In a recent article by Erkinjuntti et al., galantamine, an acetylcholinesterase inhibitor, was shown to be effective in the treatment of probable vascular dementia (VaD) and Alzheimer’s disease (AD) combined with cerebrovascular disease (CVD).

The study was of seemingly unusual design in that 2 apparently disparate conditions were merged together, although this is not the only trial to have used this methodology. The authors’ rationale lies partly in their statement that “differentiation between AD and VaD on clinical grounds can be difficult,” and the trial is therefore using a pragmatic approach, being a trial of treatment of cognitive impairment in the presence of CVD regardless of coexistent conditions. In fact, the study population was probably, and inadvertently, more homogeneous than the title suggests. The reason for this lies in mixed dementia and the diagnostic criteria used. These were the now-outdated NINDS-AIREN criteria for probable VaD and the NINCDS-ADRDA criteria for possible AD, coupled with a requirement for radiological evidence of significant cerebrovascular disease. Mixed dementia—a coexistence of CVD with AD—is now known to be very common and may be the single commonest form of dementia. Both the NINDS-AIREN and NINCDS-ADRDA criteria were prepared before this was recognized. When these criteria were prepared, small amounts of CVD were routinely ignored when seen in conjunction with what was otherwise thought to be AD. There is now convincing evidence for a powerful interaction between these disease processes when coexistent and further evidence that these conditions coexist more often than would be expected by chance as a result of shared risk factors and possibly patho-etiological mechanisms. The criteria have other faults in that they use an Alzheimer-based paradigm, with considerable emphasis on memory loss, for the diagnosis of VaD. Subcortical cognitive impairment is now known to be the most prominent pattern seen in cerebrovascular disease. In essence, the NINDS-AIREN criteria require an Alzheimer-like dementing process coupled with the presence of cerebrovascular disease. As such, these criteria are probably better criteria for mixed dementia than they are for VaD, albeit not generally recognized as such. This is particularly likely when the patients are recruited from “memory” clinics where the patients are preselected for AD. The NINCDS-ADRDA “possible AD” category specifically allows for the coexistence of 2 conditions. As implemented in the galantamine study with its requirement for imaging evidence of cerebrovascular disease, patients recruited under these criteria probably had mixed disease. Thus both sets of criteria used in this study probably identify the same broad group of patients, ie, those with mixed disease, albeit with some differences of emphasis.

If the galantamine study is to be reinterpreted as a study of mixed disease, was this a useful study? As mixed disease is common and as the interaction between the 2 processes is significant, there is a good case for diagnosing mixed disease. Paradoxically, there are no criteria at all for doing this. The study is therefore relevant to clinical practice. In practical terms, it encourages the clinician to make a diagnosis of mixed dementia on seeing a patient with an amnestic syndrome suggestive of AD combined with ischemic changes on imaging and to consider the appropriate management of both conditions.

Consideration of the management leads to the next important failing of both the NINDS-AIREN and NINCDS-ADRDA criteria, which is the requirement for the presence of fully developed dementia. This does not necessarily affect symptomatic treatment but is relevant to prevention. As CVD is preventable, it is self-evident that cases should be identified as soon as possible. This early stage, in the context of pure vascular disease, is termed vascular cognitive impairment (VCI). The matter of a similar concept for early mixed disease has scarcely been thought of, although it will be necessary to develop this. A term such as vascular Alzheimer mixed cognitive impairment (VAMCI) might be appropriate. The names of the conditions contributing to the mixed syndrome should be retained so that the term can be modified to handle other combinations, such as vascular Lewy-body mixed cognitive impairment (VLMI), and so forth.
The level of cognitive impairment at which the galantamine trial was aimed is, however, not necessarily inappropriate; clearly a drug aimed at symptomatic improvement must be targeted at a level of cognitive impairment at which it can produce a worthwhile improvement. It is usually assumed that this is at the level of mild-to-moderately severe dementia. However, the choice of level of cognitive impairment is often made more on the basis of regulatory considerations than on the basis of the underlying biology. For the same historical reasons as outlined above, the NINDS-AIREN criteria are those accepted by regulatory authorities for drug trials. A study looking outside these criteria is unlikely to be supported by pharmaceutical companies because the diagnostic criteria would necessarily be ad hoc and a positive result would not be useful in licensing. More important is the effect of such criteria and considerations on trials of preventative therapy. The lack of criteria acceptable to the regulatory authorities, and hence to the pharmaceutical industry, for the identification of early VCI or VAMCI hampers research on preventative therapy in early disease. Criteria that focus on early disease are urgently needed. However, it is essential to wait until there are sufficient data to formulate valid criteria than to hasten unduly and, in the absence of sufficient knowledge, produce another set of misleading criteria. The ultimate goal is, of course, to identify patients at the presymptomatic “brain-at-risk” stage. Neurprotective agents as well as risk-factor modification have the greatest potential to work when applied at this stage, but the only trials so far using memantine, a noncompetitive N-methyl-D-aspartate (NMDA) antagonist and therefore a drug that conceivably could have a protective action, used NINDS-AIREN criteria with a 28-week follow-up suitable only for assessing symptomatic effects, which were of similar magnitude to acetylcholinesterase inhibitors. Researchers in stroke in general can greatly assist by including simple ratings of cognition in their study designs. It is clear that cognitive loss without substantial physical handicap is a common and important outcome of CVD, but until recently most “stroke” trials have not assessed cognition.

