Commentary

An innovative approach to involve patients in measuring treatment effects in drug trials

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The role of cholinesterase inhibitors in treating patients with mild to moderate Alzheimer's disease is controversial. Of 22 randomized controlled double-blind trials published to date, 19 reported that the cholinesterase inhibitor under study was superior to placebo in at least one of the primary end points. However, the measured treatment effects were small, and the interpretation of the results remains unclear. Although some view the results as proof of the clinical efficacy of cholinesterase inhibitors,[1] others regard them as statistically significant but clinically irrelevant,[2] and still others question the results in light of the flawed methodology of the trials.[3] In addition, the instruments used to measure treatment effects in the trials are subject to critical questioning. The US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products recommend the use of the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) to measure cognitive outcomes and the CIBIC-plus (Clinician's Interview-Based Impression of Change plus Caregiver Input) to measure overall clinical benefit. However, do the effects measured by these instruments reflect clinical relevance? And are these instruments sensitive enough to map the effects suggested by clinicians, caregivers and patients?

In this issue, Rockwood and colleagues report the results of a randomized controlled double-blind trial of the cholinesterase inhibitor galantamine.[4] They randomly assigned 130 patients with mild to moderate Alzheimer's disease to receive either galantamine or placebo for 4 months, followed by a 4-month open-label extension during which all of the patients received galantamine. The primary outcome measures were separate assessments by clinicians and by patients or their caregivers of the attainment of goals set before treatment. For the assessments, they used the Goal Attainment Scaling (GAS) instrument, a personalized outcome measure in which people set goals according to their own needs and define improved or worsened states in their own words. In addition to GAS, 4 other measures were used as secondary end points. After 4 months, at the end of placebo-controlled phase of the trial, clinicians reported statistically significant improvements in GAS scores in the galantamine group compared with the placebo group, whereas the patients and caregivers did not. Furthermore only 2 of the 4 secondary outcome measures showed statistically significant differences.

This study had a small sample, the duration was short, and the analysis was merely exploratory and not confirmatory. Because of the study's selection criteria, external validity is limited to patients not residing in nursing homes, those without communication difficulties or other active medical issues, and patients who have more mild than moderate impairment (73% had mild impairment in the galantamine group, 61% in the placebo group).

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Although readers at first glance may think that the results of this trial demonstrate the efficacy of galantamine, this is not the case. However, this trial does demonstrate the feasibility of using GAS as an outcome measure in clinical trials of anti-dementia drugs. The use of GAS highlights the views of patients and caregivers as to whether treatment is seen as meaningful. No previous randomized controlled trial of cholinesterase inhibitors has come this close to measuring the efficacy of treatment as experienced by the patients and their caregivers. This instrument should therefore play an important role in future research even though the data presented do not support the assumption that GAS is more sensitive than other commonly used instruments in detecting treatment effects in cholinesterase inhibitor trials.

Some further details of the trial deserve consideration. First, unlike the clinicians, the patients and caregivers did not

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detect meaningful treatment effects. It would be interesting to discuss whose assessment is most accurate: that of the experts of care or that of the experts of their own illness? Second, as in other trials of cholinesterase inhibitors, there was clearly an effect of the intervention itself, as evidenced by a slight improvement in all groups. This underlines the importance of involving patients and their caregivers and having them feel that they are being cared for. Finally, it is unclear why, after 2 months of galantamine use, patients who received the drug for the first time during the open-label phase did not improve in the same way as patients who received it for the first time during the placebo-controlled phase. One explanation may be that the open-label data are not reliable owing to selection bias.

In conclusion, although Rockwood and colleagues do not present convincing evidence of the efficacy of galantamine in the treatment of mild to moderate Alzheimer's disease, they do introduce an interesting instrument for dementia research.

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REFERENCES

1. Birks J. Cholinesterase inhibitors for Alzheimer's disease [Cochrane review]. In: The Cochrane Library; Issue 1, 2006. Oxford: Update Software
2. Schneider LS. AD2000: Donepezil in Alzheimer's disease. *Lancet* 2004;363:2100-1.
3. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, et al. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. *BMJ* 2005;331:321-7.
4. Rockwood K, Fay S, Song X, et al. Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial. *CMAJ* 2006;174(8):1099-105.

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The economic case for planned cesarean section for breech presentation at term

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Breech presentation occurs in 3%–4% of deliveries. The optimal method for delivering these babies has been a controversial issue in obstetrics. The Term Breech Trial compared the efficacy of planned caesarean section with that of planned vaginal delivery for breech presentation at term.[1] The combined outcome of perinatal or neonatal death and serious neonatal morbidity was significantly and substantially lower with planned cesarean section than with planned vaginal delivery (1.6% v. 5.0%; relative risk 0.33, 95% confidence interval 0.9 to 10.56). The paper by Roberto Palencia and colleagues published in this issue of the Journal[2] presents a detailed study of the costs incurred by the 2 arms of the Term Breech Trial, which were analyzed by intention to treat.

The investigators found that costs were lower in the group allocated to planned cesarean section than in the group allocated to vaginal delivery ($7165 v. $8042 [all costs in 2002 Canadian dollars]; average difference –$877, 95% credible interval –$1286 to –$473), which makes this option both more efficacious and less costly. A policy of planned cesarean section for breech presentation can therefore be viewed as "dominant" in broader cost-effectiveness terms.[3]

The difference in costs between the 2 groups was largely related to the relatively high physician fees for carrying out a vaginal breech delivery as well as to the higher costs of epidural analgesia, in-hospital costs of labour and delivery and costs of neonatal intermediate and intensive care. It is worth noting that 43% of women allocated to vaginal delivery subsequently delivered by cesarean section, 36% after labour began. Costs incurred by this group therefore included both the higher labour costs as well as the operating theatre costs associated with a cesarean section. Because the analysis was, correctly, by intention to treat, costs are not presented separately for those women who planned to and did deliver vaginally. Therefore, comparisons with most other studies in this area are problematic.[4]

Costs incurred from the time of randomization up to 6 weeks postnatally and related to both the mother and infant were included. Although the trial was carried out in 26 countries, the costing study was limited to the 16 countries with rates of perinatal death of 20/1000 or less to increase generalizability to the Canadian health care system. Although resource utilization data were included from all of these 16 countries, unit costs were taken from only 7 Canadian hospitals, which were selected on the basis of their accessibility and the quality of their financial information. Although the 7 centres were a mixture of teaching and community hospitals, we do not know how representative they are of the trial participating centres, and we know still less of the generality of obstetric units. Even among the 7 centres, there was wide vari-

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