Safety, efficacy, and tolerability of memantine for cognitive and adaptive outcome measures in adolescents and young adults with Down syndrome: a randomised, double-blind, placebo-controlled phase 2 trial

Alberto C S Costa, Ana C Brandão, Richard Boada, Veridiana L Barrionuevo, Hudson G Taylor, Elizabeth Roth, Melissa R Stasko, Mark W Johnson, Fernanda F Assir, Maria P Roberto, Patrícia Salmona, Guilherme Abreu-Silveira, Ilya Bederman, Erin Prendergast, Anke Hüls, Sarina Abrishamcar, Zan Mustacchi, Thomas Scheidemantel, Nancy J Roizen, Stephen Ruedrich

Summary

Background Down syndrome is a chromosomal disorder with considerable neurodevelopmental impact and neurodegenerative morbidity. In a pilot trial in young adults with Down syndrome, memantine (a drug approved for Alzheimer's disease) showed a significant effect on a secondary measure of episodic memory. We aimed to test whether memantine would improve episodic memory in adolescents and young adults with Down syndrome.

Methods We did a randomised, double-blind, placebo-controlled phase 2 trial with a parallel design, stratified by age and sex. Participants (aged 15–32 years) with either trisomy 21 or complete unbalanced translocation of chromosome 21 and in general good health were recruited from the community at one site in Brazil and another in the USA. Participants were randomly assigned (1:1) to receive either memantine (20 mg/day orally) or placebo for 16 weeks. Computer-generated randomisation tables for both sites (allocating a placebo or drug label to each member of a unique pair of participants) were centrally produced by an independent statistician and were shared only with investigational pharmacists at participating sites until unblinding of the study. Participants and investigators were masked to treatment assignments. Neuropsychological assessments were done at baseline (T1) and week 16 (T2). The primary outcome measure was change from baseline to week 16 in the California Verbal Learning Test–second edition short-form (CVLT-II-sf) total free recall score, assessed in the per-protocol population (ie, participants who completed 16 weeks of treatment and had neuropsychological assessments at T1 and T2). Linear mixed effect models were fit to data from the per-protocol population. Safety and tolerability were monitored and analysed in all participants who started treatment. Steady-state concentrations in plasma of memantine were measured at the end of the trial. This study is registered at ClinicalTrials.gov, number NCT02304302.

Findings From May 13, 2015, to July 22, 2020, 185 participants with Down syndrome were assessed for eligibility and 160 (86%) were randomly assigned either memantine (n=81) or placebo (n=79). All participants received their allocated treatment. Linear mixed effect models were fit to data from 149 (81%) participants, 73 in the memantine group and 76 in the placebo group, after 11 people (eight in the memantine group and three in the placebo group) discontinued due to COVID-19 restrictions, illness of their caregiver, adverse events, or low compliance. The primary outcome measure did not differ between groups (CVLT-II-sf total free recall score, change from baseline 0·34 points [95% CI –0·98 to 1·67], p=0·61). Memantine was well tolerated, with infrequent mild-to-moderate adverse events, the most common being viral upper respiratory infection (nine [11%] participants in the memantine group and 12 [15%] in the placebo group) and transient dizziness (eight [10%] in the memantine group and six [8%] in the placebo group). No serious adverse events were observed. Amounts of memantine in plasma were substantially lower than those considered therapeutic for Alzheimer's disease.

Interpretation Memantine was well tolerated, but cognition-enhancing effects were not recorded with a 20 mg/day dose in adolescents and young adults with Down syndrome. Exploratory analyses point to a need for future work.

Funding Alana Foundation.

Introduction

Down syndrome is the classic eponymic designation for the set of phenotypes of variable expressivity that typically results from trisomy 21,[1] with an incidence of one per 732 live births.[2] People with Down syndrome are especially susceptible to neurodevelopmental and neurodegenerative disorders. The intellectual disability displayed by individuals with Down syndrome is generalised in nature, resulting in a mean intelligence quotient that is more than 3 SDs lower in school-age individuals with

Lancet Neurol 2022; 21: 31–41

See Comment page 22

For the Portuguese translation of the abstract see Online for appendix 1

Department of Pediatrics (Prof A C S Costa MD, E Roth PhD, M R Stasko MA, M W Johnson PhD, Prof N J Roizen MD), **Department of Psychiatry** (Prof A C S Costa, T Scheidemantel MD, Prof S Ruedrich MD), **and Department of Genetics and Genome Sciences** (I Bederman PhD, E Prendergast BS), **School of Medicine, Case Western Reserve University, Cleveland, OH, USA; Hospital Israelita Albert Einstein, São Paulo, Brazil** (A C Brandão MD, F F Assir MS, M P Roberto MS, G Abreu-Silveira MD); **Department of Pediatrics, School of Medicine, University of Colorado Aurora, CO, USA** (R Boada PhD); **São Paulo Center for Clinical Studies and Research–CEPEC-SP, São Paulo, Brazil** (V L Barrionuevo BS, P Salmona MD, Z Mustacchi MD); **Center for Biobehavioral Health, Nationwide Children's Hospital Research Institute, Ohio State University, Columbus, OH, USA** (Prof H G Taylor PhD); **Department of Epidemiology** (A Hüls PhD, S Abrishamcar BS) **and Gangarosa Department of Environmental Health** (A Hüls), **Rollins School of Public Health, Emory University, Atlanta, GA, USA**

Correspondence to:
Prof Alberto C S Costa, Division of Neurology and Epilepsy, Department of Pediatrics, School of Medicine, Case Western Reserve University, Cleveland 44106, OH, USA
alberto.costa@case.edu

Research in context

Evidence before this study

We searched PubMed from database inception to May 13, 2015, using the search terms "(Down syndrome) AND (memantine)", with no language restrictions. Memantine, the uncompetitive antagonist of the NMDA subtype of glutamate receptors, enhanced memory and learning and reversed alterations in synaptic plasticity in a mouse model of Down syndrome. Moreover, in a pilot randomised trial involving young, otherwise healthy, adults with Down syndrome, 16 weeks' treatment with memantine (20 mg/day) was shown to improve scores in one of the secondary measures, the California Verbal Learning Test–second edition short-form (CVLT-II-sf) total free recall score (a measure of episodic memory). However, a larger phase 2 randomised trial of 1-year treatment with memantine (10 mg/kg) in adults with Down syndrome older than 40 years found no efficacy signal of memantine in improving cognitive and adaptive function. Since many participants in that study were already affected by dementia, it was difficult to establish whether the absence of measurable cognitive efficacy in that trial was being masked by the coexistence of neurodegenerative processes in the study participants.

Added value of this study

We did this study to assess the safety and efficacy of memantine for enhancing episodic memory of individuals with Down syndrome. This randomised, double-blind, placebo-controlled phase 2 trial is one of the largest clinical trials in the field of Down syndrome to date. In addition to well established measures of cognitive function and clinical assessments, including CVLT-II-sf, the study provides data on anxiety measures, QTc interval, and concentrations in plasma of memantine in otherwise healthy adolescents and young adults with Down syndrome.

Implications of all the available evidence

As of Nov 17, 2021, no drug targeting cognitive deficits or dementia associated with Down syndrome has shown efficacy in this population. Therefore, pharmacological therapies to counteract both the neurodevelopmental and neurodegenerative aspects of Down syndrome are major unmet needs for people with this genetic disorder. Although the proof-of-principle that these aspects of Down syndrome can be addressed pharmacologically remains elusive, the possibility that larger doses of memantine than those approved for the treatment of people with Alzheimer's disease could be efficacious in enhancing episodic memory and short-term (or working) memory in individuals with Down syndrome should be investigated further.

