Safety and efficacy of memantine and trazodone versus placebo for motor neuron disease (MND SMART): stage two interim analysis from the first cycle of a phase 3, multiarm, multistage, randomised, adaptive platform trial

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Summary

Background Motor neuron disease represents a group of progressive and incurable diseases that are characterised by selective loss of motor neurons, resulting in an urgent need for rapid identification of effective disease-modifying therapies. The MND SMART trial aims to test the safety and efficacy of promising interventions efficiently and definitively against a single contemporaneous placebo control group. We now report results of the stage two interim analysis for memantine and trazodone.

Methods MND SMART is an investigator-led, phase 3, double-blind, placebo-controlled, multiarm, multistage, randomised, adaptive platform trial recruiting at 20 hospital centres in the UK. Individuals older than 18 years with a confirmed diagnosis of either amyotrophic lateral sclerosis classified by the revised El Escorial criteria, primary lateral sclerosis, progressive muscular atrophy, or progressive bulbar palsy, regardless of disease duration, were eligible for screening. Participants were randomised (1:1:1) to receive oral trazodone 200 mg once a day, oral memantine 20 mg once a day, or matched placebo using a computer-generated minimisation algorithm delivered via a secure web-based system. Co-primary outcome measures were clinical functioning, measured by rate of change in the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R), and survival. Comparisons were conducted in four stages, with predefined criteria for stopping at the end of stages one and two. We report interim analysis from the stage two results, which was done when 100 participants per group (excluding long survivors, defined as >8 years since diagnosis at baseline) completed a minimum of 12 months of follow-up for the candidate investigational medicinal products. The trial is registered on the European Clinical Trials Registry, 2019–000099–41, and ClinicalTrials.gov, NCT04302870, and is ongoing.

Findings Between Feb 27, 2020, and July 24, 2023 (database lock for interim analysis two), 554 people with a motor neuron disease were randomly allocated to memantine (183 [33%]), trazodone (185 [33%]), or placebo (186 [34%]). The primary interim analysis population comprised 530 participants, of whom 175 (33%) had been allocated memantine, 175 (33%) had been allocated trazodone, and 180 (34%) had been allocated placebo. Over 12 months of follow-up, the mean rate of change per month in ALSFRS-R was –0·650 for memantine, –0·625 for trazodone, and –0·655 for placebo (memantine versus placebo estimated mean difference 0·033, one-sided 90% CI lower level –0·085; one-sided p=0·36; trazodone *vs* placebo: 0·065, –0·051; one-sided p=0·24). The one-sided p values were both above the significance threshold of 10%, indicating that neither memantine nor trazodone groups met the criteria for continuation. There were 483 participants with at least one adverse event (145 [77%] on placebo, 170 [91%] on memantine, and 168 [90%] on trazodone). There were 88 participants with at least one serious adverse event (37 [20%] on memantine, 27 [14%] on trazodone, and 24 [13%] on placebo). A total of 11 serious adverse event led to treatment discontinuation. There was no survival difference between comparisons, with 49 deaths in the memantine group, 52 deaths in the trazodone group, and 48 deaths in the placebo group.

Interpretation Neither memantine nor trazodone improved efficacy outcomes compared with placebo. This result is sufficiently powered to warrant no further testing of trazodone or memantine in motor neuron disease at the doses evaluated in this study. The multiarm multistage design shows important benefits in reducing the time, cost, and participant numbers to reach a definitive result.

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Research in context

Evidence before this study

We searched Clinicaltrials.gov, WHO International Clinical Trials Registry Platform, European Clinical Trials Register, and PubMed on April 9, 2019, using the search terms "amyotrophic lateral sclerosis", "motor neuron disease", and "clinical trials", and applied "Phase 2" and "Phase 3" filters in the International Clinical Trials Registry Platform and European Clinical Trials Register. We searched for clinical trials assessing potential disease-modifying treatments for motor neuron disease that were registered, completed, or published between Jan 1, 2008, and April 9, 2019, with no language restrictions, and found 125 trials investigating 76 drugs and recruiting more than 15 000 participants. 90% of the trials used traditional fixed designs and none identified new treatments. Furthermore, fewer than 5% of people in the UK and 8% in the USA with a motor neuron disease have historically participated in a clinical trial. There is an urgent need for innovation in both identification of new candidate medicines and their efficient testing in trials.

Added value of this study

The MND SMART trial is an innovative, investigator-led, multiarm, multistage, phase 3, randomised, adaptive platforms trial that aimed to test the safety and efficacy of promising interventions efficiently and definitively, with a contemporaneous placebo control group. Co-production of the trial alongside people with motor neuron disease ensured results had robust performance characteristics, the trial met all assumptions underlying power calculations and was sensitive to detect any neuroprotective effect of the two drugs, and participant withdrawal rate (10%) was lower than in historical motor neuron disease trials (around 20%). The current analysis was done when 100 participants per group completed a minimum of 12 months of follow-up for the candidate interventions, which were oral trazodone (200 mg once a day) and oral memantine (20 mg once a day).

Implications of all the available evidence

The findings of the prespecified interim analysis showed that both memantine and trazodone had no effect on the co-primary outcome of Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised, compared with placebo, and no effect on survival. By historical standards, the MND SMART trial is efficient in time and number of participants recruited. Innovative trial designs such as multiarm and multistage should be considered the standard in future disease-modifying trials for neurodegenerative disorders.

