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Letter to the Editor

Treatment of Aggressive Behavior in Dementia With the Anticonvulsant Topiramate: A Retrospective Pilot Study

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Aggressive behavior in dementia often has a severe impact on the quality of life of the patient and the caregivers, and is therefore important to handle. The strategy of treatment should be broad. Non-pharmacological interventions, including environmental adjustments and supporting and training the caregivers, should always be considered. Pharmacological treatment of aggressive behavior in patients with dementia often includes the use of neuroleptics. The atypical compounds clozapine, risperidone, and olanzapine have been shown to have an effect on aggressive behavior at low dosage with limited extrapyramidal side effects. The anticonvulsants carbamazepine and sodium valproate are further alternatives. In treatment-resistant cases, buspirone or lithium may be tried, although the effect of these substances on aggressive behavior in dementia has not been well established. In the end, however, a considerable degree of aggressive behavior sometimes remains after careful treatment trials, particularly in patients with severe aggressive behavior. In addition, treatment is sometimes limited by side effects.

The anticonvulsant topiramate has sometimes been found useful in the treatment of mania in patients with bipolar disorder (see, e.g., Mitchell & Malhi, 2002). Based on this knowledge, we began to examine the possible efficacy of the compound on treatment-resistant severe aggression in patients with dementia. The clinical improvement was found satisfactory or good in the majority of cases. As a consequence, we eventually began to primarily treat the most severely aggressive patients with topiramate alone, or topiramate combined with a neuroleptic compound. These severely affected patients were not considered to benefit from a neuroleptic drug alone.

The clinical data from 15 inpatients with dementia and severe aggressive behavior were evaluated retrospectively. The patient material represents a subgroup of all patients treated with topiramate on the ward, namely those who had received the compound alone or in combination with a neuroleptic drug, with no further addition of psychotropics (antidepressants, benzodiazepines, mood stabilizers, or other neuroleptics) to the baseline medication lists. All patients had

been thoroughly examined at an earlier stage of their dementia. Three patients fulfilled the NINCDS-ADRDA criteria for probable Alzheimer's disease (AD), two patients fulfilled the criteria for frontotemporal dementia developed by the Lund and Manchester groups, and seven patients fulfilled the NINDS-AIREN criteria for vascular dementia (VaD). One patient had an anoxic brain injury. Mixed AD/VaD dementia was diagnosed in two patients. During the period of hospital care, all patients underwent a computed tomographic examination of the brain in order to rule out novel pathology.

Eight patients (the topiramate treatment [TOP] group; three women, five men; mean age 75.0, *SD* 6.2) received topiramate alone (range 25-100 mg daily, median 75 mg), whereas seven patients (the combined treatment [COMB] group; three women, four men; mean age 79.9, *SD* 6.4) received topiramate (range 25-150 mg daily, median 50 mg) combined with risperidone (range 0.5-1.5 mg daily, median 1.0 mg) or (in one case) zuclopenthixol (12 mg per day). One patient in the TOP group and two patients in the COMB group were already on treatment with 25 mg topiramate daily at the time of admission to the ward, due to previously noted aggressive behavior; the above stated doses of topiramate do not include these previous prescriptions. The 29-item version of the Cohen-Mansfield Agitation Inventory (CMAI) was employed for rating the aggressive behavior, focusing on the 14 aggression items in the present study (minimum score 14, maximum score 98). All patients were assessed before treatment, and assessed again during treatment (mean period from initiation of treatment to final assessment: 17.6 days [*SD* 11.9, TOP group], and 16.0 days [*SD* 12.4, COMB group], respectively). The median baseline score for the total CMAI aggression items was 32 (range 24-73) for the TOP group and 39 (31-54) for the COMB group. The median final assessment scores were 16.5 (range 14-45) and 20 (14-27), respectively, whereby the scores were reduced for all 15 patients. The median score reductions were 12 (range 10-58) and 19 (8-31), respectively. The score reductions were significant for both treatment groups (p = .008 and .016, respectively; Wilcoxon signed rank test). In order to obtain some information on whether the patients would benefit further from a treatment that also included neuroleptics, group comparisons were also performed. No significant group differences could be seen with respect to score reductions or the number of days between baseline and final assessments, nor were there any significant group differences in topiramate dosages (two-sided Wilcoxon-Mann-Whitney two-sample test).

The main result of the present study was the finding that treatment with the anticonvulsant topiramate appeared to reduce the aggressive behavior in patients with dementia. Furthermore, the results indicate that the addition of a neuroleptic did not entail any further efficacy. Regarding mode of action, the possible effect of topiramate on aggressive behavior could be exerted through its proposed enhancement of GABA-evoked currents (cf. White et al., 2000). It can be speculated that further mechanisms of action could include its negatively modulating effects on the excitatory glutamate-induced current and the Ca^{2+} currents (cf. Chengappa et al., 1999).

The present study was performed in a nonrandom and retrospective fashion. Accordingly, any findings are limited by the design of the study. In addition, the

patient material was limited, heterogeneous with regard to clinical diagnoses, and represented a subgroup of all patients who have been treated with topiramate on the ward. Also, there was a substantial variation in treatment length among the patients. Finally, it is possible that the nonpharmacological care on the ward also had a favorable effect on the patients' aggressive behavior. To conclude, controlled studies of topiramate's possible effect on severe aggressive behavior in dementia appear to be warranted.

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