The most contemporary and authoritative review of psychiatric practice in this field[2] strongly endorses the use of ECT for the management of refractory Parkinson's disease, citing numerous references from the neurology and psychiatry literature in support of this endorsement. Many psychiatrists who administer ECT are aware of this literature.

I would appreciate the authors' comments on the available evidence for the effectiveness of ECT in Parkinson's disease. If warranted, ECT should then be given its appropriate place in the treatment algorithm for this illness.

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[One of the authors responds:]

Although we did not mention ECT in our article,[1] we agree that it may have a role in the treatment of specific symptoms of Parkinson's disease.

Parkinsonian patients who are severely depressed and whose condition is refractory to antidepressant therapy are candidates for ECT to treat their depression. Patients with drug-induced psychosis that is resistant to atypical neuroleptic medication who cannot tolerate reductions in their antiparkinsonian medication may also be candidates for ECT. However, ECT should not be offered to patients with dementia because there is the potential that such treatment may cause worsening of cognition and may induce delirium. There is insufficient evidence to suggest that motor symptoms related to Parkinson's disease should be treated with ECT, and in our opinion this should not be considered an indication for its use.

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The return of "negative" trials?

I was surprised that several important issues were not addressed in the original reports[1,2] and editorial[3] about rate versus rhythm control in atrial fibrillation published in the *New England Journal of Medicine*, or in the review[4] and editorial[5] published subsequently in *CMAJ*.

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) investigators found no statistically significant difference between rhythm control and rate control.[1] However, one cannot rule out the possibility of a type II error, given that a sample size of 5300 was planned[6] but only 4060 patients were enrolled in the study.

In the noninferiority study by Van Gelder and associates,[2] the efficacy of rate control was within the upper bound of the 95% confidence interval of that of rhythm control. However, 3 concerns must be addressed.

First, it is not clear if the rhythm control strategy is a suitable active comparator. Neither the authors nor the practice guidelines cited[7] provided details on any earlier trials that showed rhythm control to be consistently better than placebo. Thus, it is not possible to assess the similarity of the current trial to those earlier trials, the expected effect size of rhythm control relative to placebo[8] or the consistent responsiveness to rhythm control of the composite endpoint components[9] used in the current trial.

Second, the investigators performed an intention-to-treat analysis only, which gives a conservative estimate of the effect size and hence bias toward a conclusion of noninferiority, when a per-protocol analysis is generally preferred.[10]

Finally, neither the AFFIRM trial[1] nor the noninferiority study[2] defined or reported compliance. Poor compliance can create bias toward a conclusion of "no difference" in both cases and would be of particular interest in assessing life-long therapies with recognized adverse effects.

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Competing interests: None declared.

[Dr. Nattel responds:]

Mario de Lemos raises several points concerning the trials of atrial fibrillation management that I discussed in my commentary.[1]

First, he asks whether a type II error might have occurred in the AFFIRM trial,[2] given the difference between the planned sample size and study enrolment.[3] The selection of appropriate sample size always involves estimating a clinically relevant difference and calculating the sample size needed to detect this difference with acceptable power. The sample size was reduced to 4060 to ensure sufficient power to reliably detect a difference of 30%, which was felt to be a minimally important clinical difference.[4] The mortality rate in AFFIRM was marginally higher (by 15%, $p = 0.08$) in the rhythm-control group. The primary finding of AFFIRM was that a rate-control approach is not inferior to a rhythm-control approach. A larger sample size (and 5300 patients might not have been sufficiently large) might have detected a statistically significant increase in mortality rate with rhythm control; however, the investigators judged that the differential impact of a significant p value for this small effect was not sufficient to justify the substantial additional cost (and the potential detrimental effect of exposing additional patients to nonsuperior and more complex rhythm-control therapy) of extending the trial.

De Lemos also states that the efficacy of rate control was within the upper bound of the 95% confidence limit of that of rhythm control in the trial by Van Gelder and associates.[5] However, those authors did not use efficacy as an endpoint. Their primary endpoint was a composite index of cardiovascular death, heart failure, thromboembolic complications, bleeding, pacemaker implantation and severe adverse drug reactions. In fact, the primary endpoint (which was a negative outcome) was more prevalent in the rhythm-control group, with the 90% 2-sided confidence limit barely including a neutral effect.

De Lemos further argues that it is unclear whether the rhythm-control strategy was a suitable active comparator. This statement seems to miss the point of the trials, which was to compare the 2 widely used approaches to therapy for atrial fibrillation: rate versus rhythm control. Both studies used patient populations in which recurrence was deemed likely, so a placebo group might not have been ethical in light of presently accepted medical practice.

De Lemos also criticizes use of an intention-to-treat analysis, rather than a per-protocol analysis (in which only events while the patient is receiving active therapy are analyzed), which he claims "is generally preferred." In fact, the weight of clinical trials opinion favours intention-to-treat analyses. The simplest way to understand the advantage of an intention-to-treat approach is to imagine a therapy that has a neutral effect on outcome but a high frequency of side effects in high-risk patients. Such a drug would be discontinued in many high-risk patients. With a per-protocol analysis, there would be an appearance of a better outcome among patients maintaining therapy, but this would be due to the drop-out of high-risk patients rather than a direct benefit.

Finally, de Lemos criticizes the AFFIRM[2] and Van Gelder and associates[5] trials for not defining compliance. Because both trials assessed approaches to therapy (rate versus rhythm control), compliance would have been difficult to define. It would presumably include such standard measures as taking prescribed medication, but also reporting of events, acceptance of cardioversion when prescribed, and even physician-based components such as vigour of pursuit of heart-rate and sinus-rhythm endpoints.

It must be kept in mind that the goal of these studies was to compare 2 widely used strategies in a clinically relevant context, a goal that was largely