Introduction

Motor neuron disease represents a group of progressive incurable neurodegenerative diseases, with death typically occurring 3–5 years after symptom onset.[1] Riluzole, which was first licensed in 1995 by the US Food and Drug Administration, is the only globally approved treatment for the amyotrophic lateral sclerosis subtype of motor neuron disease and has poor treatment efficacy.[2–4] Edaravone, masitinib, AMX0035 (combined sodium phenylbutyrate and tauroursodeoxycholic acid), and tofersen (for <2% of the disease population who have monogenetic motor neuron disease due to *SOD1* mutations) have been evaluated in recent clinical trials.[5–8] Due to a shortage of definitive benefit for most of these drugs, only tofersen has received approval in Europe.[5–8] Up to now, less than 5% of people with motor neuron disease in the UK have participated in clinical trials.[9] Against this background, there is an urgent unmet need for systematic and rapid identification of effective disease-modifying therapies and their swift evaluation in unbiased randomised controlled settings.

The Motor Neuron Disease Systematic Multi-Arm Adaptive Randomised Trial (MND SMART) is an investigator-led, phase 3, double-blind, placebo-controlled, multiarm, multistage, randomised, adaptive platform trial. Alongside the phase 2/3 HEALEY platform trial (USA; NCT04297683),[10] the MND SMART trial heralds a new era of innovative trials in neurology.[11,12] This approach, templated from cancer medicine and infectious diseases, allows: (1) simultaneous definitive evaluation of multiple treatment groups against a single control group; (2) early cessation of treatments that show little or no sign of activity through multiple staged analyses against predetermined absence of activity outcomes; and (3) addition of new groups in a continuous trial platform. These features deliver considerable efficiency gains in time, cost, and sample size requirements compared with serial (conventional) two-arm studies.[13–15] Here, we describe the application of this methodology to motor neuron disease with the first cycle of results from MND SMART.

Each cycle of the MND SMART trial is conducted in four stages, and interventions only continue to the subsequent stage if the result of each staged interim analysis meets predefined criteria (figure 1).[11,12] In stages one to three, the primary outcome measure is clinical function assessed using the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R), which will be evaluated alongside the safety and tolerability of the interventions. In stage four, we will analyse the effect of interventions on survival, which is designated as a co-primary endpoint with ALSFRS-R. The full statistical analysis plan has been published previously.[12]

We have previously published our systematic, structured, and unbiased evidence-based approach to inform expert consensus in the selection of putative oral repurposed neuroprotective agents for clinical evaluation in the MND SMART trial.[16] Following extensive

engagement with patients and carers, we chose to focus on candidate medicines that were available in liquid preparation to optimise tolerability for the patient population, noting the prominence of bulbar features in motor neuron disease. Briefly, memantine and trazodone were selected following completion of a two-stage systematic process that included weighted review of clinical studies in motor neuron disease and four other neurodegenerative diseases (Alzheimer's disease, Huntington's disease, Parkinson's disease, and progressive multiple sclerosis). This approach was chosen on the basis that these disorders share common pivotal disease pathophysiological processes, such as dysfunctional protein homoeostasis, excitotoxicity, and neuroinflammation and, thus, there could be common convergent targets.

Drugs were scored and ranked using a metric evaluating safety, efficacy, study size, and study quality. In stage two, efficacy of candidate medicines in models (in vitro and in vivo) of motor neuron disease was evaluated. An expert panel including independent neurologists, neuroscientists, and methodologists considered the systematic review findings, late-breaking evidence, and mechanistic plausibility, safety, tolerability, and feasibility of evaluation in the MND SMART trial during two shortlisting rounds and a final selection round. 595 interventions were identified from the clinical review, of which 66 drugs fulfilled drug and disease pathobiology logic. 22 drugs with supportive clinical and preclinical evidence were shortlisted during round one. Seven drugs proceeded to round two. The panel reached a consensus to evaluate memantine and trazodone against placebo control as the first two active groups of the MND SMART trial.

Memantine is a non-competitive NMDA receptor antagonist used in the treatment of moderate-to-severe Alzheimer's disease. Experimental evidence of effect on underlying pathophysiological processes implicated in motor neuron disease, including blocking glutamate-mediated excitotoxicity, promoting autophagy, and downregulating inflammatory pathways in addition to delaying disease progression in the SOD1 animal model, made memantine a biologically plausible high-value candidate.[17–20] Moreover, four clinical trials in motor neuron disease have reported results confirming safety, tolerability, and raising the possibility of clinical benefit.[21–24] However, the studies were neither powered nor designed to definitively confirm or refute efficacy using ALSFRS-R as an outcome measure.

Trazodone is an atypical serotonin antagonist and reuptake inhibitor antidepressant. An unbiased phenotypic drug screen found that trazodone inhibited protein kinase RNA-like endoplasmic reticulum kinase (PERK) signalling,[25] which is a key mediator of the unfolded protein response to misfolded proteins found in neurodegenerative diseases, including TDP43 proteinopathies such as motor neuron disease and frontotemporal dementia.[26] Subsequent studies have shown modification of the unfolded protein response and improvement in survival in both animal models of prion disease and frontotemporal dementia[25] and a beneficial effect on cognition in an early-phase trial of 31 participants with frontotemporal dementia.[27]

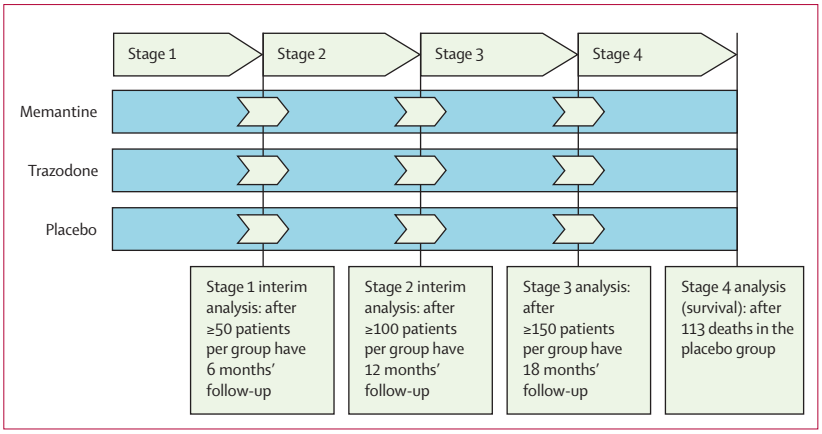


Figure 1: **The MND SMART study design**

We aimed to test the safety and efficacy of memantine and trazodone in motor neuron disease against a single contemporaneous placebo control group. All participants were on current standard of care. The stage one interim analysis for memantine and trazodone was reviewed on March 14, 2022, and both drugs were recommended for continuation by the Independent Data Monitoring Committee. We now report results of the stage two interim analysis.

