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Stimulant Treatment of Frontotemporal Dementia in 8 Patients

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Sir

Clinicians are often reluctant to use psychomotor stimulants in patients with disinhibition from frontal lobe dysfunction because of the concern that these medications will worsen behaviors or result in psychosis.[1] We contrasted the effects of dextroamphetamine and quetiapine, an atypical antipsychotic often used to treat agitation in dementia patients with cognitive and behavioral symptoms, in 8 patients with behavioral-variant frontotemporal dementia (FTD) in a double-blind crossover trial. We were interested in testing a stimulant for several reasons: (1) there is autopsy, cerebrospinal fluid, and imaging evidence of dopaminergic deficiencies in FTD (reviewed in Huey et al.[2]); (2) there is a clinical association between FTD and basal ganglia dopaminergic dysfunction (i.e., parkinsonism)[3]; and (3) executive dysfunction associated with psychiatric illness (e.g., attention-deficit/hyperactivity disorder) can improve with dopamine augmentation.[4]

Method

All 8 patients had behavioral symptoms. Over 1 week, medication daily dosage was gradually increased to either 20 mg of dextroamphetamine or 150 mg of quetiapine in divided doses. The patients returned home on the target dose for 3 weeks before returning to

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our clinic for reevaluation. At this point, the patients were tapered to half the study medication for 2 days before discontinuation and then underwent washout for 1 week, and the process was then repeated with the other medication. Medication order was randomized, and the patients, caregivers, and clinicians were blinded to the order.

The individuals assigned durable power of attorney by the patients provided written consent, and all patients gave assent. The study was approved by an institutional review board and was conducted from November 2004 to August 2006. The primary measure of behavioral symptoms was the Neuropsychiatric Inventory (NPI),[5] and the primary cognitive measure was the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[6]

Results

All patients were able to tolerate the full dose of dextroamphetamine. One patient experienced sedation on quetiapine treatment and was unable to tolerate the full dose. The most common adverse effect of both medications was sleep disturbance. The results for the total NPI can be seen in Figure 1. Using nonparametric methods (a 2-tailed Friedman test), there was a significant effect of treatment on the total NPI ($p = .05$). Post hoc Wilcoxon signed-rank tests showed that the total NPI was significantly lower than pretreatment baseline on dextroamphetamine ($p = .02$), but there was no significant difference between baseline and quetiapine, nor between quetiapine and dextroamphetamine. The NPI subscales that decreased the most on dextroamphetamine were apathy (2.8 points) and disinhibition (2.4 points). There was no significant overall effect of treatment on the RBANS.

The order of magnitude of this effect is large compared to that observed in pharmacologic trials for behavioral symptoms of Alzheimer's disease. A summary of available evidence concluded that the efficacy of atypical antipsychotics to treat behavioral symptoms in Alzheimer's disease is “small at best,” with mean reductions in the total NPI score ranging from not significantly different from placebo to 8.8 points.[7] The sample size of this study was small, and thus these results should be viewed with caution.

Contrary to conventional expectation, treatment with dextroamphetamine improved behavioral symptoms, including disinhibition, in patients with FTD. Medications that augment brain dopamine and norepinephrine, such as stimulants, are promising as a therapeutic strategy for the behavioral symptoms of FTD, which are particularly difficult for caregivers, care facilities, and clinicians to manage. However, given the small sample size and preliminary nature of this study, we do not at this lime recommend stimulant treatment for the symptoms of FTD.

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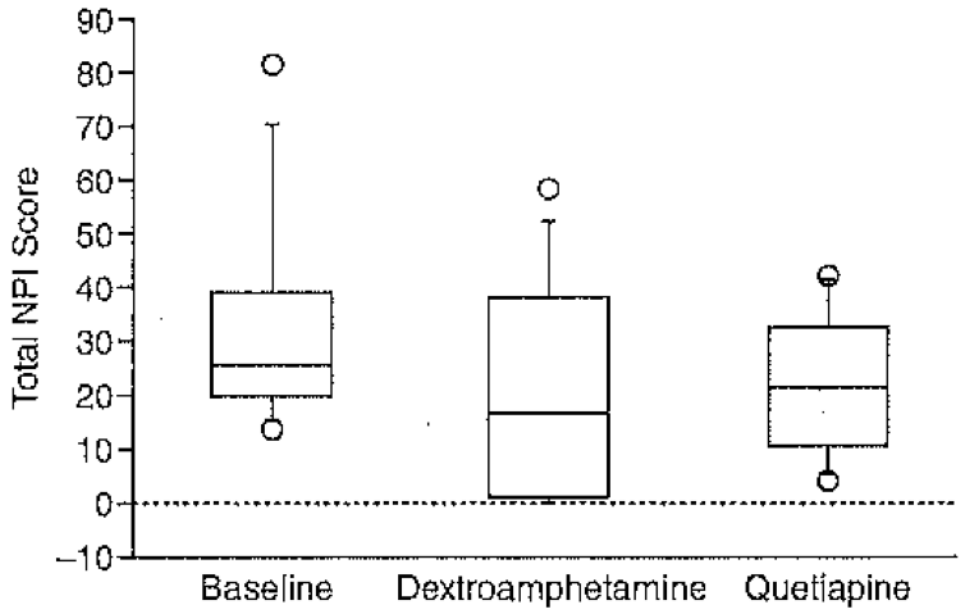

Figure 1. Total Neuropsychiatric Inventory (NPI) Score at Baseline and After Dextroamphetamine and Quetiapine Treatment[a]

[a]Box encompasses the 25th and 75lh percentiles. Horizontal line indicates the median, bars above and below the boxes indicate 10th and 90th percentiles, and points above and below the bars indicate range.