The next question is that of the drugs mode of action. Galantamine is a centrally acting acetylcholinesterase inhibitor. The development of this class of drug was based on the cholinergic hypothesis of AD. They do work in AD, although the magnitude of the benefit is unimpressive. The theoretical basis for anticipating an effect from this class of drugs in CVD is weaker than it is for AD. The cholinergic deficits seen in VaD are less pronounced and of a different pattern than those of AD. There is, as yet, no convincing evidence that acetylcholinesterase inhibitors have any significant effect in “pure” VCI or VaD. A trial of donepezil14 did show a benefit in “VaD,” but again, this study used the NINDS-AIREN criteria with the implication, for the reasons outlined above, that the study population probably contained a lot of patients with mixed dementia. While the population behaved differently from one of “probable” AD, as defined by the NINCDS-ADRDA criteria used in other studies, much of the benefit could nonetheless be attributed to an action on the Alzheimer’s component, with or without a contribution from an action on the vascular component.

The magnitude of the drug effect for both galantamine and donepezil is a further concern. On the Alzheimer’s Disease Assessment Scale, cognitive subscale (ADAS-Cog), the difference between the controls and the patients in these studies, as well as Alzheimer studies, amounts to about 3 points and, where used, to <1 point on the Mini-Mental State Examination (MMSE). While statistically significant, these effects are so slight that they may not be useful routine treatments but rather treatments that should be tried in all but maintained only in individual responders. Effects of similar magnitude are seen with drugs with a completely different mode of action such as memantine, suggesting that the benefits may be nonspecific. Conversely, it may be argued that the rating scales used in trials of anticholinergics in “VaD” are inappropriately based on AD and may be insensitive to changes seen in VaD. This is almost certainly the case with the ADAS-Cog and MMSE, although other rating scales based on a clinicians and carers ratings of change should be rather more global in their applicability. Nonetheless, use of the unmodified ADAS-Cog and MMSE may produce artifically modest results where more appropriate rating scales would produce more persuasive results.

Overall, therefore, there is evidence from the both the galantamine and donepezil studies of a therapeutic effect for acetylcholinesterase inhibitors in VaD, or mixed AD and VaD, although in reality both studies are probably studies of mixed disease. AD and VaD commonly coexist and interact to exacerbate cognitive decline. The first important message is that for symptomatic treatment, a precise diagnosis is not essential. On current evidence, an acetylcholinesterase inhibitor could reasonably be tried for a patient anywhere on the spectrum of AD through mixed disease to VaD. Individual responsiveness should determine whether treatment continues or not. What the studies do not do, and what is probably more important in reducing the burden of disease, is emphasize the importance of early identification of cases with a vascular component to their cognitive decline, as these patients are candidates for preventative therapy rather than just symptomatic treatment. Development of this field would be aided by the inclusion of an appropriate cognitive rating scales in all “stroke” trials.

References


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