Methods

Study design

The MND SMART trial is an investigator-led, phase 3, double-blind, placebo-controlled, multiarm, multistage, randomised, adaptive platform trial recruiting people with motor neuron disease at 20 hospital centres in the UK. The study was conducted in accordance with the protocol (with approved amendments), the Recommendations for Interventional Trials guidelines, and the International Council for Harmonisation Good Clinical Practice guidelines. The study was approved by the West of Scotland Research Ethics Committee on Oct 2, 2019 (REC reference: 19/WS/0123).

Throughout its development and delivery, the MND SMART trial has been co-produced with people living with a motor neuron disease and their families and carers via a patient and public involvement and engagement advisory group. This group expressed strong support for a study design that enables definitive testing of drugs with promising efficacy, has broad inclusion criteria, and has design features that minimise participant burden and mitigate against the risks of attrition including remote study assessments, non-invasive outcome measures, liquid medication that can be administered in more advanced stages of disease, and

drugs with favourable safety and tolerability profiles. They were also supportive of using a study design incorporating a contemporaneous placebo group.[28]

Participants

Any individual older than 18 years with a confirmed diagnosis of motor neuron disease (including the following subtypes: amyotrophic lateral sclerosis classified by the revised El Escorial criteria [possible, probable laboratory supported, probable, and definite], primary lateral sclerosis, progressive muscular atrophy, and progressive bulbar palsy), regardless of disease duration, was eligible for screening. Broad inclusion criteria were strongly advocated by the patient and public involvement and engagement group and have increased the generalisability of the results. The exclusion criteria included frontotemporal dementia, other substantial psychiatric disorders, alcoholism, deranged liver function (alanine aminotransferase, alkaline phosphatase, bilirubin, or gamma-glutamyltransferase three times the upper limit of normal), impaired renal function (creatinine clearance or estimated glomerular filtration rate <30 mL/min), serum free T4 more than 25 pmol/L, or thyroid-stimulating hormone less than 0·2 mU/L, a corrected QT interval on 12 lead electrocardiogram more than 450 ms, ventricular arrhythmias, people already taking any of the investigational medicinal products in the protocol, and contraindications to any of the interventional medicinal products according to the summary of product characteristics. Further details on the protocol, eligibility criteria, and study design have been published previously.[11] Data on sex were self-reported and options included male or female sex assigned at birth.

All participants provided written informed consent before entering. Safety oversight was the responsibility of the Independent Data Monitoring Committee, which reviewed the accruing participant and group level data every 6 months and made recommendations to the Trial Steering Committee. Individual site monitoring for data integrity was also mandated. This clinical trial is reported in adherence to the CONSORT reporting guidelines.

Randomisation and masking

Participants were randomised (1:1:1) by a research doctor, nurse, or other trained delegated personnel using a computer-generated minimisation algorithm delivered via a secure web-based system to receive either placebo or one of the two active interventions: memantine or trazodone. The two interventions and placebo were matched in appearance and taste. The investigational medicinal products were in liquid form and could be delivered via a gastrostomy or nasogastric tube if necessary.

An Edinburgh Clinical Trials Unit programmer created the minimisation algorithm using computer-generated pseudo-random numbers to maintain unpredictability. Minimisation was based on three factors: riluzole use, use of non-invasive ventilation or gastrostomy (or both), and whether the participant was a long survivor (8 years of more since diagnosis) at the point of randomisation. Participants were allocated to the intervention that gave the best balance across all of the minimisation factors with a probability of 80%, and to another intervention with a probability of 20%.

All participants and others involved in the trial, including people giving the interventions, those assessing outcomes, and those analysing the data, were blinded to treatment allocations, except for the Independent Data Monitoring Committee, unblinded statisticians, and the central expectedness team, who reviewed adverse reactions and serious adverse reaction events.

A further investigational medicinal product, amantadine, was added to the platform on April 17, 2023, at which point the randomisation evolved to a 1:1:1:1 ratio. Introduction of amantadine was within 3 months of the data cutoff for stage two interim analysis point and thus did not contribute to this analysis.

Procedures

The investigational medicinal products or matched placebo were delivered orally as a liquid preparation and participants were titrated up to the maximum tolerated dose, which for memantine was 20 mg once a day and for trazodone was 200 mg once a day. Participants completed five appointments in the first 4–8 weeks to cover screening, baseline, and drug titration, followed by assessments every 2 months (remotely by video call or in person) until trial completion, in addition to the ALSFRS-R, we completed King's staging and safety monitoring every 2 months. The EuroQol 5 Dimension 5 Level (EQ-5D-5L), Hospital Anxiety and Depression Scale (HADS), Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS), forced vital capacity, and research bloods were completed every 6 months. Full details can be found in the protocol paper.[11]

Outcomes

The co-primary outcome measures were function, as measured by rate of change in the ALSFRS-R, and—conditional on identifying benefit on this outcome measure—survival. Comparisons were conducted in four stages with predefined criteria for futility at the end of stages one and two. Secondary objectives were to assess the adverse effect profile of candidate drugs and their effects on time to King's stage 4a (nutritional failure), time to King's stage 4b (respiratory failure), cognitive function and behaviour as assessed using the ECAS, respiratory function measured by forced vital capacity, anxiety and depression measured by the HADS, and quality of life evaluation using EQ-5D-5L. The analysis plan proposed subgroup analyses by participant characteristics, including survival duration, motor neuron disease subtypes, and genetics. Noting that the

trial design pre-specifies a futility decision based solely on rate of change of ALSFRS-R, endorsed by our patient and public involvement and engagement group, Independent Data Monitoring Committee, Trial Steering Committee, and funders, this report focuses on expeditious reporting of the primary interim analysis outcome. The statistical analysis plan for this trial prespecifies that analyses of secondary outcomes occur after formal closure of the groups, and a further round of data cleaning and analysis, which will be reported separately.

