

Correspondence

Edited by Kiriakos Xenitidis and Colin Campbell

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A request for clarifications and additional data

While I congratulate Eady and colleagues¹ on their attempt to explore the important issue of treatment outcomes for individuals with Down syndrome and dementia and the considerable effort that has gone into collating this data, I am concerned about the way some of the data are presented and are used to support the conclusions drawn in this article. I would like to request some clarifications and additional data.

Three of these relate to the increased survival for those on drug treatment. First, the abstract states a difference in mean survival of 5.59 versus 3.45 years for treated versus untreated groups but as far as I can see these figures are not adjusted for the fact that the 'no treatment' group are older at the time of diagnosis (means 56.66 versus 53.81 years, similar standard deviations) and have significantly higher Dementia Questionnaire for People with Learning Disabilities (DLD) scores 'indicating that this group had more severe symptoms of dementia at diagnosis' (p. 156). It would be informative to know the means and standard deviations for actual age at death of both groups. Second, the Kaplan–Meier survival curves (Fig. 1, p. 157) do not seem to take into account the age differences between the groups at diagnosis and in my view are therefore misleading. Third, the Cox regression calculations of hazard ratios reported, suggesting that treatment extends survival, do not include any control for the individual variations in the extent of the progression of the disease in the analyses. The paper states that the authors have data on DLD scores and clinician's stage assessments (early, middle, late, p. 156) at diagnosis and these differ between the drug treatment/no treatment groups. While these measures are estimates of disease progression at best, why was one of them not used as well as age at diagnosis as a covariate? Without any control for differences in disease progression I do not think the strong claim of a survival benefit for treatment can be substantiated.

Regarding the short-term benefits of treatment, there are no benefits evident on DLD social scores and the benefits (slowing of decline) on DLD cognitive scores at 6 months are lost at 12 months. In my view, this should have been made explicit in the abstract and discussed more fully in the paper. In addition, I am aware that this pattern of 'benefit' is similar in patients with Alzheimer's disease in the general population but for individuals with an intellectual disability a slowing of cognitive decline followed by a more rapid decline as indicated by these data may

be more difficult for them to cope with. It would be informative to see the actual means and standard deviations for the DLD measures at the 6-month and 12-month time points. I also understand a more rapid decline is experienced when these drugs are stopped.

Finally, authors, reviewers and publishers need to recognise that many people searching for information will not read beyond the abstract and take care to ensure it is a fully accurate summary when publishing findings and their implications.

- ¹ Eady N, Sheehan R, Rantell K, Sinai A, Bernal J, Bohnen I, et al. Impact of cholinesterase inhibitors or memantine on survival in adults with Down syndrome and dementia: clinical cohort study. *Br J Psychiatry* 2018; **212**: 155–60.

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doi:10.1192/bjp.2018.193

Author's reply

There is a lack of research into the effect of pharmacological interventions for dementia in people with Down syndrome and Alzheimer's disease. In this paper we used routinely collected clinical data to explore the effect of cholinesterase inhibitors and/or memantine on survival and function in this group. These therapies are recommended by the National Institute for Health and Clinical Excellence for dementia treatment and the guideline includes people with Down syndrome.¹ Although subject to limitations given the observational rather than randomised design (discussed in more detail in the paper) our results support the use of antedementia drugs for people with Down syndrome who develop Alzheimer's disease.

We welcome Professor Buckley's interest in our work, and she is right to highlight the complexities of medication decision-making. We would expect that individual treatment decisions consider the best available evidence, personal circumstances and comorbidities, and incorporate the views and preferences of people with intellectual disability and their carers. Indeed, it is the aim of our analysis to expand the evidence base to enable informed decision-making. We will address Professor Buckley's concerns in turn.

Professor Buckley questioned our use of Kaplan–Meier estimates, a standard approach to survival analysis, and the figures based on these. This type of survival analysis enables use of data from all individuals to be included in the analysis, by censoring participants either at the date of death or at the date of their last clinic assessment so that information contained in survival times is taken into account accurately. It would be inaccurate to report average ages of death as these cannot be compared meaningfully between both groups because not all of those in the cohort died and those in the treated group were less likely to die; this would not be captured by reporting the age of death of only those known to have died.

Factors other than medication prescription that might influence survival were accounted for using Cox regression (Table 2). Variables added to the final analysis were site, age at dementia diagnosis, gender and degree of intellectual disability. Professor Buckley points out that we did not account for stage of dementia as a potential confounder. We agree that this would have been desirable, but there is no standard method of recording this that is in regular use in clinical services. She suggested that the DLD (a screening tool for dementia in individuals with intellectual disabilities) could be used for this purpose, but the scores obtained from the DLD reflect both degree of intellectual disability and dementia-related decline, with higher scores indicating lower levels of functioning, whether because of intellectual disability or dementia or a

combination of both conditions.² For that reason the authors of the tool have recommended it be used sequentially to identify decline over time from an individual baseline. It cannot be used as a cross-sectional staging tool because a high score could indicate a long-standing level of intellectual ability rather than dementia and a low score might not exclude dementia in those with mild intellectual impairment. Unfortunately clinician ratings of mild, moderate or severe dementia were incompletely recorded in clinical notes (Table 1) and these data were not recorded beyond baseline, thus could not be included in our analyses.