Down syndrome than that in their typically developing peers.[3] Additionally, disproportionate deficits in the cognitive processes that are heavily dependent on the hippocampus and prefrontal cortex have consistently been reported.[4,5] Alzheimer's disease neuropathology is universal by 40 years of age in people with Down syndrome, and the mean age of onset of clinical dementia is about 55 years.[6] Therefore, pharmacological therapies to counteract the neurodevelopmental and neurodegenerative aspects of Down syndrome are major unmet needs.

During the past two decades, many reports have been published on the pharmacological rescuing of learning and memory deficits or on the prevention of cholinergic or adrenergic neurodegeneration in mouse models of Down syndrome.[7–10] However, there is still no solid clinical evidence supporting the notion that cognitive ability can be enhanced or that the neurodegeneration typical of Alzheimer's disease can be delayed by pharmacological means in people with Down syndrome.

Memantine, an uncompetitive antagonist of the NMDA subtype of glutamate receptors, was approved in the EU and USA in the early 2000s for the treatment of individuals with moderate-to-severe Alzheimer's disease.[11] This drug displays detectable but modest efficacy in the treatment of Alzheimer's disease when used alone or in combination with cholinesterase inhibitors.[12]

On the basis of preclinical evidence from mouse models of Down syndrome,[7,13,14] we hypothesised that dysfunction of NMDA receptors might have a substantial pathogenic role in both the neurodevelopmental and neurodegenerative components of Down syndrome.[15] In a pilot trial of memantine aimed at enhancing the hippocampus-dependent cognitive abilities of young adults with Down syndrome,[16] no significant differences were observed between the memantine and placebo groups on two primary outcome measures. However, a significant improvement in the memantine group was detected on one of the secondary measures of hippocampus-dependent function, the California Verbal Learning Test–second edition short-form (CVLT-II-sf) total free recall score. A post-hoc power analysis of these data provided results that were encouraging enough to warrant the design and implementation of a follow-up clinical trial of memantine in people with Down syndrome.[17] We aimed to study the effects of 16 weeks of memantine treatment on cognitive function of adolescents and young adults with Down syndrome.

Methods

Study design and participants

We did a randomised, double-blind, placebo-controlled, phase 2 trial, with a parallel design, stratified by age and sex, in adolescents and young adults with Down syndrome. Participants were recruited from two sites,

one in Brazil (Hospital Israelita Albert Einstein, São Paulo) and the other in the USA (University Hospitals, Cleveland, OH).

Participants were recruited from the community with the support of several Down syndrome parent associations and clinics. The complete list of inclusion and exclusion criteria for participants can be found in the appendix 2 (p 1). Briefly, we recruited individuals (aged 15–32 years) with cytogenetically documented trisomy 21 or complete unbalanced translocation of chromosome 21 who were in generally good health (appendix 2, p 1). A reliable family member or caregiver agreed to accompany the participant to all visits, provide information about the participant as required by the protocol, ensure compliance with the medication schedule, and help the participant complete the study assessments. We used no specific cognitive level to exclude participants. Instead, the principal investigator of each site would make a clinical determination on the basis of their experience regarding each participant's ability to cope with the demands of the study, in consultation with the family member or caregiver.

Written informed consent was obtained from the participant and their caregiver. Assents were obtained directly from the participants after a simplified explanation of the study procedures. The protocol for the study (appendix 3) was approved by the Institutional Review Board of the University Hospitals in Cleveland (#06-14-41). The study received additional approval by the Institutional Review Board of Hospital Israelita Albert Einstein in São Paulo (#1.543.943) and the Brazilian Federal Ethics Committee (CONEP, CAAE: 54952916.7.0000.0071). The trial was done according to the principles outlined in the Declaration of Helsinki.

Randomisation and masking

We balanced the groups of the study in a systematic way by recruiting pairs of participants harmonised by sex and age (within 3 years) at each study site. Computer-generated randomisation tables for both sites (allocating either a placebo or memantine label to each member of a unique pair of participants) were produced by an independent statistician assigned to our study by the Clinical and Translational Science Collaborative of Cleveland (appendix 2, pp 2–3). Randomisation table contents were shared only with the investigational pharmacy at each study site until formal unblinding at the end of the trial data collection phase. To document that no post-hoc changes were made to the data, before unblinding of the trial, the principal investigator of the study (ACSC) submitted an electronic copy of the collected data to an independent statistician at the Clinical and Translational Science Collaborative of Cleveland, and only then made a formal request for the randomisation tables to the pharmacists of both sites (appendix 2, pp 2–3).

Commercial-grade memantine capsules were purchased from either Forest Laboratories (New York, NY, USA) or Dr Reddy's Laboratories (Shreveport, LA, USA) and were over-encapsulated by University of Iowa Pharmaceuticals (Iowa City, IA, USA). Identical, matching placebo capsules consisting of gelatin shells filled with microcrystalline cellulose were manufactured by University of Iowa Pharmaceuticals. Containers were marked with the randomisation code, without any information about their content, which masked the participant and investigators to the treatment assignment.

Procedures

See Online for appendix 2

All participants were screened by the principal investigator at their study site, which was witnessed by a study coordinator. The screening visit was followed by a 1-h clinical (baseline) visit to confirm the participant met inclusion criteria, to take a clinical history, and to do a physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory assessments. Neuropsychological assessments were done at a separate visit lasting 2·0–2·5 h (T1 [baseline] visit), at which tests were applied methodically and interactively by a neuropsychologist or a psychometrist under direct supervision of a neuropsychologist. At week 8 of treatment, participants had a follow-up clinical visit lasting 30–45 min and comprising a physical examination, monitoring of vital signs, reporting of adverse events, and assessment of compliance. At week 16 of treatment, participants had a second neuropsychological visit lasting 2·0–2·5 h (T2 visit), at which visit the same test battery was done as at the T1 (baseline) visit. For both T1 and T2 visits, neuropsychological assessments always started at 1000 h (range 0900–1100 h) to avoid circadian effect confounders. The T2 visit was followed by a final (week 16) clinical visit lasting 1 h, consisting of a physical examination, ECG, clinical laboratory tests, and adverse event and compliance assessments (appendix 2, pp 5–6).

See Online for appendix 3

Drug dosage followed the standard titration schedule for memantine in the treatment of Alzheimer's disease (week 1, 5 mg once a day; week 2, 5 mg twice a day; week 3, 15 mg given in two divided doses per day [one 5 mg and the other 10 mg]; week 4–16, 10 mg twice a day). Caregivers took responsibility for overseeing administration of medication to the participants. Medication compliance was assessed at the week 8 clinical visit and at the final (week 16) clinical visit. At each of these visits, the medication bottles from the previous treatment period were returned to the investigator. Compliance was calculated by dividing the number of daily doses removed from the bottle by the number of days of the treatment period. After compliance was recorded in the case report form, bottles with remaining capsules were returned to the sites' investigational pharmacies for documentation and disposal. We set minimum compliance at 80% for a participant in the memantine group to be included in the efficacy analysis (appendix 2, pp 20–21).

Concentrations in plasma of memantine were measured as previously reported,[18] after all clinical

data had been collected, by two researchers (IB and EP) who were unaware of treatment assignments (appendix 2, p 7).

Outcomes

The primary efficacy measure was CVLT-II-sf total free recall score, a measure of episodic verbal memory chosen specifically because it was the only measure that showed a significant difference in performance between memantine and placebo in a pilot study.[16] We hypothesised that participants assigned memantine would show a greater change from baseline to week 16 in CVLT-II-sf total free recall scores than participants assigned placebo. The primary outcome was assessed in the per-protocol population, which consisted of participants who completed 16 weeks of treatment and were evaluated neuropsychologically at T1 and T2.