Statistical analysis

The target number of participants was based on the co-primary outcomes of ALSFRS-R and survival. The sample size calculation was based on a simulation method, informed by ALSFRS-R data from 3789 motor neuron disease patients obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Open Access ALS Clinical Trial database.[11,12] A sample size of 100 participants per group, excluding long survivors at the second interim analysis, would provide 86% probability of the treatment group continuing beyond the stage two analysis into stage three, given that the treatment has passed the stage one analysis and if there was a true 25% reduction in the rate of decline of ALSFRS-R.

ALSFRS-R comparisons were conducted at three points in time (stages), with the opportunity to stop randomisation and follow-up groups that did not meet the predefined continuation criteria at the end of stages one and two. Stage one was completed for memantine and trazodone on March 14, 2022, when a minimum of 50 participants per group (excluding long survivors, defined as >8 years since diagnosis at baseline) completed 6 months of treatment. Both memantine and trazodone were assessed against a prespecified futility measure at interim analysis one (95% CI of the rate of change in ALSFRS-R compared with placebo must include a relative improvement of 25% in the rate of decline) and both progressed to stage two. Stage two interim analysis was completed after a minimum 100 participants per group (excluding long survivors) completed a minimum of 12 months of follow-up. At the end of stage two, improvement in the rate of change in ALSFRS-R compared with placebo was required to be significant at the pairwise one-sided 10% significance level for the treatment to justify continuation to stage three. These guidelines for progression are non-binding criteria such that survival or other data could have a bearing on the decision to progress beyond each stage.

Our analysis population included all randomised participants except any participants who were long survivors at baseline, or who did not record any ALSFRS-R outcome values. Data were analysed according to the group assigned in the randomisation schedule. Full details regarding our statistical analysis and the formal interim analysis method can be found in the published statistical analysis plan.[12]

Our primary interest was in the mean difference in rate of ALSFRS-R change between each intervention and placebo. A hierarchical normal linear model (ie, mixed model) incorporating an unstructured correlation matrix for the random effects was fitted to the ALSFRS-R outcome (ALSFRS-R measured at all timepoints up to 18 months' follow-up including baseline) with the following explanatory variables: (1) measurement of time (eg, 0, 2, 4, 6 months' visit) as a factor variable; (2) interaction between time and treatment, in which treatment was a factor variable (placebo is the reference category and two dummy variables for the active treatments) and time was a continuous linear term; (3) riluzole (baseline minimisation variable); (4) non-invasive ventilation or gastrostomy (or both; baseline minimisation variable); (5) random intercept for patient; and (6) time as a random effect (random slope). For this second interim analysis, we also adjusted for stage of randomisation (stage one or two). Participants were regarded as being in stage one if they were randomised on or before March 14, 2022, which was the date the Independent Data Monitoring Committee Chair informed the Trial Steering Committee of the former's recommendation concerning continuation of the study. Participants were regarded as being in stage two if they were randomised after this date.

The model has no main effect term for treatment because randomised treatment cannot affect the pre-randomisation value of the outcome at time 0. Including the main effect for time as a factor variable allows for possible non-linear time effects.

Continuation to stage three was based on the statistical significance of the improvement in the rate of change in ALSFRS-R compared with placebo, based on the second interaction term in the earlier statistical model, using a one-sided 10% significance level. Negative values of the interaction term suggest that the active treatment is worse than placebo (ie, implies there is a stronger decline in ALSFRS-R over time in the active treatment group relative to placebo), whereas positive values imply a benefit of the active treatment relative to placebo.

For the primary analysis, all missing observations were left as missing and were assumed to be missing-at-random. Several sensitivity analyses for missing data handling were also performed as prespecified in our statistical analysis plan.[12]

A Kaplan-Meier plot was produced to compare product limit survival estimates between treatment arms, and all analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

The trial was registered on the European Clinical Trials Registry, trial registration number 2019–000099–41, and ClinicalTrials.gov on March 10, 2020, NCT04302870, and the trial is ongoing.

Role of the funding source

The funders of the study had no role in the study design or writing of the trial protocol, data collection, data

analysis, data interpretation, writing of the manuscript, or the decision to submit for publication.

Results

651 individuals were screened for enrolment to the study, of whom 80 (12%) were ineligible or declined to participate (figure 2). The first participant was randomly assigned on Feb 27, 2020. The stage two interim analysis data lock took place on July 24, 2023, by which date 554 people with motor neuron disease had been randomly assigned to memantine (183 [33%]), trazodone (185 [33%]), or placebo (186 [34%]). An amantadine treatment group was added to the trial on April 17, 2023. An additional 17 individuals had been randomly assigned to the amantadine group, but these patients are not considered further here as the amantadine group had not recruited a sufficient number to reach any of the predefined interim analysis stages. 16 (3%) long survivors at baseline were excluded from the analyses. Eight (1%) individuals were randomised with no ALSFRS-R data recorded (due to one or more sub-scores missing). The primary interim analysis population comprised 530 participants, of whom 175 (33%) had been allocated memantine, 175 (33%) had been allocated trazodone, and 180 (34%) had been allocated placebo.

