EDITORIAL

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Tacrine for Alzheimer's disease: a complex decision

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Clinicians, regulators and investigators have been dealing with the question of the utility of tacrine treatment for Alzheimer's disease over the last few years. Sometimes contentious, this question has often generated more emotionality than objectivity. The purpose of this editorial is to define the critical questions, and offer some opinion on the future course for the many different interest groups that have addressed this problem.

It is best to separate the issue of tacrine into the following questions:

- Should tacrine be made available in the market place?
- Should tacrine be prescribed?
- What are appropriate expectations for the effect of tacrine on patients and caregivers?

Turning to the first question, tacrine's approval. This is a regulatory issue. Criteria have been established in the US[1] and in Europe[2] that define the standards that a drug for the palliative treatment of Alzheimer's disease needs to reach. These guidelines necessitate that a drug have a statistically significant advantage over placebo on a psychometric scale, usually the ADAS, and global impression scale, completed by the clinician. In addition, in Europe, but not the US, a statistically significant effect of the drug, as reflected on a measure of activities of daily living, also needs to be reached.

The US Food and Drug Administration, after three hearings, reached a unanimous conclusion that tacrine met the US standards. The drug showed a statistically significant effect on the ADAS,[3] and on the Clinicians' Global Impression of Change scale, in two large multicentre studies.[4] It was also judged that the most significant adverse event, the elevation of liver enzymes, though frequent, was not so severe as to jeopardise patients. Hence, the risk/benefit ratio was seen as satisfactory.

The standards for approval in Europe are somewhat more strenuous than in the US, with the additional requirement of efficacy on a scale of activities of daily living. However, reviews of the tacrine trials indicate that statistically significant advantages of the drug over placebo on such scales, particularly the Progressive Deterioration Scale, were found.[3,4] Hence, the guidelines that have been established by the European Union have also been met. Nonetheless, approval of tacrine in Europe has only occurred in a few countries.

In so far as the guidelines for approval were established *a priori*, and apply to all potential therapeutic agents for Alzheimer's disease, the question then exists as to why the reticence of approving a drug that meets the standards. The answer lies in the delineation of the drug's magnitude of effect and adverse event profile. It has been argued that the size does not justify the safety risk inherent in the drug's administration.

The difficulty seems to be that the regulatory authorities are in search of a standard that will best be determined in clinical practice and are confusing the regulatory issues with issues of clinical practice. Whether the drug is available for physicians or patients is the question for the regulators. Whether the drug is prescribed is the question to be determined in the doctor/patient relationship. The regulatory guidelines that have been established by both the US and the EU, are reasonable guidelines that are fair to determine whether a drug is made available in the market place. The ultimate utility of that drug is a complex decision that requires an informed process between physician, caregiver and patient, and must evaluate whether a statistically significant effect on a series of scales, corresponds to a clinically meaningful change with an adequate magnitude of drug effect.

Many patients are completely unresponsive to the effects of cholinesterase inhibitors in Alzheimer's disease. Although a substantial subgroup of patients have some response to these kinds of drugs, only a small subgroup have what might be described as "dramatic improvements". Dramatic response is considered to be patients who have had more than a seven point change on the ADAS cognitive subscale. The incremental difference between patients on placebo and patients on tacrine is only 15% of the population of patients who are able to tolerate the drug. This is to say that if a patient is able to tolerate tacrine, there is an approximately one in seven chance that they will have a relatively obvious change in their cognitive performance. When superimposed on these numbers is the likelihood that the number of patients who cannot tolerate tacrine at its highest dose, because of elevations in liver enzyme, is quite high, the number of patients who both begin treatment and are likely to have a seven point ADAS change is approximately one in 20. Currently the most relevant question that the physician,