Antidepressant treatment in Alzheimer’s disease

The negative results from the UK Health Technology Assessment (HTA) Study of the Use of Antidepressants for Depression in Dementia (SADD) trial reported by Sube Banerjee and colleagues in The Lancet are important for several reasons, not least because of the compelling size of the study. 326 participants with Alzheimer’s disease and depression were randomly allocated to receive sertraline, mirtazapine, or placebo, making this landmark study the largest trial of antidepressant drugs in dementia ever and almost equaling the combined total from previously published work.2

Second, depression in dementia is very common, affecting around 20% of the 36 million people with dementia worldwide.3 Third, previous results of trials of antidepressants for depression in people with Alzheimer’s disease have been unconvincing.2 The promise offered by the first Depression in Alzheimer Disease Study (DIADS) study,4 which reported benefit with sertraline, a selective serotonin reuptake inhibitor, was dashed by the negative findings at 12 or 24 weeks from the larger DIADS-2 trial.5

Fourth, the absence of efficacy of antidepressants in the dementia population raises questions about whether there are different pathogenic mechanisms at play in depression in Alzheimer’s disease. Antidepressants have moderate but robust benefits for people with depression in general (effect size 0.497 for drugs compared with placebo)6 as well as in elderly people with depression.7 Although vascular depression might have a poorer response rate, participants in the SADD trial predominantly had Alzheimer’s disease as suggested by a mean Hachinski index of 2.2.

The trial mimicked clinical practice. Participants were aged about 80 years, had moderately severe Alzheimer’s disease with average mini-mental state examination scores of around 18, were mainly living in the community (about 85%), had clinically significant depression with more than half of participants having Cornell scale for depression in dementia (CSDD) scores of 12 or more, had been depressed for a substantial amount of time (68% for more than 6 months), and had been referred to old-age psychiatric services. Drug doses were escalated to three tablets per day of sertraline 50 mg, mirtazapine 15 mg, or placebo. There were few exclusions. Withdrawal rates ranged from 24% to 35%. Mean doses achieved were 95 mg per day for sertraline and 30 mg per day for mirtazapine, which is typical for clinical practice in this population. There was no difference between groups in terms of the primary outcome (change in CSDD score) at 13 weeks or 39 weeks, or in nearly all other outcome measures for participants or carers. Adverse effects occurred more often in active drug groups than they did in the placebo group, and possibly more often in the sertraline than the mirtazapine group.

Caveats are that the results might not be applicable to primary care settings, to individuals whose depression was very severe (ie, those who were critically ill or suicidal), to other types of dementia, or, necessarily, to other antidepressant drugs. The trial did not include a responder analysis, and subgroups of participants not yet identified might be responsive to drugs. The possibility that raised CSDD scores result from non-depressive dementia symptoms might mitigate proof of responsiveness to antidepressants. However, the sensitivity analysis that did not show a difference in the primary outcome for participants with CSDD scores of 12 or more partially militates against this possibility.

What are clinicians confronted by these findings to do? Banerjee and colleagues emphasise a stepped care approach of watchful waiting, followed-up by low-intensity psychosocial interventions and, if unsuccessful, by more complex and intense interventions.8 The authors recommend 13 weeks’ watchful waiting in view

Published Online
July 18, 2011
DOI:10.1016/S0140-6736(11)61031-3
See Articles page 403
of the 43% reduction in CSDD scores in the placebo group in that time. If waiting is too distressing for patients or their families, the next step of psychosocial interventions could occur sooner.

Evidence of improvement in rates and severity of depression exists for several community based-interventions involving carers of people with Alzheimer’s disease: carer-given problem solving therapy or pleasurable events schedules; exercises and carer-given behaviour management therapy; interpersonal therapy; or occupational therapist training in compensatory and environmental strategies combined with cognitive behavioural therapy provided to carers.

The HTA-SADD trial does not advocate abandonment of antidepressants in people with Alzheimer’s disease and depression. Anecdotally, clinicians report successful treatment of patients with antidepressants. Therapeutic trials for individual patients are warranted, although not as first-line treatment unless depression is severe. Antidepressants might have benefits to other psychiatric symptoms secondary to dementia, as indicated by reports that hallucinations, delusions, and agitation benefit from citalopram. Finally, there are anecdotal accounts of use of electroconvulsive therapy in severe depression.

The HTA-SADD trial has underscored the need for clinicians to think about creative alternatives to drug treatment for management of depression in people with dementia, and to use evidence-based techniques and partnerships with family carers.

Henry Brodaty
Brain and Ageing Research Program and Primary Dementia Collaborative Research Centre, School of Psychiatry, Faculty of Medicine, University of New South Wales, NSW 2052, Australia
h.brodaty@unsw.edu.au

I declare that I have no conflicts of interest.

References

New hope for immune intervention therapy in type 1 diabetes

In the wake of disappointing results from the first phase 3 immune intervention trials in type 1 diabetes mellitus, a report by Tihamer Orban and colleagues in The Lancet could provide a much desired glimmer of hope that the course of disease progression can be altered by immunotherapy after all. Treatment of patients with recent-onset type 1 diabetes for 2 years with abatacept (CTLA4 immunoglobulin fusion protein), believed to interfere with priming and activation of T cells, effectively delayed loss of β-cell function for 9 months. This protective effect was preserved for the complete period of 2 years’ therapy. This trial is yet another important deliverable from the international Diabetes TrialNet Consortium, which has an impressive efficiency in designing and executing clinical immune intervention trials in type 1 diabetes with swift recruitment of eligible patients.

Cytotoxic T-lymphocyte antigen 4 (CTLA4) is an essential negative regulator of T-cell immune responses (figure). T cells need a co-stimulatory signal in addition to the main antigen-driven signal. Abatacept modulates co-stimulation and prevents full T-cell activation. Conversely, blockade of CTLA4 by ipilimumab augments T-cell activation and proliferation and improved overall survival in a phase 3 study in patients with metastatic melanoma. Because T-cell autoimmunity is pivotal...