Withdrawals were evenly distributed across treatment groups. Where a reason was given, the most frequent responses were: perceived lack of benefit (n=9), too ill to continue (n=7), burden of trial appointments (n=6), and adverse events (n=5).

Characteristics of the participants, including age, sex, years since first symptoms, years since diagnosis, ALSFRS-R score, motor neuron disease subtype, and site of onset, were similar across the groups (table 1). Approximately two-thirds of participants were male, with a mean age of 62 (SD 11) years, median of 2 years since first symptoms (IQR 1–4 years), and a mean ALSFRS-R score at baseline of 34 (SD 8·2).

The mean rate of change per month in ALSFRS-R was –0·650 for memantine, –0·625 for trazodone, and –0·655 for placebo (table 2, figure 3). Both one-sided p values for the mean difference between the investigational treatment and placebo were above the significance threshold of 10%, indicating that neither

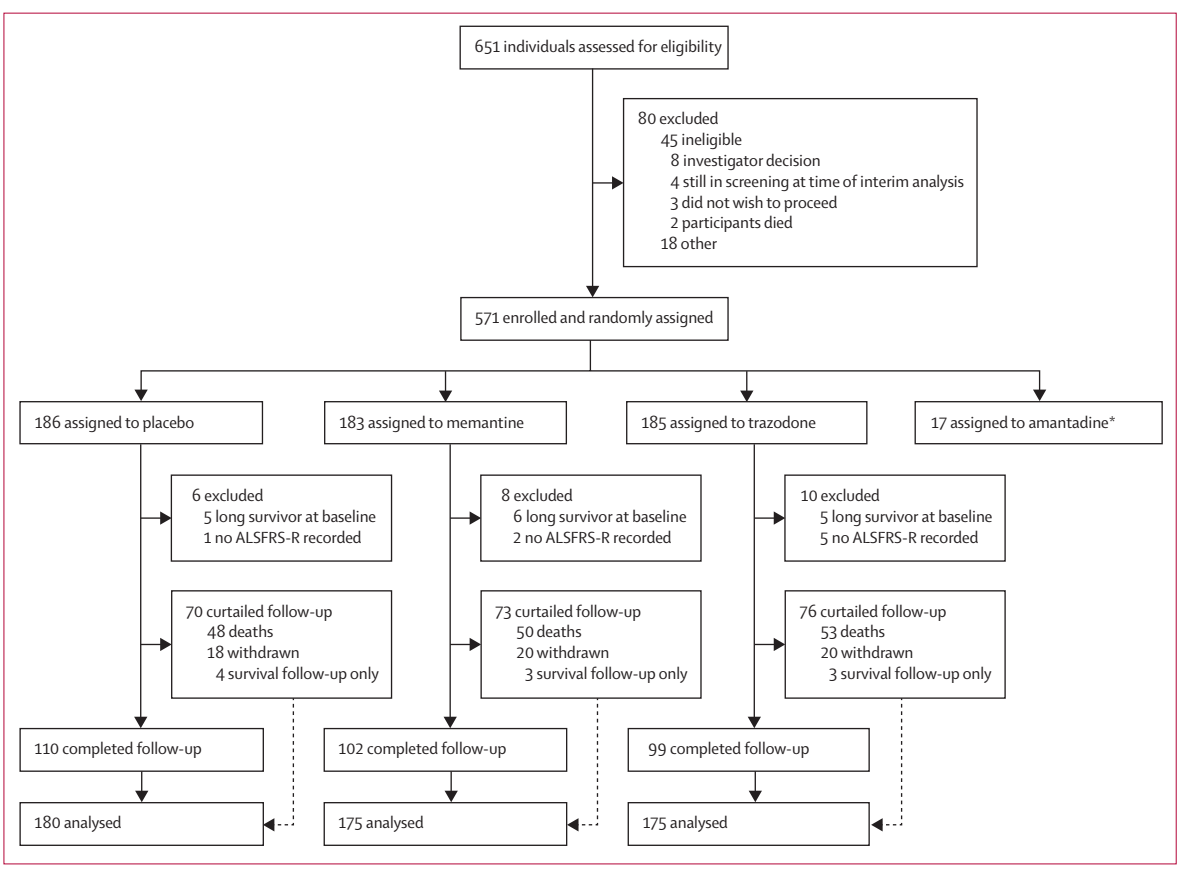


Figure 2: **Trial profile**
ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised. *The amantadine treatment group was introduced from 17 April, 2023, such that there was randomisation 1:1:1:1 into four treatment groups including amantadine from that point onwards. 17 participants were randomly assigned to amantadine up to the point of the stage 2 data cutoff for memantine and trazodone. The participants assessed for eligibility were potentially to be randomly assigned to amantadine from April 17, 2023, and therefore are not exclusive to the comparison of each of memantine and trazodone with placebo. Disregarding the amantadine treatment group, there were 554 patients randomly assigned to the comparisons reported here.

