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Contents ■ Aripiprazole – data on efficacy and associated mortality

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El-Sayeh *et al* (2006) raise some important issues regarding the design and reporting of clinical trials. However, we feel that the conclusion that 'aripiprazole has been licensed despite the fact that few reliable data on this drug are publicly available' merits further clarification. Aripiprazole was first approved in November 2002 in the USA, and in 2004 in Europe, based on the submission of a substantial body of evidence to the regulatory authorities on more than 4000 patients. However, Bristol-Myers Squibb and Otsuka Pharmaceuticals are committed to reporting trial results as completely as possible, and publication of pivotal studies has taken place subsequent to approval.

All the aripiprazole clinical studies were conducted in accordance with regulatory requirements and using accepted standards (Marder *et al*, 2003; Naber & Lambert, 2004). Such studies have inherent restrictions, and we recognise that patients enrolled may not always reflect those seen in everyday care. We understand the value of all study types – randomised controlled trials, naturalistic, retrospective, observational – in helping to determine the benefit–risk profile, and have recently completed a series of studies with more naturalistic designs and with large sample sizes, to explore the benefits in a wide range of patients (Tandon *et al*, 2006; Kerwin *et al*, 2007, details of the other study can be obtained from http://www.clinical trials.gov, trial number NCT00237939). These complete studies support the profile of aripiprazole established in the clinical studies reviewed by El-Sayeh *et al* in their systematic analysis.

With respect to the suggestion that deaths occurring during the aripiprazole studies have not been widely reported, it is our practice to report any deaths or adverse events applicable to a study and we have done so consistently in our publications. Deaths unfortunately do occur during studies, just as they do in real-world situations.

We are committed to continued openness and disclosure of clinical study results, and as such will continue to work closely with El-Sayeh *et al*.

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Kerwin, R., Millet, B., Herman, E., *et al* (2007) A multicentre, randomized naturalistic open-label study between aripiprazole and standard of care in the management of community-treated schizophrenic patients. Schizophrenia Trial of Aripiprazole (STAR Study). *European Psychiatry*, in press.

Marder, S. R., McQuade, R. D., Stock, E., *et al* (2003) Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. *Schizophrenia Research*, **61**, 123–136.

Naber, D. & Lambert, M. (2004) Aripiprazole: a new atypical antipsychotic with a different pharmacological mechanism. *Progress in Neuropsychopharmacology and Biological Psychiatry*, **28**, 1218–1219.

Tandon, R., Marcus, R. N., Stock, E. G., *et al* (2006) A prospective, multicenter, randomized, parallel-group, open-label study of aripiprazole in the management of patients with schizophrenia or schizoaffective disorder in general psychiatric practice: Broad Effectiveness Trial with Aripiprazole (BETA). *Schizophrenia Research*, **84**, 77–89.

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Declaration of interest

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The main finding of El-Sayeh *et al*'s systematic review that 'compared with placebo, aripiprazole treatment was associated with a significant decrease in relapse rates, increased compliance with the study protocol, and a decrease in prolactic levels below the expected values' is overshadowed by a background of complaint about lack of data. What one wants to know is what was the spectrum of activity with respect to symptoms? A substantial body of data was collected with standard rating scales on 4125 patients in ten separate trials. With no single exception, El-Sayeh *et al* record that these data were either 'unusable' or that standard deviations were not available (Table 1); they therefore conducted no analysis.

It seems incredible that after contacting relevant authors and the manufacturers of aripiprazole El-Sayeh *et al* came up with such a barren yield. There surely are data available and a systematic reviewer has a duty to obtain them and make them available in comparative form.

A more serious deficiency relates to the authors' clear innuendo that reports of deaths which are possibly drug related have not been widely disseminated. They further argue that 'not disseminating clear information regarding these people's outcomes . . . breaks that unspoken contract that occurs between researchers and trial participants at the point of gaining informed consent'. In a poster presentation at the Winter Workshop on Schizophrenia Research in February 2006 the authors were even more explicit, 'In two studies 8 people allocated aripiprazole died. Even if the mortality of people with schizophrenia is 2–3 times that of the general population, the age-standardised death rate in these studies exceeds even that pessimistic estimate by 400–500 percent . . . Mortality data are concerning'. To make the point crystal clear the poster included a representation of a coffin.

It appears that El-Sayeh *et al* made a simple mistake – they thought that a number of deaths recorded in trials on the Food and Drug Administration (FDA) website (http://www.fda.gov) related differentially to patients on aripiprazole, whereas in fact these deaths were in the uncontrolled follow-up phase and were neither selective to aripiprazole, nor in excess relative to age and gender norms. The data were accessible, and were known to the FDA and to the relevant companies. Authors of systematic reviews no doubt have a duty to draw attention to deficiencies of trial data as they see them, but they also have a