Secondary neuropsychological outcome measures were: the matrices subtest of the Differential Ability Scales II (DAS-II); Test for Reception of Grammar II; Peabody Picture Vocabulary Test IV (PPVT-IV); DAS-II recall of digits forward; spatial span (from the Cambridge Neuropsychological Test Automated Battery [CANTAB]); paired associates learning (from CANTAB); pattern recognition memory (from CANTAB); spatial working memory (from CANTAB); Go–No Go task; and Revised Scales of Independent Behavior (SIB-R). We also quantified the CVLT-II-sf recall discriminability subscore. Some tests were implemented as corroborating measures (ie, measures aiming at overlapping cognitive domains to the CVLT-II-sf) and some measures were simply discriminant measures (ie, measures for which we had no previous reason to suspect that they would change in response to memantine treatment and, as such, were included to help assess whether any observed effect of memantine was specific to the known mode of action of this drug; appendix 2, pp 8–9).[17] Secondary outcome measures were assessed in the per-protocol population.

All assessments used in the neuropsychological test battery were selected with the overall cognitive ability of the participants in mind. For most tests, age-norms were not applicable. Raw scores were used as dependent variables in almost all cases, except for the SIB-R and DAS-II matrices subtest. An intermediate ability score derived from Rasch scaling methodology was used for the DAS-II matrices subtest, which allows comparison among participants but is not a standard score. For the SIB-R and PPVT-IV, standard USA score tables were used to provide a unified metric to integrate data across sites in the description of the baseline characteristics of the study groups. Finally, because increased anxiety was reported by two participants in the memantine group during the pilot study,[15] we used the Screen for Childhood Anxiety Related Emotional Disorders (a self-report instrument) as a means of detecting and quantifying this potentially important adverse event. Data on these outcomes were assessed at both the Cleveland and São Paulo sites (appendix 2, pp 18–20).

The trial protocol also included (as exploratory parallel experiments) collection of evoked EEG data, to test auditory brainstem response and mismatch negativity, and 7-Tesla MRI. Analysis of EEG data is underway and will be reported separately. Baseline 7-Tesla MRI data have been published elsewhere.[19] MRI data were only collected at the Cleveland site and were only intended to be obtained in a subgroup of 30 participants. Because of expected factors (ie, use of metallic orthodontic appliances) and unexpected factors (ie, early termination of trial procedures due to COVID-19), not enough data were collected for robust statistical analysis of potential effects of memantine on MRI measures.

To assess the effect of memantine concentrations in plasma on neuropsychological measures, we did two post-hoc analyses. First, we validated the results of the drug-versus-placebo comparison by estimating associations between plasma memantine concentrations of more than 0·4 µmol/L versus less than or equal to 0·4 µmol/L, with changes in neuropsychological outcomes. Second, we restricted the analyses to data from participants with memantine concentrations in plasma of more than 0·4 µmol/L and their matched placebo counterparts, to remove potential bias caused by concentrations in plasma of memantine well below the therapeutic range.

Adverse events were analysed in the safety population, which consisted of participants who started treatment, even if they then discontinued it. Adverse events were reported to the clinician by the participant or caregiver at the week 8 clinical visit and at the final (week 16) clinical visit, but participants had access to the study coordinators and clinicians at all times if necessary. Periodic review of progress and adverse events in this trial were done through annual meetings of the Data Safety Monitoring Board. The function of the Data Safety Monitoring Board was to monitor the safety data being generated by the clinicians in this trial to establish if the risk–benefit ratio was acceptable to continue this trial and report to the University Hospitals' Institutional Review Board.

Statistical analysis

The sample size for the study was calculated using data from the pilot study of memantine versus placebo.[16] 100 participants per treatment group were expected to provide more than 99·9% conditional power to detect a between-group mean difference (from baseline to week 16) of 4 points on the CVLT-II-sf total free recall score, with a two-tailed paired design and an α threshold of 0·05 (PASS 12 software [NCSS, Kaysville, UT, USA]; calculated during the planning stages of this study on Sept 30, 2013). These calculations were based on the number of participants in the pilot study (n=37) and an SD of 8·3. Because of the proof-of-principle nature of the pilot trial, we had no means of predicting whether this

4-point change would be clinically significant in individuals with Down syndrome. The predicted power using this method was 55·8%. Other methods to calculate power were used contemporaneously, including calculations for a trial not using a paired design. For example, the power calculation for a simple parallel design, with an effect size of 4 and an SD of 8·3, would give a sample size of 92, which was still consistent with 100 participants per group.

Risk differences and 95% (Wilson) CIs between adverse event frequencies in the memantine and placebo groups of the safety population were calculated in R (version 4.0.0) using the binom.confint function. For the main analyses of primary and predefined secondary outcome measures, linear mixed models were implemented in the per-protocol population, with visit (baseline *vs* 16 weeks) as the within-participant variable and medication status (placebo *vs* memantine) as the between-participant variable, using a restricted maximum likelihood approach for the estimate of parameters. Each primary and secondary cognitive and adaptive functioning variable was independently tested as the dependent measure. Analyses were done in R using the lmer function in the lme4 package.[20] An unstructured covariance matrix was used, and degrees of freedom were calculated using the Satterthwaite's method as implemented in lme4.[20] Any observation with missing data was dropped to ensure a complete-case analysis. As a random intercept was included for pair assignment, analyses were not restricted to participants with a matched counterpart who completed the treatment. Primary analyses tested for a significant association between medication status (treatment *vs* placebo) and change in neuropsychological outcomes between T1 and T2. Sensitivity analyses were done, in which all associations were adjusted for fixed effects of sex, study site, age, level of intellectual disability, and highest education among parents. PPVT-4 scaled scores were used as a proxy for level of general intelligence. A two-sided α of 0·050 was selected as the criterion for significance for the primary outcome, and 0·025 was selected for the predefined secondary outcomes on the basis of least-square means. Analyses of multiple secondary outcomes were not adjusted for multiple testing because findings for secondary outcomes were treated as exploratory results, which require further confirmatory studies to support them.[21]

Due to the slow pace of recruitment in the initial years of the study, an important protocol alteration was made to include a provision that participants who dropped out because of adverse events (but not serious adverse events) could be replaced. Under this modification, participants who dropped out because of adverse events would still be counted for the purpose of safety and tolerability statistics. This modification was done because of concerns about a potential excess of missing data for efficacy and loss of power due to dropouts. However, only three participants were replaced in the data analysis. A description of how this study was affected by COVID-19, in accordance with the CONSERVE guidelines,[22] is included in the appendix 2 (p 7).

This study is registered at ClinicalTrials.gov, number NCT02304302.

Role of the funding source

The trial investigators developed the protocol, which was then approved by the funder. The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication.

Results

From May 13, 2015, to July 22, 2020, 185 individuals with Down syndrome (aged 15–32 years) were recruited. After assessment for eligibility, 160 (86%) people were randomly assigned either memantine (n=81) or placebo (n=79; figure 1). Although the sample size calculation required 200 participants to be recruited, restrictions imposed due to the COVID-19 pandemic compelled us to