	Memantine (n=183)	Trazodone (n=185)	Placebo (n=186)	Overall (N=554)
Age, years	62·8 (9·9)	62·7 (11·1)	60·7 (11·1)	62·1 (10·8)
Sex				
Male	121 (66%)	104 (56%)	127 (68%)	352 (64%)
Female	62 (34%)	81 (44%)	59 (32%)	202 (36%)
Motor neuron disease subtype				
Amyotrophic lateral sclerosis	151 (83%)	144 (78%)	151 (81%)	446 (81%)
Primary lateral sclerosis	9 (5%)	13 (7%)	9 (5%)	31 (6%)
Progressive muscular atrophy	9 (5%)	11 (6%)	10 (5 %)	30 (5%)
Progressive bulbar palsy	10 (5%)	12 (6%)	9 (5%)	31 (6%)
Unclear or missing	4 (2%)	5 (3%)	7 (4%)	16 (3%)
Site of onset				
Bulbar	45 (25%)	50 (27%)	38 (20%)	133 (24%)
Spinal	132 (72%)	130 (70%)	141 (76%)	403 (73%)
Respiratory	3 (2%)	1 (1%)	6 (3%)	10 (2%)
Generalised	3 (2%)	4 (2%)	1 (1%)	8 (1%)
Long survivor at baseline				
No	177 (97%)	180 (97%)	181 (97%)	538 (97%)
Yes	6 (3%)	5 (3%)	5 (3%)	16 (3%)
Use of riluzole				
No	74 (40 %)	72 (39%)	71 (38%)	217 (39%)
Yes	109 (60%)	113 (61%)	115 (62%)	337 (61%)
Non-invasive ventilation or gastrostomy (or both)				
No	131 (72%)	132 (71 %)	134 (72%)	397 (72%)
Yes	52 (28%)	53 (29%)	52 (28%)	157 (28%)
King's stage at baseline				
Missing	4 (2%)	6 (3%)	2 (1%)	12 (2%)
1	19 (10%)	5 (3%)	17 (9%)	41 (7%)
2	43 (23%)	50 (27%)	51 (27%)	144 (26%)
3	49 (27%)	50 (27%)	48 (26%)	147 (27%)
4	68 (37%)	74 (40%)	68 (37%)	210 (38%)
Years since first symptoms	2·0 (1·0–4·0)	2·0 (2·0–4·0)	2·0 (1·0–5·0)	2·0 (1·0–4·0)
Years since diagnosis	0·8 (0·3–2·1)	0·8 (0·4–2·0)	0·8 (0·3–2·1)	0·8 (0·3–2·1)
ALSFRS-R total score at baseline	34·8 (8·0)	32·9 (8·2)	33·8 (8·2)	33·8 (8·2)
Participants with data available, n	179	180	184	543
Percentage predicted forced vital capacity	68·4 (28·9)	64·3 (32·0)	69·2 (26·7)	67·2 (29·3)
Participants with data available, n	74	73	64	211
EQ-5D-5L Index	0·6 (0·4–0·7)	0·5 (0·2–0·7)	0·6 (0·3–0·7)	0·5 (0·3–0·7)
Participants with data available, n	178	179	184	541
HADS total score	8·0 (5·0–13·0)	9·0 (5·0–13·0)	8·0 (5·0–12·0)	8·0 (5·0–13·0)
Participants with data available, n	178	179	184	541
ECAS amyotrophic lateral sclerosis specific total score	84·0 (77·0–89·0)	85·0 (76·0–89·0)	84·0 (75·0–89·0)	84·0 (76·0–89·0)
Participants with data available, n	177	165	173	515
ECAS amyotrophic lateral sclerosis non-specific total score	28·0 (25·0–30·0)	28·0 (26·0–31·0)	28·0 (25·0–30·0)	28·0 (25·0–30·0)
Participants with data available, n	177	165	173	515
ECAS total score	111·0 (102·0–118·0)	112·0 (103·0–119·0)	111·0 (101·0–118·0)	111·0 (102·0–118·0)
Participants with data available, n	177	165	173	515

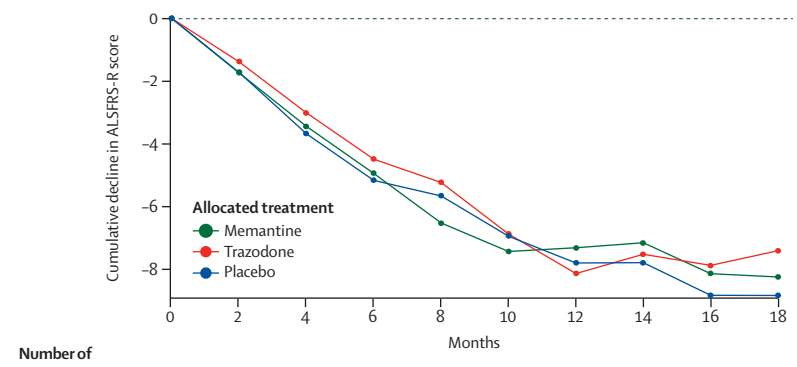
Data are n (%), median (IQR), or mean (SD) unless specified otherwise. Percents might not sum to 100 due to rounding. ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised. EQ-5D-5L=EuroQol 5 Dimension 5 Level. HADS=Hospital Anxiety and Depression Scale. ECAS=Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen.

Table 1: **Baseline characteristics of all randomised participants, including long survivors**

	Memantine	Trazodone	Placebo
Mean ALSFRS-R change per month	–0·650	–0·625	–0·655
Mean difference* (investigational treatment minus placebo)	0·033	0·065	..
One-sided 90% CI lower limit†	–0·085	–0·051	..
One-sided p value	0·36	0·24	..

ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised. *Mean absolute difference in rate of change of ALSFRS-R per month versus placebo, adjusted for measurement time as a factor variable, riluzole, non-invasive ventilation or both non-invasive ventilation and gastrostomy, random intercept for patient, study stage, and random slope (for time). Positive values indicate an improvement over placebo. †Will be more than 0 if significant at the one-sided 10% level.

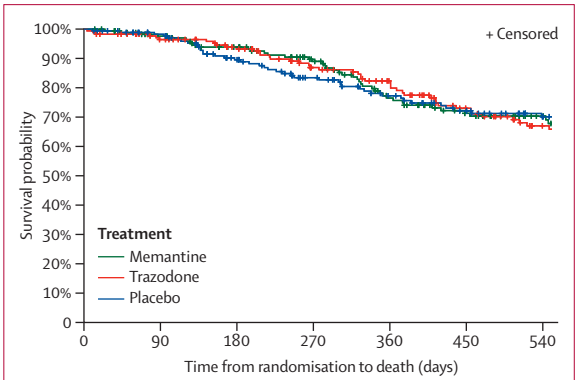
Table 2: **Summary of ALSFRS-R analyses**



Number of participants										
Memantine	173	153	132	121	107	88	71	61	46	35
Trazodone	175	150	140	129	108	96	81	62	53	43
Placebo	179	160	145	115	103	90	74	65	57	46

Figure 3: **Cumulative bimonthly rate of change in ALSFRS-R with each treatment group**
ALSFRS-R=Amyotrophic Lateral Sclerosis Functional Rating Scale Revised.

