

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 US¹ and in Europe² 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,

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patient and caregiver must address is whether a likelihood of response that ranges from 15 to five is worth the cost of treatment. However, is it only when the regulators make a drug available, that those who are most affected with this illness can even have the ability to make that decision.

For many clinicians, the odds on achieving a dramatic response with tacrine may be perceived from the data so far obtained to be too small to justify the demands of weekly blood drawings and close monitoring. However, subsequent experience with tacrine suggests approaches that may enhance the utility of the drug, and the number of patients who could respond. The number of patients ultimately able to tolerate tacrine administration is greater than that experienced in the large multicentre trials, because those trials did not use a rechallenge strategy for patients who had elevations in liver transaminases. Subsequent experience⁵ indicates that it is possible to rechallenge patients with the doses at or lower than those previously found to be associated with liver enzyme elevations while maintaining liver transaminases below 2.5 times the upper limit of normal. With continued treatment, such patients are often able to reach tacrine doses that exceeded those at which they first experience transaminase elevations. Hence, such patients may be able to reach doses of 120mg or even 160mg tacrine, and experience a more robust response. Thus, the assumption that only 25% to 30% of patients who are exposed to tacrine will ultimately be able to tolerate a dose of 160mg, as occurred in the multicentre study in which this dose was achieved, is based on a dose scheduling that is far less flexible than is available to the clinician. This more flexible dosing makes possible greater tolerability.

There is a great deal of impression in the measurement of pharmacologically induced change in the Alzheimer's patient. It has proven difficult to anchor those changes to life events. However, a step towards rectifying this problem was taken in the testing of Mentane, the hydroxylated metabolite of tacrine. In a multicentre placebo controlled trial, Mentane was found to produce small but significant changes in the cognitive subscale of the ADAS, and in the Clinicians' Global Impression of Change, but to reduce the amount of time care-givers spend taking care of their Alzheimer's patients by over two hours a day.⁶ Thus, relatively small changes in current outcome measures, translated into substantial and positive alterations in a caregiver's burden, as reflected in hours per days spent taking

care of an Alzheimer's patient, help address the question of what are appropriate expectations for patients and care-givers. Hence, a drug seeming to have small effects that are measurable even by the psychometrician, let alone by the clinician in an unstructured interview, can have clear benefit at home. These kinds of results emphasise the need to include in the process underlying the decision to prescribe tacrine, and continue its administration once prescribed, the meaningful input of the caregiver.

Given the scientific investment in Alzheimer's disease research over the last decade, it is not surprising that many constituencies hoped that the first drug approved for Alzheimer's disease would have robust effects. With 'medical miracles' regularly being reported in the lay press, disappointment at the first treatment for Alzheimer's disease was, in many ways, predictable. If anything, this disappointment was made even more likely by the overly optimistic first report of the effects of tacrine in a prominent medical journal.⁷ However, these attitudes and events should not diminish the fact that tacrine has statistically significant effects on all key outcome measures that had been *a priori* stipulated as tests for drug efficacy. As such it represents a first compound, among a class of compounds, the cholinesterase inhibitors. This group of compounds are likely to offer a more favourable risk/benefit ratio as subsequent members of this class become available throughout the world in the next decade. One can only hope, as occurred in the treatment of hypertension or childhood leukemia, that these first steps with tacrine will be succeeded by agents as they have been in other diseases, by drugs that have become the standard armamentarium in the treatment of these conditions.

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Original manuscript received March 23, 1995.

Final revision accepted July 3, 1995.

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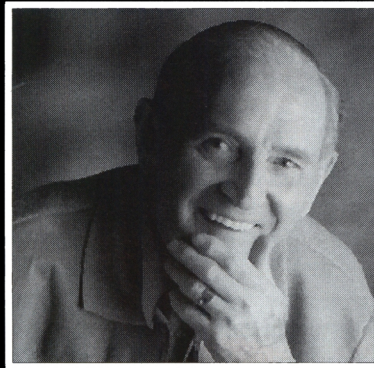
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