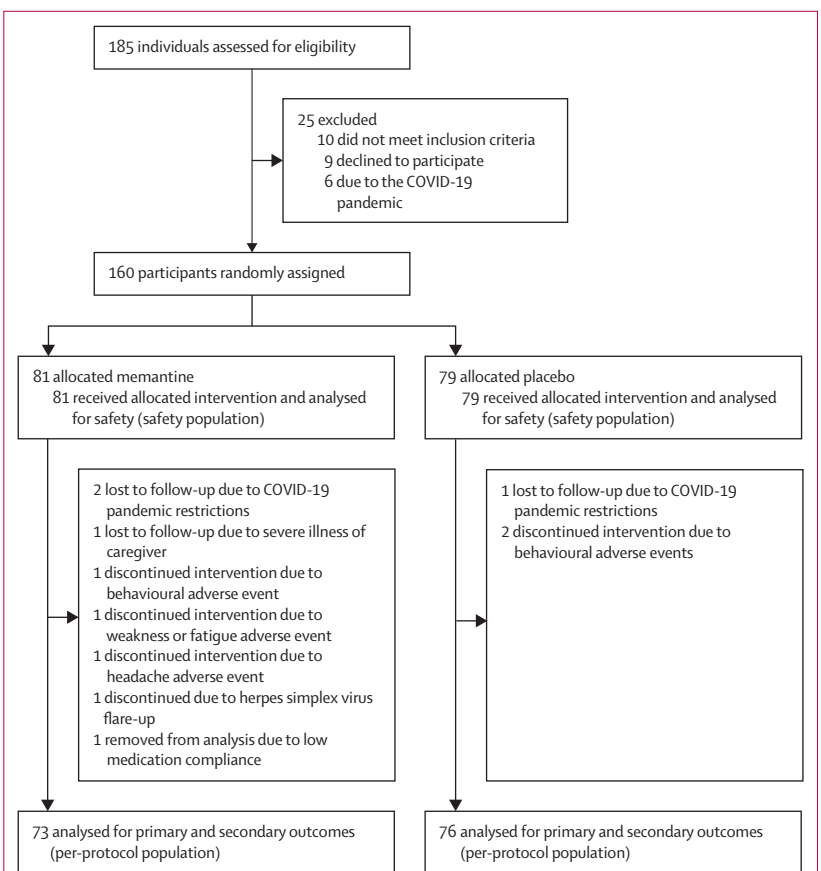

Figure 1: **Trial profile**
Excluded participants did not receive study medication and were not assessed for the primary or secondary outcome measures. Participants who discontinued received the study medication and had neuropsychological assessments at baseline but not at week 16.

lower our recruitment goal. Data collection ended on July 22, 2020, at the Cleveland and São Paulo sites. Seven people assigned memantine and three people assigned placebo did not complete 16 weeks of treatment or have neuropsychological assessments at T1 and T2 visits. Additionally, one person in the memantine group was excluded from the outcome analysis because of medication compliance less than 80%. Thus, the per-protocol population consisted of 73 participants assigned memantine and 76 participants assigned placebo. All participants received their assigned treatment; therefore, the safety population consisted of 81 participants in the memantine group and 79 participants in the placebo group.

Of the 160 randomly assigned participants, 153 had cytogenetic diagnostics of trisomy 21, six had complete unbalanced Robertsonian translocations (five involved chromosomes 14 and 21; one involved two chromosomes 21), and one had trisomy 21 with a balanced reciprocal translocation of chromosomes 2 and 16. Baseline characteristics were similar in the placebo and memantine groups (table 1). Use of concomitant medications did not differ between groups. Antihistamines (in 31 [19%] individuals), antibiotics used to treat intervening bacterial infections (25 [16%]), nasal steroids (11 [7%]), and bronchodilators (8 [5%]) were the most common. In terms of common comorbidities of Down syndrome relevant to general clinical practice, the three most frequent conditions observed were hypothyroidism (37 [47%] individuals in the placebo group and 41 [51%] in the memantine group), obesity (24 [30%] and 25 [31%]), and obstructive sleep apnoea (11 [14%] and 13 [16%]). Participants with hypothyroidism were required to be on a stable dose of levothyroxine for at least 3 months before screening and have normal amounts in serum of thyroxine and thyroid-stimulating hormone at screening. Other frequent conditions were refraction errors (44 [56%] in the memantine group and 40 [49%] in the placebo group), strabismus (12 [15%] and 16 [20%]), sinus bradycardia (heart rate <60 beats per min; 14 [18%] and 12 [15%]), and a history of surgically corrected or clinically quiescent congenital heart defect (17 [20%] and 20 [15%]). The memantine and placebo groups were similar in terms of incidence of these comorbid medical conditions.

All but one participant in the memantine group recorded at least 80% treatment compliance at 16 weeks (most had documented compliance of more than 90%).

	Memantine group (n=81)	Placebo group (n=79)
Cleveland site	35 (43%)	32 (41%)
São Paulo site	46 (57%)	47 (59%)
Sex		
Male	38 (47%)	36 (46%)
Female	43 (53%)	43 (54%)
Age at time of randomisation (years)	20·4 (4·7)	20·3 (4·2)
Socioeconomic status (parent years of education)		
Mother	14·4 (3·8)	14·6 (3·9)
Father	14·5 (3·9)	13·8 (4·3)
Comorbidities		
Hypothyroidism*	41 (51%)	37 (47%)
Obesity†	25 (31%)	24 (30%)
Sleep apnoea	13 (16%)	11 (14%)
Diabetes	3 (4%)	0
CVLT-II-sf total free recall score	12·8 (6·4)	14·2 (7·1)
DAS-II matrices ability score‡	51·4 (13·4)	51·5 (12·3)
SIB-R broad independence standard score	43·0 (22·8)	45·9 (25·7)
PPVT-IV§		
Standard score	45·4 (20·7)	46·6 (18·6)
Level of intellectual disability		
Severe	30 (37%)	22 (28%)
Moderate	25 (31%)	29 (37%)
Mild to typical	26 (32%)	28 (35%)
(Continued from previous column)		
Concomitant medications¶		
Antihistamines	13 (16%)	18 (23%)
Antibiotics	14 (17%)	11 (14%)
Nasal steroids	6 (7%)	5 (6%)
Bronchodilators	3 (4%)	5 (6%)
Proton pump inhibitors	5 (6%)	3 (4%)
Serotonin reuptake inhibitors	1 (1%)	4 (5%)
Inhaled corticosteroids	2 (2%)	3 (4%)
Methylphenidate	3 (4%)	2 (3%)
Simvastatin	3 (4%)	1 (1%)
Metformin	3 (4%)	0
Angiotensin-converting enzyme inhibitors	2 (2%)	0

Data are n (%) or mean (SD), unless otherwise stated. Because of differences in the accepted standards for recording ethnicity between the USA and Brazil, we did not record this characteristic. CVLT=California Verbal Learning Test. DAS=Differential Ability Scales. PPVT=Peabody Picture Vocabulary Test. SIB-R=Scales of Independent Behavior-Revised. *Controlled with levothyroxine. †Body-mass index 30 kg/m^2 or higher. Scaled scores below the floor value were set to zero. ‡Rasch model-weighted intermediate score used to convert raw scores to T-scores when different sets of items are administered to patients; it is not equivalent to a standard score. DAS-II does not have norms for participants older than 17 years. §PPVT-IV standard scores are provided for describing the population with respect to level of cognitive functioning. PPVT-IV raw scores were used in all other analyses. ¶Concomitant medications taken by two or more participants during the trial (other than nutritional supplements and over-the-counter pain medications). Some medications were for an acute condition (eg, antibiotics to treat streptococcal pharyngitis or acute otitis media) whereas others were used chronically (eg, serotonin reuptake inhibitors, typically used for control of anxiety in this cohort; or angiotensin-converting enzyme inhibitors). A few participants were taking stable doses of centrally acting medications before and during this study, comprising methylphenidate (n=5), sertraline (n=3), citalopram (n=1), fluoxetine (n=1), phenytoin (n=1), clonazepam (n=1), lithium (n=1), amfetamine and dexamfetamine (n=1), and clonidine (n=1).

Table 1: **Baseline characteristics of randomised participants (safety population)**

In the placebo group, three of 76 participants had treatment compliance that was slightly less than 80% (75%, 79%, and 79%), but these people were included in the analysis of primary and secondary outcomes since medication levels should not be affected by compliance in the placebo group (appendix 2, pp 2–21).

Results of linear mixed effect model analyses in the per-protocol population showed no significant differences between memantine and placebo for the primary outcome of change from baseline in CVLT-II-sf total free recall score (0·34 points [95% CI –0·98 to 1·67]; p=0·61) or for any secondary outcome measure (figure 2, table 2). All associations were robust to additional adjustments for sex, study site, age, level of intellectual disability, and socioeconomic status (appendix 2, pp 13–14).