See Online for appendix



Time from randomisation to death (days)	0	90	180	270	360	250	540
Memantine	175	160 (11)	142 (23)	121 (37)	93 (49)	74 (62)	56 (79)
Trazodone	175	158 (11)	140 (24)	117 (38)	101 (48)	78 (60)	58 (74)
Placebo	180	165 (12)	137 (26)	114 (40)	95 (51)	78 (62)	62 (76)

Figure 4: **Kaplan-Meier survival plot**
Hazard ratios and 95% CIs are not provided as formal inferential comparison of survival was not prespecified for this interim analysis.

memantine nor trazodone groups met the criteria for continuation (memantine *vs* placebo: estimated mean difference 0·033, one-sided 90% CI lower level –0·085; one-sided p=0·36; trazodone *vs* placebo: 0·065, –0·051; one-sided p=0·24; table 2). Both treatment groups were discontinued. The robustness of these findings was confirmed in the sensitivity analyses for approaches to handling missing data (appendix pp 2–3). Survival estimates for each treatment group are shown in figure 4. There was no significant survival difference shown between comparisons, with 49 deaths in the memantine group, 52 deaths in the trazodone group, and 48 deaths in the placebo group (appendix p 4). There were 483 participants with at least one adverse event (145 [77%] on placebo, 170 [91%] on memantine, and 168 [90%] on trazodone; table 3). There were 88 participants with at least one serious adverse event (37 [20%] on memantine, 27 [14%] on trazodone, and 24 [13%] on placebo). A total of 11 serious adverse events led to treatment discontinuation.

Discussion

The findings of this prespecified interim analysis from the MND SMART trial showed that both memantine and trazodone had little or no effect on the primary outcome of rate of change in the ALSFRS-R at the doses evaluated, compared with placebo. Additionally, there was no evidence of a survival difference between these intervention groups and placebo. Participants randomly assigned to the memantine and trazodone groups, and those randomly assigned to placebo before the introduction of amantadine, stopped treatment and were withdrawn from the study after this lack of benefit was shown. Participants were downtitrated as per the study protocol from October, 2023, with the last participant stopping treatment on Jan 11, 2024.

Memantine and trazodone were both generally well tolerated in people with motor neuron disease, with no significant increase in adverse effects compared with placebo. The MND SMART trial is notable for reporting within 3·5 years of launch—notwithstanding COVID-19 pandemic interruptions—conclusive results for two separate interventions. If individual trials had taken place, we have estimated that these two results would have taken a minimum of 8 years to report.[9] Importantly, this trial was powered to be definitive and, therefore, unlike many other underpowered trials in motor neuron disease, means that neither of these drugs needs be tested again in motor neuron disease at the doses evaluated.[9] By historical standards, the trial is highly efficient in terms of both time and number of participants recruited and retained with high-quality data integrity.

Co-production of MND SMART alongside people living with a motor neuron disease ensured the trial met all assumptions underlying power calculations and was sensitive to detect any neuroprotective effect of the

two drugs tested, with a participant withdrawal rate (10%) lower than in historical motor neuron disease trials (around 20%).[9] The treatment groups were well matched in terms of baseline characteristics, including age, sex, site of onset, duration of disease, severity of disease at baseline, and motor neuron disease subtype. Interventions, such as use of riluzole, non-invasive ventilation, and gastrostomy, were minimised and, hence, balanced across the groups of the trials. Shortfalls in missing data bring some potential for bias; however, sensitivity analyses (including multiple imputation analyses) were supportive of the findings of the primary analysis. Broad inclusion criteria (including no restrictions on age or use of riluzole, motor neuron disease subtype, or disease stage) enabled wide participation. Baseline characteristics of participants were similar between stage one and stage two of the design (appendix pp 4–5), indicating no evidence of operational bias resulting from the multiarm, multistage design of the MND SMART trial.

In addition to the benchmark clinical outcomes of ALSFRS-R and survival, blood-based and neurophysiological measures have emerged as potential trial metrics. Neurofilament light chain has gained increasing traction as a surrogate, although it is a non-specific biomarker of axonal damage in amyotrophic lateral sclerosis. Increased emphasis has been placed on its use in motor neuron disease trials since the description of its use as a secondary outcome measure showing change in the clinical trial of tofersen in *SOD1* ALS.[8] Neurofilament light will be included as a secondary outcome measure in study protocols for future investigational groups in the MND SMART trial. In contrast, neurophysiological outcome measures are comparatively burdensome and, furthermore, there is no standardised approach for assessment and interpretation. Noting that both memantine and trazodone failed to alter the co-primary clinical outcomes of ALSFRS-R and survival following a long duration of follow-up of a large number of participants, additional secondary outcome data derived from neurofilament light and neurophysiological measures would not have changed the overall outcome of this phase 3 study.

Repurposing of old drugs for a new indication due to an off-target effect or a newly recognised on-target effect is not a new concept and, indeed, is undergoing something of a revival.[29] This approach reflects both escalating costs and time for target-led drug discovery to reach regulatory approval and powerful new methods to identify high-value de-risked repurposed drugs for a candidate disease. The MND SMART trial has adopted an integrated, structured, and unbiased approach to drug selection using both in-silico and experimental methods, which has been adapted from our earlier systems used for the neurodegenerative phase of progressive multiple sclerosis.[16,30] Central to this approach is the assessment of the provenance of claims of efficacy or mechanism engagement in preclinical and clinical literature. Nonetheless, despite strong evidence from our drug selection strategy that memantine and trazodone had biological mechanistic plausibility to be neuroprotective, our findings confirm that testing in robustly designed, adequately powered, and efficiently conducted clinical trials is necessary for definitive evaluation.

