treatment, indicating that during this week the patient's electrocardiogram (ECG) 'normalised'. The following week (2 weeks post-rivastigmine) it increased to 477 ms. The QTc prolongation (pre-rivastigmine to 2 weeks post-rivastigmine) was less than 11%. Nevertheless, since this change was above the 30 ms usually considered relevant, it is important to assess in an unbiased manner whether it was drug-induced.

The patient was already at risk of cardiac abnormalities owing to: previous increased QTc; hypokalaemia (a risk factor for QTc change; De Ponti *et al*, 2002) 2 weeks before starting rivastigmine treatment (no potassium values were reported at the time of the ECG finding); concomitant use of diltiazem, which is known to cause atrio-ventricular blockade and bradycardia (risk factors for QTc change; De Ponti *et al*, 2002); a history of hypertension, ischaemic heart disease, myocardial infarction and cerebrovascular accident, reflecting the presence of clinically significant heart disease (another risk factor for QTc change; De Ponti *et al*, 2002): concurrent Lewy body dementia, which is associated with autonomic failure (McKeith, 2000) and frontal lobe deficits that may influence QT intervals (Kubota *et al*, 2001).

My review of the cholinesterase inhibitors (Inglis, 2002) included an analysis of 2791 patients involved in pivotal studies of rivastigmine in Alzheimer's disease (Morganroth *et al*, 2002). About 30% and 10% of these patients had cardiovascular disorders and heart rate/rhythm disorders, respectively. About 35% were receiving concomitant cardiovascular treatments. Even in this relatively at-risk population, heart rate, PQ, PR, QT and QRS intervals were very similar in rivastigmine- and placebo-treated patients, indicating that rivastigmine did not produce adverse effects on cardiac function as assessed by ECG. The lack of cardiac effects associated with rivastigmine may be explained by its selectivity for central over peripheral cholinesterases, and an apparent brain-region selectivity that may avoid areas such as the medullary cardiorespiratory nucleus (Enz *et al*, 1993).

Case reports are an important means of communicating clinical observations. However, it is important that the facts are presented clearly to allow a balanced judgement on the available evidence. I would suggest that the prolonged QTc described in this single case report is more likely to be due to the confounding factors described above than to a causal association with rivastigmine treatment. The cholinesterase inhibitors form an invaluable part of our limited armamentarium in managing patients with dementia. It would be unfortunate if patients who might benefit from these treatments were deprived of them because of false-positive associations with cardiotoxicity.

Declaration of interest

F.I. has conducted research for and been supported by research grants from Janssen-Cilag, Novartis Pharmaceuticals and Shire Pharmaceuticals. He has lectured for Janssen-Cilag and is a member of the Novartis Speakers Bureau.

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F. Inglis Glasgow Memory Clinic, Golden Jubilee National Hospital, Beardmore Street, Clydebank G81 4HX, UK

Author's reply: Prolonged QTc interval is defined as a QTc longer than 440 ms (Khan, 2002); therefore, by this definition, the patient did not have a documented prolonged QTc interval prior to the introduction of rivastigmine.

As detailed in the original report of this case to Novartis, the patient had been admitted a number of weeks previously to a medical ward where he developed diarrhoea which was deemed responsible for the lowering of his potassium. As a result he received potassium supplements while the diarrhoea was ongoing and once the diarrhoea stopped the potassium was rechecked and the potassium supplements were discontinued. The patient had no diarrhoea at any stage during his treatment with rivastigmine that could have led to a further development of hypokalaemia. The patient had been receiving his other medications on a long-standing basis, including diltiazem for 5 years, and electrolytes checked intermittently had not shown previous problems with hypokalaemia. It is therefore unlikely that the patient was hypokalaemic at the time of the prolonged QTc interval.

The patient had no recent history of cardiac abnormalities apart from a myocardial infarct 6 years previously and long-standing hypertension. The patient had been on long-standing medication and there was no evidence of a prolonged QTc while on these medications. Although the patient had symptoms suggestive of dementia with Lewy bodies he did not fulfil the criteria for a diagnosis of probable dementia with Lewy bodies (McKeith *et al*, 1996).

In conclusion, this patient had evidence of a normal QTc interval prior to the introduction of the rivastigmine and developed a prolonged QTc while on the treatment which reverted to normal on discontinuation of the drug. His concomitant medication had been long-standing, he had no recent history of cardiac abnormalities and his previous hypokalaemia secondary to diarrhoea had been corrected. Therefore, we suggest there is a possibility of a causal relationship between rivastigmine and prolonged QTc interval. Independently, Novartis have received two isolated reports of QT interval prolongation, which the company have attributed to confounding factors such as co-medication and electrolyte abnormalities as well as insufficient/discrepancies in documentation (J. Collins (Novartis), personal communication, 2001).