No serious adverse events or clinically relevant laboratory changes were reported, including no evidence of memantine-induced QT or QTc interval prolongation or anxiogenic effects (appendix 2, pp 17–20). Recorded adverse events were few and mild, and were similar in frequency between the memantine and placebo groups (table 3). The most common adverse event was viral upper respiratory infection in participants from both groups during the study. In the clinicians' expert opinion based on narrative description by the caregiver or participant and on physical examination, transient episodes of dizziness appeared to be more intense in those taking memantine. Except for one participant whose episodes resolved spontaneously after the end of the study intervention, dizziness episodes resolved spontaneously during the study; all participants with dizziness completed 16 weeks of treatment. Visual hallucinations (perceived distortion of their mirror-

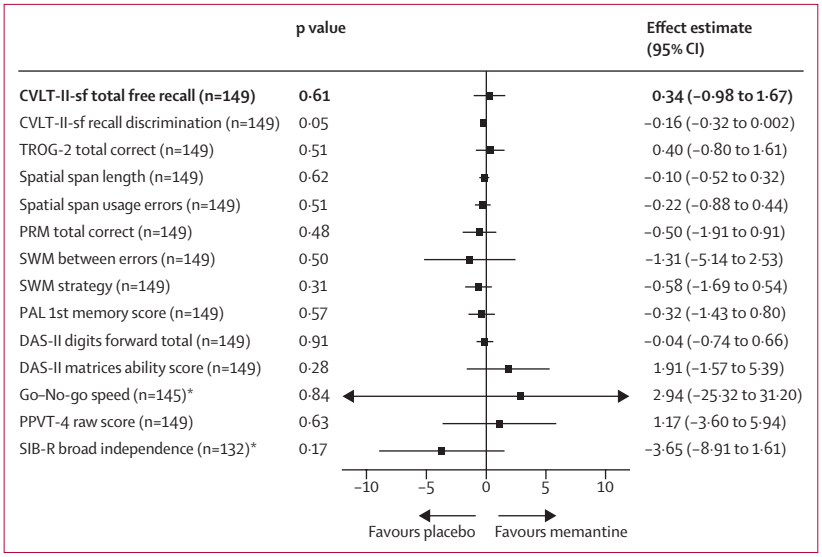

Figure 2: **Neuropsychological outcomes in the per-protocol population**
Effect estimates and 95% CIs for group differences in test scores from baseline to week 16 are presented. CVLT=California Verbal Learning Test. DAS=Differential Ability Scales. PAL=paired associates learning. PPVT=Peabody Picture Vocabulary Test. PRM=pattern recognition memory. SIB-R=Scales of Independent Behavior-Revised. SWM=spatial working memory. TROG=Test for Reception of Grammar. *Some participants chose not to undergo the questionnaire or task, or stopped midway.

	Memantine group (n=73)			Placebo group (n=76)			Group difference (95% CI)	p value
	Baseline	Week 16	Change from baseline	Baseline	Week 16	Change from baseline		
CVLT-II-sf total free recall correct	12·73 (6·60)	16·22 (8·03)	3·49 (4·50)	14·29 (7·05)	17·59 (6·85)	3·30 (5·15)	0·34 (–0·98 to 1·67)	0·61
CVLT-II-sf recall discrimination score	0·96 (0·81)	1·15 (0·92)	0·19 (0·51)	1·04 (0·85)	1·40 (0·79)	0·36 (0·60)	–0·16 (–0·32 to 0·002)	0·050
TROG-2 total correct	18·58 (5·84)	19·47 (6·70)	0·89 (3·39)	18·75 (5·90)	19·24 (5·96)	0·49 (4·01)	0·40 (–0·80 to 1·61)	0·51
Spatial span length	3·15 (1·43)	3·18 (1·58)	0·03 (1·29)	2·78 (1·77)	2·91 (1·57)	0·13 (1·30)	–0·10 (–0·52 to 0·32)	0·62
Spatial span usage errors	2·52 (1·88)	2·56 (1·89)	–0·04 (2·31)	2·36 (1·85)	2·20 (1·76)	0·16 (1·96)	–0·22 (–0·88 to 0·44)	0·51
PRM total correct	22·41 (5·83)	22·36 (5·33)	–0·05 (4·48)	22·71 (5·93)	23·16 (5·79)	0·45 (4·24)	–0·50 (–1·91 to 0·91)	0·48
SWM between errors	69·60 (14·07)	71·00 (13·00)	–1·40 (11·66)	71·74 (16·78)	71·83 (18·58)	–0·09 (11·99)	–1·31 (–5·14 to 2·53)	0·50
SWM strategy score	38·70 (2·83)	38·85 (3·11)	–0·15 (3·46)	38·49 (3·78)	38·07 (3·83)	0·42 (3·58)	–0·58 (–1·69 to 0·54)	0·31
PAL 1st memory score	7·81 (4·09)	8·48 (4·28)	0·67 (3·82)	7·92 (4·27)	8·92 (4·75)	1·00 (3·76)	–0·32 (–1·43 to 0·80)	0·57
DAS-II digits forward total score	8·70 (4·19)	8·68 (4·06)	–0·01 (1·93)	8·49 (4·46)	8·51 (4·51)	0·03 (2·37)	–0·04 (–0·74 to 0·66)	0·91
DAS-II matrices ability score	51·05 (13·69)	53·71 (13·75)	2·66 (12·12)	51·68 (12·51)	52·43 (14·20)	0·75 (9·22)	1·91 (–1·57 to 5·39)	0·28
Go–No-go speed (ms)*	555·19 (127·94)	554·87 (127·98)	0·22 (111·28)	556·71 (135·73)	558·72 (146·69)	–2·52 (96·08)	2·94 (–25·32 to 31·20)	0·84
PPVT-4 raw score	104·07 (41·09)	109·70 (42·88)	5·63 (16·38)	109·12 (37·78)	113·58 (38·73)	4·46 (12·96)	1·17 (–3·60 to 5·94)	0·63
SIB-R broad independence score*	43·55 (21·99)	49·42 (19·65)	3·23 (13·32)	50·73 (22·31)	56·37 (23·72)	6·88 (16·93)	–3·65 (–8·91 to 1·61)	0·17

Mean (SD) of neuropsychological outcome scores at baseline (T1), 16 weeks (T2), and change from baseline are presented for both placebo and memantine groups. Effect estimates, 95% CIs, and p values for the group differences of the difference (T2–T1) in scores are also presented. A contrast effect, based on our a priori hypothesis, tested whether the participants in the memantine group had a significant improvement in test scores over the 16-week interval compared with the participants in the placebo group. No significant differences were found in this analysis for any of these measures. For reference, mean (SD) for all the dependent variables (including several additional subscores) are shown in the appendix (pp 8–12). CVLT=California Verbal Learning Test. DAS=Differential Ability Scales. PAL=paired associates learning. PPVT=Peabody Picture Vocabulary Test. PRM=pattern recognition memory. SIB-R=Scales of Independent Behavior-Revised. SWM=spatial working memory. TROG=Test for Reception of Grammar. *Some participants chose not to undergo the questionnaire or task, or stopped midway.

