Down syndrome (DS) is associated with early onset of neuropathology that is indistinguishable from Alzheimer disease (AD), and is typically followed by cognitive decline two decades later. A recent study has reported that the AD drug memantine failed to improve cognitive performance and function in middle-aged patients with DS.

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Down syndrome (DS) is the most common genetically driven intellectual disability. Neuropathological evidence of an association between Alzheimer disease (AD) and DS was published 11 years before trisomy 21 was described as the cause of DS. AD-type pathology is almost universal in patients with DS in their 40s, although the development of clinically detectable cognitive decline typically lags behind the pathology by 20–25 years. As life expectancy of patients with DS approaches 60 years in developed countries, comorbidity of DS and AD is becoming an increasingly important clinical issue. Clinical trials of approved AD therapies for patients with DS are, therefore, welcome. Previous work included pioneering case series and one inconclusive randomized placebo-controlled trial of the anticholinesterase drug donepezil.

A recent study by Hanney et al. named Memantine for dementia in adults older than 40 years with Down’s syndrome (MEADOWS; NCT00240760 at clinicaltrials.gov), is an important addition to the field. This study was a randomized, double-blind, placebo-controlled trial to assess safety and efficacy of memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist that is approved for the treatment of cognitive decline in AD, in individuals with DS. Although 1-year-long treatment with memantine was well-tolerated in this patient population, efficacy data were disappointing.

The MEADOWS trial was well-conducted and is a commendable achievement, given the difficulties of recruiting and assuring protocol compliance in patients with DS. The trial design was based on previous findings by members of the same research team that people with DS over the age of 40 years without clinically detectable dementia experienced, on average, an 11% decline in neuropsychological measures of attention, executive function and memory over the course of 1 year. The study involved 173 patients with DS, 88 of whom were randomly assigned to memantine and 85 of whom were randomly assigned to placebo. The primary end points were change in cognition and function, as measured on the DS attention, memory and executive function scales (DAMES) score and the adaptive behaviour scale (ABS) parts I and II. After 1 year of treatment, no differences in these measures were observed between the memantine and control groups.

It is worth noting that the ‘D’ in ‘MEADOWS’ might be misleading, given that only 35% of patients had a confirmed diagnosis of dementia. As such, the study was only powered to detect fairly large effects of memantine on dementia with the blunt neuropsychological assessment tools (DAMES and ABS) that were employed. Given the limitations of this study, the conclusion that “therapies that are effective for the treatment of Alzheimer’s disease are not necessarily also effective in people with Down’s syndrome,” might be premature. This issue is a particularly sensitive area given a history of withholding potentially beneficial treatments from disabled patients and an increasing trend in the current health environment towards therapy rationing.

Several other factors could have contributed to the negative result of MEADOWS. The mean age of patients was about 51 years, which is a relatively advanced age for individuals with DS. In addition, both groups in the trial had health issues that necessitated the chronic use of other medications: cholinesterase inhibitors (6% versus 5% of patients in the memantine and placebo groups, respectively), antidepressants (23% versus 13%), neuroleptics (11% versus 5%), anxiolytics (2% versus 3%), hypnotics (6% versus 2%), and “medications for physical problems” (both 74%). The advanced age and concomitant health issues in the patient cohort are reflected in the deaths of five patients in the memantine group and four in the placebo group during the trial. Health issues in ageing adults with DS are numerous, and their potential role in any observed decline in cognitive function and daily living skills should not be underestimated. These issues include unreported chronic pain, depression, hypothyroidism, sensory deficits, and other physical and psychiatric disorders. In the general population, AD leads to death about 10 years after diagnosis, whereas the prognosis for patients with DS who have dementia is approximately 5 years of survival after the dementia diagnosis.

Although a certain degree of frustration is to be expected after such a great effort by the MEADOWS team, this setback should not detract from the fact that the field of DS research is witnessing exciting times. Not only has the pace of discovery in the areas of genetics and neurobiology related to DS increased over the past few years, but our knowledge of DS neuropsychology has also expanded considerably. For example, neuropsychological assessments have shown disproportionally large deficits in hippocampus-dependent tasks in patients with DS compared with healthy, mental-age-matched individuals. Moreover, pharmacological rescue of learning and memory deficits in mouse models of DS have led to the design of a new generation of clinical trials. Work on a mouse model of DS, Ts65Dn, by my research team and others has shown convincing evidence of NMDA...
receptor dysfunction and preclinical efficacy of memantine in enhancing learning and memory, as well as reversing hippocampal synaptic plasticity alterations.8,9

I am currently leading a pilot clinical trial to test the safety and efficacy of memantine in enhancing cognition in healthy young adults with DS, as assessed through hippocampus-dependent measures. We are convinced that if NMDA receptor dysfunction is an important issue in patients with DS, early intervention will be crucial to improve outcomes. Although testing of healthy participants might not directly address the issue of efficacy in DS, the results of our trial are less likely to be affected by confounding factors linked to age-related comorbidities.

The design of the MEADOWS trial was completed in 2005, preceding many important recent findings in the field of DS research. The trial did not, therefore, benefit from this newly available information. For example, neuropsychological assessments of hippocampus-dependent measures were not included in the protocol. The researchers questioned the usefulness of animal models of DS for testing potential treatments, but a study on the Ts65Dn mouse model cited by the authors10 shows agreement with the findings of the MEADOWS trial. In this preclinical study, the investigators note that despite memory improvements in Ts65Dn mice, “histological analysis found no morphological signs of neuroprotection of basal forebrain cholinergic or locus coeruleus neurons”10 (that is, no disease-modifying effects) in animals chronically treated with memantine.

Although MEADOWS did not include histological analysis, the study was originally designed and powered as a disease-course-modification trial in that memantine was expected to slow or halt the average 11% decline in neuropsychological measures of attention, executive function and memory over the course of 1 year. A relevant point to note is that, to date, no clear clinical evidence of disease-modifying effects of memantine has been found in AD.

“...interventions before the ‘point of no return’ could be a crucial step towards effective treatment...”

As in the case of several recent therapeutic trials in the field of AD, the failure of the MEADOWS trial might be another case of trying to close the barn door after the horse has bolted. So, by the time treatment began, pathological cellular cascades were already triggered and the disease process might have reached an irreversible stage. Clinical trials of interventions before the ‘point of no return’ could be a crucial step towards effective treatment for dementia in DS.

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Competing interests
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