I agree with Dr Inglis that the cholinesterase inhibitors are an invaluable part of our limited armamentarium in managing people with dementia but as with any new treatment only when a large number of patients are treated, many of whom will be taking multiple medications, have different comorbidities and be subject to other conditions that were not represented in the original trial population, will adverse effects become manifest that were otherwise not recognised, appreciated or expected. It is important that clinicians

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monitor, document and report adverse events. Unfortunately, experience demonstrates that this is frequently lacking and can result in the delayed recognition of potentially serious side-effects and interactions.

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E. Walsh Department of Liaison Psychiatry, Stobhill Hospital, 133 Balornock Road, Glasgow G21 3UW, UK

The antidepressant debate should move on

In her editorial Moncrieff (2002) ignored decades of work and focused on a few pieces of research, one of them from 1965. The editorial was followed by a letter criticising this view (Malt, 2002), which was, however, published under the title 'The antidepressant debate continues'. This title might leave the impression that the effectiveness of antidepressants is still questionable.

Some of our colleagues might conclude that antidepressants have no proven effect and their patients should discontinue them. The consequences of such actions have been researched extensively: the relapse rates are approximately twice as high for patients who stop their medication in the first 2–6 months beyond the point of remission, compared with those who continue treatment (e.g. Anderson *et al*, 2000; Hirschfeld, 2001). Other patients might be denied an effective treatment. Going through all the evidence, which includes comparisons with other treatments and between different classes of antidepressants, animal work, and tryptophan and noradrenalin depletion experiments in people responsive to antidepressants, would be like reinventing the wheel, and is not the subject of this letter. As the rest of us continue to learn of advancements being made to refine and improve the pharmacotherapy of depression, is it possible that there is a group believing that antidepressants really do not have an effect? There is indeed an antidepressant debate – but it is not whether they work but rather how they work that is the current focus of interest.

Declaration of interest

G.K. and A.K. have received grants from Janssen Research Foundation and GlaxoSmithKline for conducting molecular genetic studies in psychiatric disorders. G.K. has received honoraria from Janssen Cilag for delivering lectures.

Anderson, I. M., Nutt, D. J. & Deakin, J. F. W. (2000) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. *Journal of Psychopharmacology*, **14**, 3–20.

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G. Kirov, A. Korszun Neuropsychiatric Genetics Unit, Tenovus Building, University of Wales College of Medicine, Heath Park, Cardiff CF14 4XN, UK

In her editorial, 'The antidepressant debate', Moncrieff (2002) provocatively questioned the orthodox view that antidepressants are efficacious (i.e. work under clinical trial conditions) in the treatment of depressive illness. Questioning accepted views is valuable but Moncrieff missed the real question, which relates to effectiveness, that is when are antidepressants useful clinically? The efficacy argument at the head of her critique, based on individual, often old and poor-quality, studies flies in the face of consistent findings of antidepressant efficacy in systematic reviews and meta-analyses (e.g. Anderson *et al*, 2000). Even the argument of bias due to unblinding because of side-effects is contradicted by her own meta-analysis, which showed a significant benefit for antidepressants over 'active' placebo (Moncrieff *et al*, 1998). Even more compelling is the evidence from continuation/maintenance studies which show that antidepressants have a robust effect in reducing rates of relapse and recurrence (Carney *et al*, 2001), a cumulative effect over months or years. Explaining this by a placebo effect is difficult to accept, or else demands re-evaluation of the nature of placebo.

This is not to say that 'negative' studies, where antidepressants are no better than placebo, should be ignored. An important factor is probably related to severity of depression. Khan *et al* (2002) found that the proportion of studies favouring antidepressants over placebo increased with the severity of depression; the response to placebo declined with increasing severity whereas that to antidepressants increased. This raises the fundamental question of when (i.e. at what severity) in real life practice does someone with depression clearly benefit from antidepressant drug treatment. Put another way, is the current trend to wider use of antidepressants for milder depression justified? This can only be answered empirically in appropriate naturalistic trials, and even then will require value judgement about the size of the benefit.

Perhaps the most worrying aspect of Moncrieff's editorial was the implication that we should take either a psychosocial *or* a physical approach to the treatment of depression. Surely we should have put this rather tired dualist view of psychiatry behind us by now? A holistic view combining drug and psychological treatments is to be preferred and evidence is accumulating that this leads to better outcomes. To conclude, a balanced view of the evidence for antidepressants firmly places them as an established and important therapeutic option (alongside others) in the treatment of depression, with their role becoming more central with increasing severity. The true debate is about the best way to use them.

Declaration of interest

I.M.A. and P.M.H. have both received honoraria for speaking, been members of advisory boards, received research grants and had support for attending scientific meetings from several pharmaceutical companies involved in the manufacture and marketing of antidepressants.

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