Table 2: **Primary and secondary outcomes (per-protocol population)**

	Memantine (n=81)	Placebo (n=79)	Risk difference (95% CI)
Signs and symptoms of upper respiratory viral infection*	9 (11%)	12 (15%)	0·041 (–0·010 to 0·149)
Transient dizziness	8 (10%)	6 (8%)	–0·023 (–0·116 to 0·070)
Anxiety	6 (7%)	4 (5%)	–0·023 (–0·108 to 0·059)
Mood changes or irritability	2 (3%)	5 (6%)	0·039 (–0·032 to 0·117)
Mood changes or sadness	3 (4%)	3 (4%)	0·000 (–0·070 to 0·073)
Oppositional or aggressive behaviour	1 (1%)	2 (3%)†	0·013 (–0·044 to 0·076)
Headache	3 (4%)‡	3 (4%)	0·000 (–0·070 to 0·073)
Drowsiness	2 (3%)	4 (5%)	0·026 (–0·042 to 0·101)
Diarrhoea	5 (6%)	4 (5%)	–0·011 (–0·092 to 0·069)
Nausea or vomiting	3 (4%)	2 (3%)	–0·012 (–0·080 to 0·055)
Weakness or fatigue	3 (4%)‡	1 (1 %)	–0·024 (–0·091 to 0·036)
Abdominal pain	2 (3%)	1 (1 %)	–0·012 (–0·074 to 0·046)
Insomnia	3 (4%)	0	–0·037 (–0·103 to 0·015)
Clinically significant increase in thyroid-stimulating hormone concentrations in participant with hypothyroidism between screening and follow-up visits	0	3 (4%)	0·103 (–0·014 to 0·106)
Urinary incontinence	1 (1 %)	1 (1%)	0·000 (0·057 to –0·055)
Increased self-talk	0	2 (3%)	0·025 (0·088 to –0·024)
Increased appetite	0	2 (3%)	0·025 (0·088 to –0·024)
Tonsillitis	0	2 (3%)	0·025 (0·088 to –0·024)
Visual hallucinations	1 (1%)‡	0	–0·012 (0·035 to –0·087)
Herpes simplex flair-up	1 (1%)‡	0	–0·012 (0·035 to –0·087)

No significant differences in the frequency of adverse events were noted between groups. No severe adverse events were reported. *Because of the historical high incidence of viral upper respiratory infections in people with Down syndrome, this adverse event can be considered as anticipated. †Discontinued treatment. ‡One person discontinued treatment.

Table 3: **Adverse events (safety population)**

reflected image) led to treatment discontinuation for one participant, who stopped reporting such incidents within a week of treatment discontinuation. Three other participants in the memantine group discontinued treatment, due to headache, weakness or fatigue, and herpes simplex flair up (n=1 for each). Two participants in the placebo group discontinued treatment because of oppositional or aggressive behaviour, which might have resulted from external sources of stress or simply from the stress of participating in a clinical trial.

In 64 of 71 usable samples of plasma, concentrations of memantine fell below the therapeutic range for the treatment of Alzheimer's disease of 0·5–1·0 µmol/L (figure 3A). The mean concentration of memantine in plasma was 0·37 µmol/L (95% CI 0·34 to 0·40). In a post-hoc analysis, outcome associations appeared stronger when considering concentrations in plasma of memantine as a treatment variable (1·81 [95% CI –0·47 to 4·10]; p=0·12; appendix 2, p 17). This finding suggested the null effects in our main analyses might be driven by low concentrations in plasma of memantine.

A post-hoc linear mixed model analysis was done, restricted to 23 participants with concentrations of memantine in plasma of more than 0·4 µmol/L and their matched placebo counterparts (figure 3B). Between baseline and week 16, a significant difference between groups was noted for CVLT-II-sf total free recall score (3·04 points [95% CI 1·55 to 4·54]; p<0·0001) and DAS-II recall of digits forward score (2·04 points [0·73 to 3·35]; p=0·0016), favouring memantine versus placebo. These findings were robust to adjustments for sex, study site, age, level of intellectual disability, and socioeconomic status (appendix 2, p 15). Differences between groups in SIB-R broad independence scores in this exploratory post-hoc analysis favoured placebo versus memantine (–11·41 points [–21·90 to –0·92]; p=0·028; appendix 2, p 15). No other outcome measures were significant in this exploratory analysis. Post-hoc analysis of data from 16 participants with memantine concentrations in plasma of more than 0·45 µmol/L (and their matched counterparts) also produced a significant efficacy signal for the CVLT-II-sf total free recall score (2·56 points [95% CI 0·63 to 4·50]; p=0·0066). However, only seven participants had concentrations of memantine in plasma of more than 0·50 µmol/L, so no further analysis was done, and a post-hoc dose–response association could not be inferred.

Discussion

The findings of this randomised, placebo-controlled phase 2 trial showed no evidence of cognitive-enhancing effects of memantine at a dose of 20 mg/day. Post-hoc exploratory analysis of data from a subset of the participants with memantine concentrations in plasma higher than 0·4 µmol/L suggests that memantine might potentially be effective at improving some cognitive test scores above this dose concentration.

More than a decade since the publication of the first study on the effect of memantine in the Ts65Dn mouse model of Down syndrome, the glutamatergic hypothesis remains a fertile line of inquiry in this field. It has received preclinical support from behavioural and electrophysiological data in mouse models of Down syndrome by different research teams.[15] Yet, the molecular mechanism underlying the potential NMDA receptor dysfunction in Down syndrome remains unclear. Among competing hypotheses,[7] it is possible that the function of synaptic or extrasynaptic NMDA receptors, or both, is dysregulated in people with Down syndrome by one major factor or a combination of factors, such as overexpression of the gene *RCAN1*, oxidative stress, toxic effects of amyloid β peptides, or chronic neuroinflammation.

The subtherapeutic concentrations of memantine in plasma found in many of the study participants raises an issue regarding the translation of preclinical results to potentially successful clinical trials. In two preclinical studies of the effect of memantine on a mouse model of Down syndrome, the drug produced robust pharmacological rescuing of context discrimination performance at concentrations of 1·7 µmol/L.[14,18] Another preclinical

