Correspondence

EDITED BY KIRIAKOS XENITIDIS and COLIN CAMPBELL

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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*.

El-Sayeh, H. G., Morganti, C. & Adams, C. E. (2006) Aripiprazole for schizophrenia. Systematic review. *British Journal of Psychiatry*, **189**, 102–108.

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G. A. Silver Bristol-Myers Squibb, Uxbridge, UK
R. Gutierrez-Esteinou Bristol-Myers Squibb, Princeton, New Jersey, USA. Email: rolando.gutierrez-esteinou@bms.com
R. D. McQuade Otsuka America Pharmaceutical, Princeton, New Jersey, USA
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Declaration of interest

G.A.S. and R.G.-E are employees of Bristol-Myers Squibb. R.D.M. is an employee of Otsuka Pharmaceutical Development and Commercialization Inc.

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

responsibility to marshall all the findings in a scientifically revealing way. If they make an error they have a duty to correct it.

Declaration of interest

T.J.C. is a co-organiser of the Winter Workshop for Schizophrenia Research which has been supported by Bristol-Myers Squibb and Otsuka, Janssen Pharmaceuticals, Lilly, Lundbeck and Astra Zeneca.

El-Sayeh, H. G., Morganti, C. & Adams, C. E. (2006) Aripiprazole for schizophrenia. Systematic review. *British Journal of Psychiatry*, **189**, 102–108.

T. J. Crow SANE Prince of Wales Centre, Warneford Hospital, Oxford OX3 7JX, UK. Email: tim.crow@psych.ox.ac.uk
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Author's reply: We generally concur with the views of Silver *et al* and we continue to collaborate with those at Bristol-Myers Squibb and Otsuka to obtain data which were not easily accessible to us when the review was initially conducted. The updated version of this review is much improved by the incorporation of these data (El-Sayeh & Morganti, 2006). The original version, however, was submitted to the *Journal* in June 2004.

We were interested that the review fell short of Professor Crow's expectations. Perhaps he is correct in saying that there is a grumbling background to the whole review but it was peer reviewed and there was no objection to this. Professor Crow was surprised that our searches came up with such a 'barren yield' of data. Perhaps his experience in this area is not ours. We asked employees of Bristol-Myers Squibb to check our review. Those that kindly visited us and promised data are explicitly mentioned in widely accessible versions of this review (El-Sayeh & Morganti, 2004). Other authors referred us to the company for additional information. Professor Crow goes on to say that it is the duty of systematic reviewers to make data available in comparative form. We have tried to be fair, open and explicit with what we could get. If Professor Crow can get more data we will of course be grateful for those.

Professor Crow draws attention to aripiprazole and mortality as presented in a poster at the Winter Workshop on Schizophrenia Research in February 2006. After the publication of our paper in the *Journal* we obtained clarification from Bristol-Myers Squibb regarding the eight deaths. This information was forthcoming precisely because of the poster presentation in 2006. Two years earlier we had met with representatives of the company and asked for conformation of our results before publication in the *Cochrane Database of Systematic Reviews* and a note of this meeting is made (El-Sayeh & Morganti, 2004). The offer of clarification and further contact did not materialise until after the poster presentation. Thereafter Bristol-Myers Squibb showed us how we had indeed failed to note how these people had died in the post-randomisation protracted follow-up of the two studies in question, so normalising the seemingly alarming standardised mortality ratio previously presented (El-Sayeh & Morganti, 2004). We do not think anyone would say that these data were easy to locate or are clear (Dubitsky *et al*, 2002), although Professor Crow may think otherwise.

As mentioned in our review, currently available data do not seem to support the prolific use of aripiprazole. In suggesting otherwise, there may be a danger of giving false hope to clinicians and recipients of care.

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H. G. El-Sayeh Briary Wing, Harrogate District Hospital, Harrogate HG2 7SX, UK. Email: hany.el-sayeh@chrd-pct.nhs.uk

C. Morganti Ospedale Niguarda Ca'Granda, Milan, Italy

C. E. Adams Academic Unit of Psychiatry, University of Leeds, Leeds, UK
doi: 10.1192/bjp.191.1.87

One hundred years ago

John Murray's Royal Asylum

The statistics of insanity are perhaps more lacking in precision of terms than are those relating to any other human affairs. Chief among the elastically uncertain stands the term "recovery". Yet on it depends the true history both in the positive and negative sense of our fight with the disease. Dr. Urquhart gives his interpretation of the term, and we consider that it is as fair and accurate as can be looked for:

> "The number of readmissions (15) was unprecedented in the history of the asylum, and the number of those suffering from recurrence of mental disorder (22) was also disproportionate. In these observations the word 'recovery' is used to indicate those in whom there is re-establishment of mental soundness permitting of the return of the patient to his place in the world without requiring the care and supervision of others. The 'lucid interval' may prove to be of life-long duration, it may last for years, or only for months. Doubts have been expressed regarding the propriety of liberty in many of these cases. It has been represented as a wrong to the lieges. This is a new phase of opinion. For many years we have been accustomed to accusations of undue detention in asylums, elaborate safeguards have been devised to protect the insane from that evil, and now the tide of opinion seems to be setting in the contrary direction. As the law stands there is no longer authority for the detention of a person after he ceases to be insane; and, in the great majority of cases, it would be an intolerable hardship to be detained indefinitely because of a possibility of untoward remote consequences. No doubt there are those, including many who have never been under custodial care, who should be limited in liberty of action under revised legal enactments; but the advocates of extreme measures will have to be content with less Spartan remedies than they formulate. The practice of discharge on recovery, or even on improvement, may entail occasional hardships, but on the whole it is appropriate to existing conditions."

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Researched by Henry Rollin, Emeritus Consultant Psychiatrist, Horton Hospital, Epsom, Surrey
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