Continuing medical education

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CME QUESTIONS

A) Many meta-analyses have recently examined the efficacy of antidepressants in major depressive illness. With this background, mark True or False against each of the following statements:
1. In adults with major depressive disorder, antidepressant drugs are more effective when depression is severe than when it is mild.
2. In patients with major depressive disorder, antidepressant drugs are less effective in studies that are placebo-controlled.
3. In adults with major depressive disorder, the selective serotonin reuptake inhibitors (SSRIs) are comparable in efficacy.

4. Dual-acting antidepressant drugs are superior to the SSRIs.

B) Advances in medicine and improved healthcare delivery systems have together increased the number of persons who survive into old age. Geriatric psychiatry, and particularly the treatment of the cognitive problems of the elderly, have become important areas of current research. In this context, several novel approaches have been studied towards the prevention or treatment of cognitive deficits in the elderly, in those with mild cognitive impairment, and in those with dementia. With this background, mark True or False against each of the following statements:
1. The nonsteroidal antiinflammatory drugs (NSAIDs) naproxen and celecoxib prevent cognitive deterioration in old age.
2. Statins may protect against incident dementia.
3. Omega-3 fatty acids improve cognition in the elderly.
4. Disease-modifying treatments for Alzheimer's disease are beyond reach.
5. Diverting CSF away from the brain can reduce the exposure of the brain to amyloid and tau; this novel approach can benefit patients with Alzheimer's disease.
CME ANSWERS

A) Efficacy of antidepressant drugs in major depressive disorder

Answers: 1. False; 2. True; 3. False; 4. True.

1. Depression severity and antidepressant efficacy

Kirsch et al.\[11\] described a meta-analysis of complete datasets on all trials (n=47) of newer antidepressant drugs in major depressive disorder, submitted for regulatory approval to the Food and Drug Administration in the USA. The final analysis was based on 35 placebo-controlled trials of fluoxetine, venlafaxine, nefazodone, and paroxetine. Kirsch et al. found that the response to placebo was almost as good as the response to antidepressants when depression was mild; however, the placebo response decreased as the severity of depression increased. Therefore, antidepressant medication was significantly superior to placebo only when depression was more severe. This finding notwithstanding, the efficacy of antidepressant drugs was quite uniform across the spectrum of severity of depressive illness.

2. Antidepressant efficacy in placebo-controlled studies

In a meta-analysis of studies in geriatric depression, Sneed et al.\[2\] showed that the antidepressant response rates were lower in trials which compared antidepressant with placebo than in trials which compared two antidepressants. Thus, just as the response to placebo is enhanced by a belief that the medication is effective, the response to antidepressant medication is diminished if patients think that they may be receiving placebo.

3. Comparative efficacy of selective serotonin reuptake inhibitors

Kennedy et al.\[3\] meta-analyzed all randomized controlled trials in which escitalopram (10-20 mg/day) had been compared with other antidepressant drugs in adults with major depressive disorder. There were ten trials; these compared escitalopram with citalopram (20-40 mg/day), fluoxetine (20-40 mg/day), paroxetine (20-40 mg/day), sertraline (50-150 mg/day), and venlafaxine (75-225 mg/day). Escitalopram was found to be as effective as venlafaxine and slightly more effective than the other SSRIs. The advantage for escitalopram was more apparent in more severely depressed patients and was most evident at the 20 mg/day dose. The adverse event drop out rate did not differ between escitalopram and the other SSRIs but was lower with escitalopram than with venlafaxine. Interestingly, in a more recent, pooled analysis of two randomized controlled trials,\[4\] escitalopram (10-20 mg/day) was associated with higher response and remission rates, and with lower drop out rates, than the dual acting antidepressant duloxetine (60 mg/day) in patients with major depressive disorder; the superiority of escitalopram over duloxetine was evident even in a subset of patients with severe depression.

4. Dual-acting drugs vs. SSRIs

Papakostas and Fava\[5\] found that, its dual mechanism of action notwithstanding, milnacipran (100-200 mg/day) was not more effective than fluoxetine (20 mg/day), fluvoxamine (200 mg/day), or paroxetine (20 mg/day) in adults with major depressive disorder (however, its dual mechanism of action notwithstanding, milnacipran was not associated with more dropouts than these SSRIs). In the pooled analysis referred earlier,\[6\] escitalopram was found to be superior to the dual-acting drug duloxetine. The controversies associated with the subject notwithstanding, most data do support the advantage for dual-acting drugs over the SSRIs. A very recent meta-analysis\[6\] found that the advantage is significant but small; the number needed to treat was 24, meaning that 24 depressed patients would need to be treated with a dual-acting drug (as opposed to an SSRI) for one additional patient to respond.

B) Novel approaches to the treatment of cognitive states in the elderly

Answers: 1. False; 2. True; 3. False; 4. False; 5. False.

1. Nonsteroidal antiinflammatory drugs

A large body of epidemiological literature suggests that the long-term use of NSAIDs in conditions such as arthritis is associated with a decreased risk of Alzheimer's disease.\[7,8\] However, in a large (n=2528), randomized, double-blind, placebo-controlled trial, the Alzheimer's disease anti-inflammatory prevention trial (ADAPT) Research Group\[9,10\] found that two years of treatment with naproxen (220 mg twice daily) or celecoxib (200 mg twice daily) did not protect against cognitive decline in cognitively healthy men and women aged 70 years and older; these drugs, in fact, appeared to worsen cognitive outcomes.\[9\] Furthermore, naproxen and celecoxib either did not prevent or actually increased the risk of Alzheimer's disease.\[10\]

There is no logical reason to suspect that, in the epidemiological studies,\[7,8\] cognitively healthier patients were more likely to receive NSAID treatment for arthritis, or that arthritis protected against Alzheimer's disease. So, if NSAIDs truly protect against Alzheimer's disease, why were the results of the ADAPT study\[9,10\] negative? One reason could relate to the drugs and doses examined; for example, indomethacin and ibuprofen may be neuroprotective whereas naproxen and celecoxib are not. Another reason could be that the window of opportunity was lost in the ADAPT study; NSAIDs may be neuroprotective in younger subjects, before the neuropathology of Alzheimer's disease is established.

