

WHEN TO STOP CHE-IS TREATMENT IN AD PATIENTS

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The cholinesterase inhibitors (ChEIs) donepezil, rivastigmine and galantamine are the current mainstays in the drug treatment of Alzheimer's disease (AD). There is convincing evidence that these agents provide at least modest cognitive, behavioural and functional benefit for 6-12 months at all stages of the disease. The most frequent reasons for discontinuation were a change in the doctors treating the patients, so-called "ineffectiveness" and gastrointestinal side-effects, in patients with CDR=1 or 2, changes of doctors were the most frequent reason for discontinuation in a Japanese study with donepezil. However, in patients with CDR=3, perceived ineffectiveness of the medication was the major reason for discontinuation. (Umegaki H, 2008).

The reasons which support the idea to stop ChE-Is after 6-12 months are: 1. Longer term benefits are not evidence-based, i.e. there have been no placebo-controlled trials of longer duration, or methodologically sound open-label studies, which suggest efficacy. 2. There are some plausible biological reasons why ChEIs might be expected to lose their efficacy after prolonged period of time 3. The most contentious issue regarding long-term treatment is cost-effectiveness; this is documented also in analyses from e.g. NICE. 4. There is not a single RCT that specifically addresses the issue of discontinuation and re-introduction of ChE-I's in the treatment in AD.

The reasons which support the idea not to stop after this period are: 1. The results of virtually all open-label extensions of the pivotal trials, studies of patients with AD at different levels of severity and clinical trials using other designs favour treatment over no treatment for periods of up to 5 years. 2. Studies using various markers to chart the effects of medication on long-term disease progression have yielded mixed results. 3. The majority of available economic analyses suggest net savings over the long term if patients with AD receive persistent treatment with ChEIs. 4. There are organizations –EFNS- with no guidance on discontinuation. 5. There is a study with rivastigmine which supports that patients with rapid decline have more benefit. 6. But there is a great clinical experience which supports that discontinuation is correlated with rapid decline. 7. The initial benefits of treatment with donepezil were lost during the washout period -30 days-, suggesting that further improvement would have been likely if treatment had been continued (Doody RS, 2001). 8. There is also described "Discontinuation syndrome" following donepezil cessation (Singh S, 2003). 9. AWARE study supports the idea that even patients who decline have more benefit on donepezil. Overall tendency: No premature discontinuation of treatment, "give patient best chance". The decision to discontinue AChE inhibitors therapy should also be based on careful observation of each patient, since it is common to observe worsening cognitive and functional status.