Commentary

Memantine

“Hypothesis Testing” not “Disease Modifying” in Alzheimer’s Disease

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Memantine is one of the drugs approved in both Europe and the United States for the symptomatic cognitive treatment of Alzheimer’s disease (AD). Indeed, clinical trials have shown a significant mean difference between memantine and placebo with the Severe Impairment Battery, a cognitive scale used when the Mini-Mental State Examination score is below 10—a low level of mental functioning that does not allow the application of the more precise Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-Cog) scale. Unfortunately, the effect of memantine on mild-moderate AD is much smaller than that of cholinesterase inhibitors (1 point in ADAS-Cog versus 4 points at 24 weeks).¹ On this basis, memantine has been indicated and approved for moderate-severe AD. However, the effect of memantine on cognition, even within this subgroup of AD cases, is not particularly consistent, with some trials reporting no effect.² Fluctuations of cognitive status in patients with severe dementia, together with the lack of a scale able to precisely detect changes in global mental functions, might explain such inconsistencies, yet it is clear that effects of memantine are not particularly robust even in the most positive studies.

One of the major goals in developing or assessing therapeutic modalities for AD is to target pathways that render “disease modifying effects.” Clinically, such disease modification would result in an increasing difference, over time, between treatment and placebo arms. Because amyloid and tau are the dominant scientific hypotheses of the causes of AD, it is not surprising that

they have become prime therapeutic or disease-modifying targets. In this issue of *The American Journal of Pathology*, Martinez-Coria and colleagues³ report that transgenic mice show striking reductions in oligomeric amyloid and tau phosphorylation, improved cognitive performance, and restoration of LTP after treatment with memantine. Although many may view these data as the first indication of a “disease modifying” mechanism of action for memantine, this is inconsistent with the clinical experience and reports using memantine, where only limited effects are noted.

These data, however, are extremely important in two key regards. First, perhaps more so than any other, they highlight the disparity between animal “models” of AD and human AD. It is an unfortunate fact that although the literature is replete with “cures” for various models of AD, none so far have passed muster in human clinical trials.^{4–7} As such, perhaps we should not be surprised that memantine, a drug with some clinical effects, albeit marginal, is so effective in an animal model. Second, relatedly, we should ask why such model/human differences exist.

In this vein, it is often overlooked that the amyloid hypothesis⁸ and the tau hypothesis remain as hypothetical constructs, not facts.^{9,10} Hypotheses are tested experimentally, and when supported the hypothesis remains intact; however, when experiments reveal failures in the hypothesis, the hypothesis should be changed. The triple transgenic mouse, which presents with amyloid and tau pathologies and cognitive impairments¹¹ support the hypotheses as do “therapeutic” approaches, such as presented here, whereby reductions in amyloid or tau pathologies result in cognitive improvements. On the other hand, things are not quite so clear in human AD.

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Simply put, if memantine has equivalently dramatic effects on amyloid or tau phosphorylation in human AD yet only results in minimal cognitive benefits, the hypotheses are *not* supported. Moreover, that other anti-amyloid approaches that “cure” mice also have minimal or no effect in humans would *not* support the amyloid hypothesis.

In conclusion, although the term “disease-modifying” appears to have become synonymous with “amyloid- or tau-modifying,” changes in one hypothetical molecular target or another is not “disease modification.” Rather, one also needs to show an equivalently modified disease course. As such, memantine is not a “disease-modifying” drug. However, memantine may be a “hypothesis-modifying” drug.

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