However, in order to examine change in cognitive and functional ability over time from a baseline, our analysis of DLD scores was conducted using coefficients (i.e. based upon the mean difference between the scores of those on medication and those not on medication) that did take account of baseline DLD scores (Table 3). As requested by Professor Buckley, we now report raw DLD data at baseline, and follow-up visits for all individuals for whom this is available. Mean baseline DLD cognitive score in the untreated group was 30.54 (95% CI 26.49–34.60) and in the treated group 25.35 (95% CI 23.29–27.41); at first follow-up assessment DLD cognitive scores were 27.80 (95% CI 23.24–32.35) in the untreated group and 22.34 (95% CI 20.16–24.52) in the treated group; at second follow-up 31.62 (95% CI 26.17–27.08) (untreated) and 23.90 (95% CI 21.85–25.88) (treated); and at third follow-up 34.86 (95% CI 27.49–42.23) (untreated) and 26.20 (95% CI 23.90–28.51) (treated). These unadjusted data highlight the difference between the group means in cognitive score at baseline and other time points and appear to demonstrate a generally slower rate of cognitive decline in people prescribed medication, with DLD cognitive scores of those not treated worsening by approximately 14% (increase in scores of 4.32 on average, from a baseline of 30.54) by the third follow-up visit, compared with a worsening in DLD cognitive score of only 3% on average (increase in scores of 0.85 on average) in those prescribed medication. We have included the third time point here, which we did not include in the analysis in the paper, although as indicated by the width of the confidence interval, the number of observations at this time point is small, particularly in the untreated group. The numbers included at each time point are slightly different from those reported in the paper because of missing data in certain individuals precluding adjustment by baseline value. While we agree that research abstracts are limited by word counts, we believe our reporting is balanced and fair and call for more research in this field, including clinical trials of medication where the limitations of observational designs could be overcome.

1 National Institute for Health and Care Excellence. *Dementia: Supporting People with Dementia and their Carers in Health and Social Care*. CG42. NICE, 2006.

2 Eurlings HAL, Evenhuis HM, Kengen MMF. *Dementia Questionnaire for People with Learning Disabilities (DLD)*. UK Adaptation. Harcourt Assessment, 2006.

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doi:10.1192/bjp.2018.194

Difficulties of diagnosing and managing dementia in people with Down syndrome

As practising clinicians who provide care to adults with Down syndrome, we appreciate Eady and colleagues' attempt to address a real concern in this patient population.¹ However, we have significant concerns about clinicians potentially using in their practice the conclusions drawn by the authors. The study conclusions offer false hope and may result in wasted resources.

The authors themselves state that the treated and untreated groups have significant differences that would favour the treated group: 'There were significant baseline differences between the groups prescribed and not prescribed antidementia medication. Those who were not prescribed medication were older, more likely to have severe-profound intellectual disability, and had more severe dementia symptoms at baseline'. Given those differences, it is difficult to understand how the authors can come to the conclusion that treatment with antidementia medications is of benefit.

Also of concern is the question of what the clinical significance would be from a functional perspective. Dementia takes a tremendous toll on the caregivers and families. Even if the medications do extend life, where is the benefit? What kind of life will they have? We believe quality of life would have been a more useful measured outcome.

Furthermore, there are four published studies and Cochrane reviews that show no benefit with donepezil,² rivastigmine,³ memantine,^{4,5} or galantamine.⁶ Another Cochrane Review in 2015 showed no benefit of pharmacological interventions for cognitive decline in people with Down syndrome.⁷

In our experience as the directors of Down syndrome clinics for adults, the big issue is really how the diagnosis of dementia is made. Clinicians tend to easily apply the diagnosis of Alzheimer's dementia without looking at all the potential causes of pseudodementia in this population.⁸ They often assume that loss of ability is as a result of dementia because of a study published in 1985 that showed plaques and tangles in the brain tissue of all people with Down syndrome over the age of 35.⁹ Wisniewski & Rabe subsequently wrote that there was a discrepancy between neuropathology and the occurrence of dementia in people with Down syndrome.¹⁰ Just as in the population of typically developed older adults, the diagnosis of Alzheimer's dementia in people with Down syndrome should be made only after evaluation for causes of pseudodementia.

1 Eady N, Sheehan R, Rantell K, Sinai A, Bernal J, Bohnen I, et al. Impact of cholinesterase inhibitors or memantine on survival in adults with Down syndrome and dementia: clinical cohort study. *Br J Psychiatry* 2018; **212**: 155–60.

2 Mohan M, Carpenter PK, Bennett C. Donepezil for dementia in people with Down syndrome. *Cochrane Database Syst Rev* 2009; **1**: CD007178.

3 Mohan M, Bennett C, Carpenter PK. Rivastigmine for dementia in people with Down syndrome. *Cochrane Database Syst Rev* 2009; **1**: CD007658.

4 McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database Syst Rev* 2006; **2**: CD003154.

5 Hanney M, Prasher V, Williams N, Jones EL, Aarsland D, Corbett A, 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.

6 Mohan M, Bennett C, Carpenter PK. Galantamine for dementia in people with Down syndrome. *Cochrane Database Syst Rev* 2009; **1**: CD007656.

7 Livingstone N, Hanratty J, McShane R, Macdonald G. Pharmacological interventions for cognitive decline in people with Down syndrome. *Cochrane Database Syst Rev* 2015; **10**: CD011546.