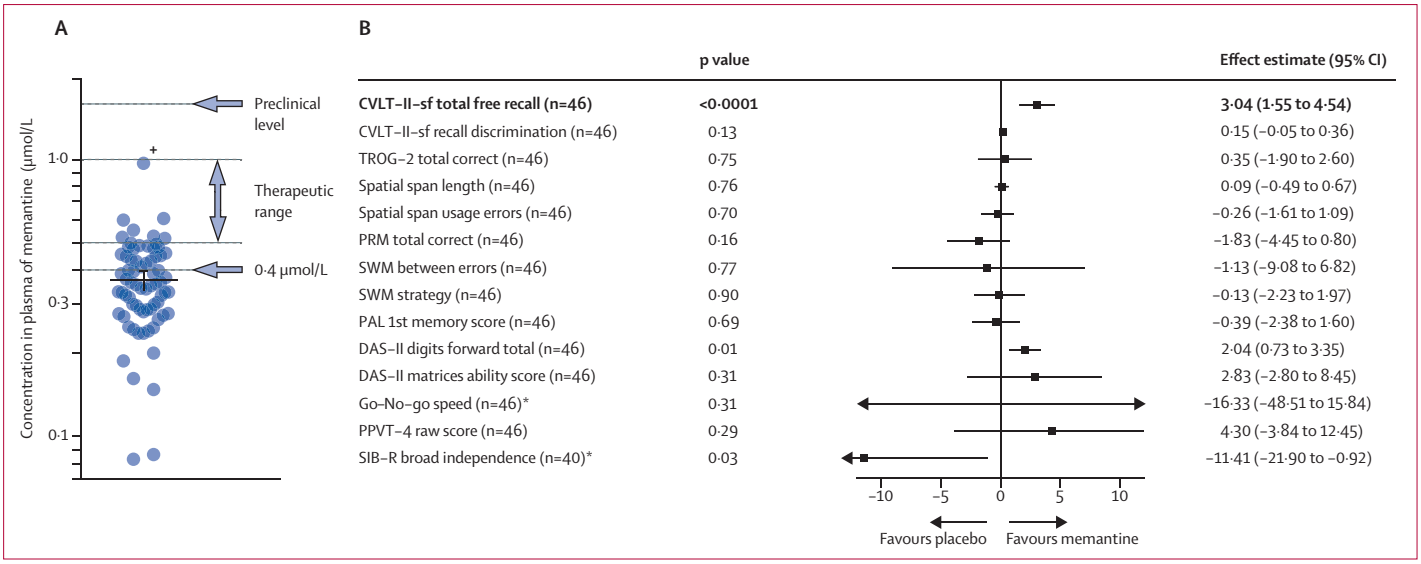

Figure 3: **Post-hoc analysis of the effect of concentrations in plasma of memantine higher than 0·4 µmol/L on neuropsychological outcomes**
(A) Dot-plot representation of concentrations in plasma of memantine for each participant in the memantine group of the study after 16 weeks of treatment. Horizontal line depicts the mean value (0·37 µmol/L) and error bars show the 95% CI (0·34–0·40). The datapoint + was judged an outlier. Upper dotted line shows the concentration of memantine from preclinical work.[18] Therapeutic range was ascertained from previous studies.[11] (B) Effect estimates and 95% CIs for group differences in test scores from baseline to week 16 are presented for 23 participants with amounts of memantine in plasma more than 0·4 µmol/L and their matched placebo counterpart (ie, 46 of 160 randomised participants). CVLT=California Verbal Learning Test. DAS=Differential Ability Scales. PAL=paired associates learning. PPVT=Peabody Picture Vocabulary Test. PRM=pattern recognition memory. SIB-R=Scales of Independent Behavior-Revised. SWM=spatial working memory. TROG=Test for Reception of Grammar. *Some participants chose not to undergo the questionnaire.

study of the same mouse model showed rescue of long-term synaptic plasticity alterations in hippocampal slices with 1 µmol/L memantine.[13] Since the concentration of memantine in CSF is estimated to be approximately 50% of that in plasma,[23] a concentration of 1·7 µmol/L in plasma translates roughly to 0·85 µmol/L in CSF, which is similar to 1 µmol/L memantine in preclinical electrophysiological experiments. In the present study, the mean measured concentration of memantine in plasma was 0·37 µmol/L, which is about a fifth of the concentration in preclinical work.

Is the finding of low concentrations in plasma of memantine unique to individuals with Down syndrome? In a study published in 2019 in people with sporadic Alzheimer's disease (age in years from late 60s to early 70s),[23] concentrations of memantine in plasma were 0·59–0·62 µmol/L, amounts that are somewhat higher but still comparable with 0·37 µmol/L reported in the present study. In that same study, memantine reached the lowest half maximal inhibitory concentration (IC_{50}) value in CSF as an NMDA antagonist in only three of 22 study participants.[23] In a second study published in 2021,[24] the potential effect of a standard dose of memantine on QT or QTc intervals was investigated in a cohort of 57 healthy individuals aged 18–55 years (mean age 29·4 years). The mean concentration in plasma of memantine was 0·37 µmol/L, which is exactly the same value reported in the present study. These studies, published since we planned this randomised trial, indicate that memantine doses routinely used for the treatment of Alzheimer's disease seem to be inherently low to consistently produce the memantine concentrations necessary to antagonise NMDA receptors effectively.[11,15,24] In young adults, with or without Down syndrome, these concentrations are even lower.[24]

In 2012, the same year that the pilot study of memantine was published,[16] Hanney and colleagues reported the findings of a randomised, double-blind placebo-controlled trial of 1 year of treatment with memantine in adults with Down syndrome older than 40 years,[25] many of whom presented with clinical dementia. That study aimed to assess the safety and efficacy of memantine in improving cognitive and adaptive function, as measured by the Down Syndrome Attention, Memory, and Executive Function Scales and the Adaptive Behavior Scale. Hanney and colleagues found that memantine produced no significant improvement on either the primary or the secondary efficacy measures but was well tolerated.[25] At that time, we speculated that a probable explanation for the absence of efficacy in that well designed trial was that irreversible neurodegeneration had already occurred and that functioning could no longer be restored.[26] However, since Hanney and colleagues used only half the typical therapeutic dose of memantine (10 mg/day) for Alzheimer's disease, it is also possible that subtherapeutic blood or CSF concentrations of memantine might also have contributed to them not detecting an efficacy signal.

The present study was one of the largest clinical trials in Down syndrome to date. However, it has several limitations. Based on findings of a pilot trial,[16] the

present study was powered a priori to detect expected changes produced by memantine with respect to the chosen primary outcome measure (CVLT-II-sf total free recall score). Because of the small size of the pilot trial, it is possible that the power analysis for the present study might have been biased by a few outliers, which means it might have been underpowered. Additionally, the short duration of treatment did not allow sufficient time for a fair assessment of changes in adaptive and daily living skills, which are the true desirable goals of therapies aimed at improving quality of life in individuals with intellectual and developmental disabilities. Moreover, participant selection was biased towards a subgroup of young individuals with Down syndrome who were generally healthy, verbal, and with no or very few behavioural issues, which does not fully represent individuals with Down syndrome. Finally, the primary outcome measure of the study was CVLT-II-sf total free recall score, a broadly used and well validated instrument in clinical and experimental neuropsychology.[27] However, the CVLT-II-sf recall discriminability subscore is generally considered superior to the CVLT-II-sf total free recall score in distinguishing the recall performance of people with Alzheimer's disease and Huntington's disease, and we did not detect a difference in the discriminability subscore on either primary or post-hoc exploratory analyses.

The significant effects of memantine recorded post hoc in a small subgroup of participants with concentrations of memantine in plasma higher than 0·4 µmol/L are an important step towards proving the principle that cognitive deficits in individuals with Down syndrome might be (at least partly) amenable to pharmacological interventions. However, these findings should be viewed with caution due to their exploratory nature and because the effect might be too small to be of clinical significance. Moreover, the same post-hoc analysis indicated a significant increase in SIB-R scores—a measure of broad independence—that favoured the placebo group, although increases in mean scores of this measure in both the placebo and memantine groups were observed. SIB-R was used as a discriminant measure. Furthermore, it is unreasonable to expect clinically significant gains in adaptive skills in such a short trial. It is possible that the noted increases in the scores of these caregiver-filled questionnaires represent heightened levels of expectation of positive effects from parents or caregivers, instead of a pharmacological effect. However, since rises in scores favoured the placebo group, the possibility that this finding is a weak signal of an adverse effect of memantine should not be completely discounted. Given the limitations of this study, no recommendations can be made about the clinical usefulness of memantine as a therapeutic agent for the amelioration of Down syndrome-associated cognitive deficits.

A prudent next step would be to do small-scale pharmacokinetic and tolerability studies in individuals with Down syndrome of various ages. Findings of such studies should provide the evidence necessary to support or reject additional trials of memantine at doses larger than the one used in the present study. In future studies of higher-than-standard therapeutic memantine doses, not only might statistically significant efficacy be detected in a broader proportion of participants with Down syndrome but also significantly higher effect sizes than those reported here might be seen. However, would such doses be tolerated? Memantine has been administered at doses of 30–60 mg/day for treatment of various neurological disorders.[28–30] However, no evidence is available to support such high doses of memantine in individuals with Down syndrome.

Contributors

All authors had full access to data in the study and had final responsibility for the integrity of the data and the decision to submit for publication. ACSC and RB contributed to the study conceptualisation and design. ACSC, ACB, VLB, HGT, ER, MRS, FFA, MPR, PS, GA-S, IB, EP, TS, NJR, and SR contributed to data acquisition and have access to the source data. ACSC, RB, MWJ, SA, and AH were responsible for data analysis and interpretation. ACSC drafted the manuscript. All authors critically reviewed the manuscript for important intellectual content. ACSC obtained funding. ACSC, ACB, and SR supervised the study.

Declaration of interests

We declare no competing interests.