It must be remembered here that a balance of mechanisms may be involved. NSAIDs may impair cognition because, by inhibiting cyclooxygenase mechanisms, they interfere with glutamate-dependent learning and memory\[11,12\] but these drugs may protect against Alzheimer's disease by inhibiting the neurodegeneration resultant from the inflammatory...
response to amyloid. The mechanism which predominates may depend on the drug and the state of the brain at the period of administration.

2. Statins
Some epidemiological data suggest that the use of statins is associated with a decreased risk of incident dementia,\[^{13,14}\] In another, very recent, epidemiological study (n= 1789), Cramer et al.\[^{20}\] found that, across a 5-year follow-up period, cognitively healthy elderly subjects who used statins enjoyed a halved risk of dementia or cognitive impairment without dementia.

How may statins reduce the risk of Alzheimer's disease? The enzymes beta- and gamma-secretase cleave amyloid precursor protein and form amyloid-beta, which in turn forms the amyloid plaque that characterizes Alzheimer's disease. Only a small quantity of amyloid precursor protein follows this pathway; the rest is cleaved by alpha-secretase to form non-toxic products. Statins inhibit beta-secretase and activate alpha secretase. In animal studies, statins have been shown to reduce amyloid-beta levels.\[^{16}\]

It should be remembered that statins may also reduce the risk of dementia and cognitive impairment by modifying the vascular risk factors that have been implicated in both vascular dementia and Alzheimer's disease.

3. Omega-3 fatty acids
Epidemiological studies suggest that fish intake reduces the risk of age-related cognitive decline and Alzheimer's disease. For example, Morris et al.\[^{17}\] found that the dietary intake of omega-3 fatty acids and an at least once-weekly consumption of fish decreased the risk of Alzheimer's disease. Huang et al.\[^{18}\] found that elderly subjects who ate fatty fish more often than twice a week had a 41% lower risk of Alzheimer's disease; though, the benefits were limited to subjects without the apolipoprotein E ε4 allele. Nurk et al.\[^{19}\] showed that elderly subjects who ate more fish and fish products had better cognitive performance across a range of cognitive domains; the effect was dose-dependent. Van Gelder et al.\[^{20}\] showed that elderly subjects who ate fish and who consumed more omega-3 fatty acids in their diet suffered less cognitive decline across 5 years; the effect was again dose-dependent.

The benefits of fish are believed to arise from the omega-3 polyunsaturated fatty acid content. However, a recent, large (n= 302), 26-week, randomized, double-blind, placebo-controlled trial\[^{21}\] found that eicosapentaenoic acid and docosahexaenoic acid supplementation in the dose of up to 1800 mg/day did not improve cognitive measures in cognitively intact elderly subjects.

How can one reconcile the contrast between the epidemiological data and the findings of this randomized controlled trial? Epidemiological studies report on behavior across years or even decades; if fish oil supplementation is at all beneficial, it may need to be sustained for long periods for cognitive benefits to be detectable. Thought must also be given to the importance of beginning healthy behavior at a younger age, when the biological capacity to respond to beneficial influences is greater, than at a later age, when systems are losing their flexibility.

4. Disease-modifying treatments for Alzheimer's disease
Statins have already been discussed as potential disease-modifying treatment for Alzheimer's disease. Nearly a dozen other drugs are currently under development. For example, immunological approaches that prevent the conversion of amyloid-beta into pathological forms and approaches that accelerate the clearance of amyloid-beta are presently under study. The challenge is to establish a favorable balance between the risks associated with the induction of an autoimmune reaction and the benefits associated with the immunological clearance of a potentially harmful endogenous protein.

PBT2 is a potentially disease-modifying drug. In Alzheimer's disease, the conversion of the amyloid-beta peptide from a physiological, water-soluble, monomeric form into neurotoxic oligomeric and fibrillar forms is an undesirable occurrence.\[^{22}\] PBT2 is a metal-protein attenuating compound that reduces the copper- and zinc-mediated toxic oligomerization of amyloid-beta. Animal data from transgenic mouse models of Alzheimer's disease suggest that PBT2 may be beneficial in Alzheimer's patients. A Phase IIa clinical trial\[^{23}\] found that, in 78 patients with early Alzheimer's disease, 12 weeks of treatment with PBT2 (250 mg/day) was associated with reduced levels of cerebrospinal fluid (CSF) amyloid-beta42 and improved performance in certain tests of executive function. PBT2 was safe and well-tolerated.

5. Diverting CSF in Alzheimer's patients
The neuropathological hallmarks of Alzheimer's disease include amyloid plaques and neurofibrillary tangles; these are formed from amyloid peptide and tau protein, respectively. If amyloid and tau are more efficiently cleared from the central nervous system (CNS), there is a theoretically lower likelihood of their deposit in the brain, and hence a lower risk of resultant neurodegeneration. Encouraged by the positive results of a pilot study,\[^{24}\] Silverberg et al.\[^{25}\] examined whether draining CSF through a ventriculoperitoneal shunt would reduce the macromolecular load on the CNS and benefit patients with Alzheimer's disease. Regrettably, this large (n= 215), 9-month, double-blind, controlled study found that a low-flow ventriculoperitoneal shunt neither improves dementia ratings nor slows deterioration in patients with probable Alzheimer's disease.
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