertaken during the final round of treatment selection by the treatment selection element. *Drug CVs were completed by 4 members of the treatment selection group – 2 with a scientific background and 2 MS specialist clinicians. **Drugs failing to reach the short list of drugs on account of a low score, could be added back for consideration at the panel meeting if reasons were proposed by a member of the treatment selection group and its rescue approved by majority vote. MDC: medicines discovery catapult; PPI: patient and public involvement.**

Figure 2. Outcome of the pilot screen of candidate interventions. Mean scores (out of 5) of each drug by voting members of the treatment selection group and invited attendees are displayed in descending order. Inset: the provisional list for prioritisation agreed by the voting members of the committee.

Figure 3. Outcome of the final meeting of the treatment selection group during the final stage of candidate screening. The mean scores (out of 5) for the 14 shortlisted compounds presented at the meeting are divided into those awarded by voting members of the panel and invited attendees.

Figure 4. Summary of the pathway of each drug through the treatment selection process to yield a final prioritised list of drugs.