TWELVE-WEEK RESPONSE TO CHOLINESTERASE INHIBITORS DOES NOT PREDICT FUTURE BENEFIT: THE AD2000 TRIAL EXPERIENCE

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Background  UK clinical guidelines recommend cholinesterase inhibitor treatment of mild to moderate Alzheimer's disease, with response assessed after about 12 weeks. Further treatment is recommended if there has been no deterioration in cognitive tests as well as improvement in functioning or behavioural symptoms.

Objectives  To investigate the value of cognitive, functional and behavioural change as predictors of benefit from further donepezil treatment.

Methods  Patients in the AD2000 trial were randomised between donepezil and placebo for 12 weeks and then to either continue indefinitely or to cross over to the other treatment arm. Mini-Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI), Bristol Activities of Daily Living Scale (BADLS), and General Health Questionnaire (GHQ-30) were administered at baseline and then at 12-weekly intervals.

Results  433 patients completed questionnaires at baseline, 12 and 24 weeks. Change in MMSE at 12 weeks was weakly correlated with change in BADLS but was not correlated with change in NPI or GHQ. Changes in MMSE, BADLS and GHQ at 12 weeks were normally distributed in both groups with no obvious cut-off point to differentiate between responders and non-responders. For patients continuing donepezil, response at 12 weeks (as defined above) did not predict subsequent response to donepezil. Instead, responders performed significantly worse than non-responders from weeks 13-24 because both groups regressed towards the mean. By 24 weeks there was no significant difference between responders and non-responders on any of the three scales.

Conclusions  Because test-retest variability (noise) exceeds treatment effect (signal), we were unable to identify reliably a group of responders at 12 weeks for whom further cholinesterase inhibitor treatment is indicated. Cognitive change is a poor predictor of change in functional ability, behavioural symptoms and carer psychopathology suggesting that these may be associated but unrelated aspects of the disease process.