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A request for clarifications and additional data

While I congratulate Eady and colleagues[1] 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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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 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 antidementia 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