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TOP CITED PAPERS IN *INTERNATIONAL PSYCHOGERIATRICS*: 3. EFFICACY OF DONEPEZIL ON BEHAVIORAL SYMPTOMS IN PATIENTS WITH MODERATE TO SEVERE ALZHEIMER'S DISEASE

Reflection

The article under discussion (Gauthier *et al.*, 2002) is based on a sub-analysis from the Moderate to Severe Alzheimer Disease (MSAD) Study, which was an investigator-driven attempt to expand the use of cholinesterase inhibitors (ChEIs) in the severe stages of Alzheimer's disease. The results of MSAD have been published in *Neurology* (Feldman *et al.*, 2001), including the Neuropsychiatric Inventory (NPI) total score, which showed a statistically significant difference between placebo and donepezil at the 24-week end-point. In the article published in *International Psychogeriatrics* in 2002, the investigators of the MSAD Study analyzed which behavioral symptoms drove the difference in NPI total score. This publication has led to a new way of analyzing data on behavioral and psychological symptoms of dementia (BPSD) from randomized clinical trials: (1) individual items of the NPI are analyzed at baseline for frequency, and clusters can be defined from the population under study; (2) symptoms not present at baseline are examined for emergence during the study period; (3) symptoms present at baseline are examined for improvement during the study period.

In the MSAD Study the total NPI-12 score difference at week 24 between donepezil and placebo was 5.6 ($p < 0.001$). Based on baseline individual NPI items scores, out of three clusters identified from a factor analysis a cluster of five items was identified as being of most clinical significance (agitation/aggression, depression/dysphoria, anxiety, apathy/indifference, irritability/lability); this "NPI-5" showed statistically significant difference between donepezil and placebo at weeks 4, 18 and 24. More importantly, the analysis of symptoms present at baseline showed improvement at week 24 for anxiety, apathy/indifference, irritability/lability. This information can be useful for clinicians monitoring treatment responses in individual patients taking donepezil. No individual symptom stood out in the prevention of emergence of individual symptoms not present at baseline, contrary to placebo-controlled memantine studies where the incidence of agitation/aggression is significantly reduced over 24 weeks (Gauthier *et al.*, 2005). One final observation from the 2002 sub-analysis: only patients not taking psychoactive medications at baseline showed a significant difference from placebo at each visit and at week-24 end point. This suggests that the behavioral effects of ChEIs are diluted by concomitant psychotropic medications, a partial explanation for the difficulty in proving benefit using donepezil in other studies.

Since the paper's publication in *International Psychogeriatrics*, the NPI item sub-analysis has led to the observation of an anti-agitation effect of memantine in moderate to severe stages of Alzheimer's disease (Cummings *et al.*, 2006; Gauthier *et al.*, 2008). A randomized clinical trial comparing memantine to placebo is under way in Canada with the specific aim of confirming in a prospective study a reduction in agitation, using the NPI and the Cohen-Mansfield Agitation Index, and a reduction in the use of psychotropic drugs, as suggested in a recent analysis from the French National Health Care Database (Vidal *et al.*, 2008).

I think the publication in *International Psychogeriatrics* of the behavioral sub-analysis of the MSAD Study has facilitated the use of behavioral outcomes in randomized clinical trials, will help regulatory agencies to recognize beneficial drug effects on BPSD, and will accelerate the reimbursement of such drugs by third-party payers. The behavioral sub-analysis may also help to provide evidence-based information to clinicians about which specific behavioral symptom or cluster of symptoms improve or decrease in incidence when using a specific drug or drug class.

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Commentary

It is now well accepted that non-cognitive features are at least as important, if not more important, than cognitive impairment in Alzheimer's disease, that some of these symptoms have (at least in part) a cholinergic basis and that there is evidence that anti-dementia drugs can improve non-cognitive as well as cognitive symptoms (Ames *et al.*, 2008).

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However, all three statements were certainly not widely accepted, or even accepted at all, at the time when Gauthier and colleagues were planning and conducting their important double-blind, randomized controlled trial of donepezil against placebo in moderate to severe Alzheimer's disease. The study was not the first to show an effect of cholinesterase medication, in this case donepezil, on behavioral symptoms, but it was one of the first to examine in a systematic way which particular types of behavioral and psychological symptoms of dementia (BPSD) were affected. BPSD has been an extremely helpful term as a profile-raiser for the importance of non-cognitive symptoms in dementia, but one of the drawbacks with such an umbrella term is that some view it incorrectly as a unitary concept or dimension, for example one that can either be helped or not helped by various interventions, whether pharmacological or psychosocial (Bird *et al.*, 2007). In fact, BPSD clearly represent a constellation of signs and symptoms, some related closely to each other but others quite distinct, some of which may share common neurobiological mechanisms while others will not. It follows, therefore, that some treatments may be effective for some types of BPSD, but have little effect on (or even worsen) others (Rabinowitz *et al.*, 2007).

By utilizing sub-analyses from the very widely used, simple, yet comprehensive Neuropsychiatric Inventory (NPI), Gauthier *et al.* (2002) clearly showed in their paper differential effects on some symptoms with particular effects for improving apathy, anxiety and dysphoria. There was also a significant change in a cluster which contained delusions and hallucinations. These findings accord well with neurochemical evidence that both psychosis and apathy are to some extent mediated by cholinergic deficit. Interestingly, in this study, there was no effect on agitation as a symptom, which has now been supported by a large randomized controlled trial of the same medication, donepezil, in people with Alzheimer's disease and clinically significant agitation which showed absolutely no suggestion of benefit of donepezil over placebo (Howard *et al.*, 2007). Gauthier and colleagues analyzed their data carefully. It is important to note that they found no detrimental effects in terms of increased side effects either in those on or not taking antipsychotics (in particular parkinsonism did not significantly worsen). It is a testament to the significance of this paper that many subsequent papers have tackled analysis of NPI subscales in a similar way, and the effect on non-cognitive symptoms has now been supported by independent meta-analyses, such as from the Cochrane collaboration (Birks and Harvey, 2006). This is especially important in view of limitations on the prescribing of other drugs such as antipsychotics (Haw *et al.*, 2008). This remains a key area of research and the authors quite rightly point out that one limitation of their study was that it did not include people who were selected on the basis of having prominent BPSD, so in many ways findings may not be generalizable to people for whom these symptoms are targets for treatment in routine clinical practice. This paper and commentary also highlight that, although there are some other studies ongoing, there remains a great need for many more well-designed studies seeking to investigate the specific effects of drugs, both anti-dementia drugs and other agents (Konovalov *et al.*, 2008), which may potentially help troublesome behaviors and distressing symptoms in those with dementia.

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