We carefully considered dose selection for both memantine and trazodone. In the absence of disease-relevant animals models for sporadic disease, prevalidated drug–target mechanisms, and opportunities to biopsy target tissues following treatment, the identification of target engagement biomarkers to accurately guide the prediction of doses of candidate drugs for complex neurodegenerative disorders such as motor neuron disease is extremely challenging. However, for approved drugs, for which sufficient clinical pharmacology information is already available, there is an opportunity to expedite clinical evaluation by extrapolation of safe and biologically active or clinically effective doses from analogous licensed indications. The doses of memantine and trazodone tested in this trial were selected judiciously, noting standard human and licensed doses used for the treatment of Alzheimer's disease (memantine) and depression (trazodone), in addition to smaller phase 2 trials conducted previously for memantine, to achieve an appropriate balance between efficacy and avoidance of attrition related to tolerability and adverse events in a vulnerable population of people with a motor neuron disease.

	Memantine	Trazodone	Placebo
Adverse events			
Participants with at least one event*	170/186 (91%)	168/187 (90%)	145/189 (77%)
Total number of events	759	940	673
Relationship to treatment			
Possibly related	295/759 (39%)	471/940 (50%)	238/673 (35%)
Unrelated	464/759 (61%)	469/940 (50%)	435/673 (65%)
Severe events	38/759 (5%)	30/940 (3%)	28/673 (4%)
Serious adverse events			
Participants with at least one event*	37/186 (20%)	27/187 (14%)	24/189 (13%)
Total number of events	41	35	28
Total events leading to treatment discontinuation	5	4	2
Total fatal events	3	3	2
Suicide	1	..	..
Bronchopneumonia	1	1	..
Urinary tract infection	1	..	..
COVID-19	..	..	1
Cardiac arrest	..	..	1
Multiorgan failure	..	1	..
Aspiration pneumonia	..	1	..

Data are n/N (%). *Number randomised at the time of the Independent Data Monitoring Committee safety report, which was on Aug 10, 2023.

Table 3: **Summary of adverse events**

Memantine and trazodone did not alter clinical outcomes in this study despite biological plausibility. This outcome is in line with most interventions tested in motor neuron disease and amyotrophic lateral sclerosis during the past decade, and reflects several challenges in the field, not least our still limited mechanistic understanding of underlying disease pathobiology. Furthermore, although there remains a possibility that there is a subgroup of individuals with motor neuron disease who would benefit from memantine or trazodone, these findings show that neither drug is generalisable to the whole population with motor neuron disease.

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Contributors
SP, JC, RS, MRM, NOC, GH, BTS, CS, JN, DL, AS, RSD, AI, SCo, ARM, NS, JRC, BV, SM, NW, BG, EM, DM, MKBP, and SCh contributed to conceptualisation of the study. SP, JN, DL, AS, RSD, AI, SCo, MKBP, and SCh contributed to the data curation. SP, JC, RS, MRM, NOC, GH, BTS, CS, JN, AS, RSD, AI, SCo, ARM, NS, JRC, RAP, CK, CJW, MKBP, and SCh contributed to the investigation. SP, JN, DL, AS, RSD, AI, SCo, DM, EM, MKBP, and SCh contributed to the funding acquisition. SP, JC, RS, MRM, NOC, GH, BTS, CS, CW, JN, DL, AS, RSD, AI, SCO, ARM, NS, JRC, RAP, CK, CJW, BV, SM, NW, BG, MKBP, and SCh contributed to the methodology. RAP, CK, and CJW contributed to the formal analysis. SP, JN, DL, AS, RSD, AI, SCo, MKBP, and SCh contributed to the project administration. SP, MKBP, and SCh contributed to resources, validation, and visualisation. SP, JN, DL, AS, RSD, AI, SCo, MKBP, and SCh contributed to the supervision of the study. SP, JC, MRM, NOC, GH, BTS, CS, JRC, RAP, CJW, MKBP, and SCh contributed to the writing of the original draft. SP, JC, RS, MRM, NOC, GH, BTS, CS, JN, DL, AS, RSD, AI, SCo, ARM, NS, JRC, RAP, CK, CJW, BV, SM, NW, BG, MKBP, and SCh contributed to the writing, review, and editing of the study. RAP and CK accessed and verified the underlying data reported in the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing
Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others in addition to individual participant data that underlie the results reported in this Article, after de-identification (text, tables, figures, and appendices). Data will be made available after direct contact with the corresponding author (suvankar.pal@ed.ac.uk). All data requests should be submitted to SP and SC for consideration in the first instance. Access to available fully anonymised data can be granted 12 months after publication, after review by SP, SC, and the sponsor (University of Edinburgh) to achieve the aims in the approved proposal. 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. Proposals can be submitted up to 36 months following Article publication. The study protocol and statistical analysis plan have been previously published (through open access). The informed consent form and clinical study report will also be available.

Declaration of interests
We declare no competing interests.

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Euan MacDonald, a co-author of this manuscript, died on Aug 21, 2024. Euan was an extraordinary man who through his vision, advocacy, and leadership brought hope and helped transform the lives of countless people living with motor neuron disease and other disabilities. Following his diagnosis of motor neuron disease, Euan and his father Donald established, through a philanthropic gift in 2007, the Euan MacDonald Centre for MND Research at the University of Edinburgh. As a direct result of this far-sighted investment, we presently lead a number of successful programmes of research from discovery science to clinical trials including the landmark MND SMART trial.

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