Data sharing

Trial data can be made available on reasonable request to the corresponding author and must be accompanied by detailed study proposals, a description of study objectives, and a statistical analysis plan. Access to available deidentified participant data and the trial protocol may be granted 12 months after publication. Any request must be approved by the corresponding author and the principal investigators of each centre. Each request will be checked for compatibility with regulatory (institutional review board and ethics committee) requirements as well as compatibility with participant informed consent.

Acknowledgments

This work was supported by a grant to the Case Western Reserve University from the Alana USA Foundation (contract 200381). Hospital Israelita Albert Einstein received funding from the Case Western Reserve University School through a subcontract to support this research, including effort support, supplies, and equipment (from planning to end of project). ACSC and MRS received salary support from charitable contributions by the Awakening Angels Foundation. AH was supported by the HERCULES Center (NIEHS P30ES019776). We thank the study participants and their parents and caregivers; none of the participants received compensation for their contributions beyond hospital parking validation and partial travel expense reimbursements. We also thank the Down Syndrome Association of Central Ohio, Up Side of Downs of Northeast Ohio, United Parent Support for Down Syndrome, Down Syndrome Guild of Southeast Michigan, Down Syndrome Association of Greater Toledo, Down Syndrome Association of the Valley, the Adult Down Syndrome Center in Park Ridge Illinois, the National Down Syndrome Society, the National Down Syndrome Congress, and Federação Brasileira das Associações de Síndrome de Down for their help with participant recruitment. We thank Anne Birnbaum and Carol Gross for their contributions to data collection. We also thank the volunteer members of the Data Safety Monitoring Board overseeing this trial: Patricia Marshall, Alan Lerner, Mark Scher, Abdus Sattar, and Melissa Armstrong-Brine. Edward Goldson provided external, independent monitoring and advice to the São Paulo site of this study.

References

1 Patterson D, Costa AC. Down syndrome and genetics: a case of linked histories. *Nat Rev Genet* 2005; **6:** 137–47.

2 Mai CT, Isenburg JL, Canfield MA, et al. National population-based estimates for major birth defects, 2010–2014. *Birth Defects Res* 2019; **111:** 1420–35.

3 Carr J, Collins S. 50 years with Down syndrome: a longitudinal study. *J Appl Res Intellect Disabil* 2018; **31:** 743–50.

4 Lee NR, Fidler DJ, Blakeley-Smith A, Daunhauer L, Robinson C, Hepburn SL. Caregiver report of executive functioning in a population-based sample of young children with Down syndrome. *Am J Intellect Dev Disabil* 2011; **116:** 290–304.

5 Pennington BF, Moon J, Edgin J, Stedron J, Nadel L. The neuropsychology of Down syndrome: evidence for hippocampal dysfunction. *Child Dev* 2003; **74:** 75–93.

6 Sinai A, Mokrysz C, Bernal J, et al. Predictors of age of diagnosis and survival of Alzheimer's disease in Down syndrome. *J Alzheimers Dis* 2018; **61:** 717–28.

7 Costa AC, Scott-McKean JJ. Prospects for improving brain function in individuals with Down syndrome. *CNS Drugs* 2013; **27:** 679–702.

8 Lee SE, Duran-Martinez M, Khantsis S, Bianchi DW, Guedj F. Challenges and opportunities for translation of therapies to improve cognition in Down syndrome. *Trends Mol Med* 2020; **26:** 150–69.

9 Dang V, Medina B, Das D, et al. Formoterol, a long-acting β2 adrenergic agonist, improves cognitive function and promotes dendritic complexity in a mouse model of Down syndrome. *Biol Psychiatry* 2014; **75:** 179–88.

10 Hamlett ED, Hjorth E, Ledreux A, Gilmore A, Schultzberg M, Granholm AC. RvE1 treatment prevents memory loss and neuroinflammation in the Ts65Dn mouse model of Down syndrome. *Glia* 2020; **68:** 1347–60.

11 Parsons CG, Stöffler A, Danysz W. Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system—too little activation is bad, too much is even worse. *Neuropharmacology* 2007; **53:** 699–723.

12 Kishi T, Matsunaga S, Oya K, Nomura I, Ikuta T, Iwata N. Memantine for Alzheimer's disease: an updated systematic review and meta-analysis. *J Alzheimers Dis* 2017; **60:** 401–25.

13 Scott-McKean JJ, Roque AL, Surewicz K, Johnson MW, Surewicz WK, Costa ACS. Pharmacological modulation of three modalities of CA1 hippocampal long-term potentiation in the Ts65Dn mouse model of Down syndrome. *Neural Plast* 2018; **2018:** 9235796.

14 Costa AC, Scott-McKean JJ, Stasko MR. Acute injections of the NMDA receptor antagonist memantine rescue performance deficits of the Ts65Dn mouse model of Down syndrome on a fear conditioning test. *Neuropsychopharmacology* 2008; **33:** 1624–32.

15 Costa AC. The glutamatergic hypothesis for Down syndrome: the potential use of N-methyl-D-aspartate receptor antagonists to enhance cognition and decelerate neurodegeneration. *CNS Neurol Disord Drug Targets* 2014; **13:** 16–25.

16 Boada R, Hutaff-Lee C, Schrader A, et al. Antagonism of NMDA receptors as a potential treatment for Down syndrome: a pilot randomized controlled trial. *Transl Psychiatry* 2012; **2:** e141.

17 Basten IA, Boada R, Taylor HG, et al. On the design of broad-based neuropsychological test batteries to assess the cognitive abilities of individuals with Down syndrome in the context of clinical trials. *Brain Sci* 2018; **8:** 205.

18 Victorino DB, Bederman IR, Costa ACS. Pharmacokinetic properties of memantine after a single intraperitoneal administration and multiple oral doses in euploid mice and in the Ts65Dn mouse model of Down's syndrome. *Basic Clin Pharmacol Toxicol* 2017; **121:** 382–89.

19 Koenig KA, Oh SH, Stasko MR, et al. High resolution structural and functional MRI of the hippocampus in young adults with Down syndrome. *Brain Commun* 2021; **3:** fcab088.

20 Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw* 2015; **67:** 48.

21 Li G, Taljaard M, Van den Heuvel ER, et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. *Int J Epidemiol* 2017; **46:** 746–55.

22 Orkin AM, Gill PJ, Ghersi D, et al. Guidelines for reporting trial protocols and completed trials modified due to the COVID-19 pandemic and other extenuating circumstances: the CONSERVE 2021 statement. *JAMA* 2021; **326:** 257–65.

23 Valis M, Herman D, Vanova N, et al. The concentration of memantine in the cerebrospinal fluid of Alzheimer's disease patients and its consequence to oxidative stress biomarkers. *Front Pharmacol* 2019; **10:** 943.

24 Park JW, Kim KA, Park JY. Effect of memantine on QT/QTc interval in a healthy Korean population. *Clin Pharmacol Drug Dev* 2021; **10:** 1209–15.

25 Hanney M, Prasher V, Williams N, et al. Memantine for dementia in adults older than 40 years with Down's syndrome (MEADOWS): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012; **379:** 528–36.

26 Costa AC. Alzheimer disease: treatment of Alzheimer disease in Down syndrome. *Nat Rev Neurol* 2012; **8:** 182–84.

27 Stegen S, Stepanov I, Cookfair D, et al. Validity of the California Verbal Learning Test-II in multiple sclerosis. *Clin Neuropsychol* 2010; **24:** 189–202.

28 Strupp M, Kremmyda O, Brandt T. Pharmacotherapy of vestibular disorders and nystagmus. *Semin Neurol* 2013; **33:** 286–96.

29 Sinis N, Birbaumer N, Gustin S, et al. Memantine treatment of complex regional pain syndrome: a preliminary report of six cases. *Clin J Pain* 2007; **23:** 237–43.

30 Ahmad-Sabry MH, Shareghi G. Effects of memantine on pain in patients with complex regional pain syndrome—a retrospective study. *Middle East J Anaesthesiol* 2015; **23:** 51–54.