Vitamin E Treatment for Tardive Dyskinesia

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Background: Several short-term, controlled trials have documented the efficacy of vitamin E in treating tardive dyskinesia. However, the persistent nature of the disease prompted us to perform a multicenter, longer-term trial of vitamin E.

Methods: The study was a prospective, randomized, 9-site trial of up to 2 years of treatment with \( d \)-vitamin E (1600 IU/d) vs matching placebo. One hundred fifty-eight subjects with tardive dyskinesia who were receiving neuroleptic medications were enrolled. The blinded assessments performed were clinical (Abnormal Involuntary Movements Scale, Barnes Akathisia Scale, and Modified Simpson-Angus [for Extrapyramidal Symptoms] Scale) and electromechanical assessments of movement disorders, psychiatric status (Brief Psychiatric Rating Scale), and functioning (Global Assessment of Functioning). There were no significant differences in baseline demographic characteristics or in study assessments between the group that received vitamin E and the group that received placebo.

Results: Vitamin E was well tolerated and subject compliance with medication was good and similar between treatment groups. One hundred seven subjects (70% of those receiving vitamin E and 66% of subjects receiving placebo) completed at least 1 year of treatment. There were no significant effects of vitamin E on total scores or subscale scores for the AIMS, electromechanical measures of dyskinesia, or scores from the other 4 scales.

Conclusion: This long-term, randomized trial of vitamin E vs placebo found no evidence for efficacy of vitamin E in the treatment of tardive dyskinesia.

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Tardive dyskinesia (TD) is a frequent side effect of treatment with neuroleptic drugs. The syndrome is persistent, often irreversible, and characterized by abnormal movements including lingual and orofacial dyskinesia, grimacing, tics, choreic movements, athetosis, and dystonia. Overall prevalence is 15% to 25% of subjects treated with neuroleptics, with increased risk associated with aging and nonschizophrenic disorders.1,4 There is no established treatment for TD.

While the pathophysiology of TD is often ascribed to the development of “degeneration” supersensitivity from prolonged dopamine receptor blockage, an alternative view blames free radical damage. Several findings have supported this free radical hypothesis. Neuroleptic drugs, by blocking dopamine receptors, may increase turnover and metabolism of dopamine and formation of dopamine quinones and hydrogen peroxide (via monoamine oxidase). Long-term exposure to neuroleptics in animals caused an increase in manganese and iron (free radical catalysts) in the central nervous system.5,6

Two articles7,8 extensively reviewed the rationale for the use of vitamin E to treat TD based on it being a lipid-soluble antioxidant that decreases free radical formation. A review of 11 controlled, therapeutic trials with vitamin E9 found that all but 2 of the trials showed efficacy for vitamin E, either in the full samples or in the subgroup with TD, for no more than 5 years, using the change from baseline in the total score (sum of items 1 to 7) for the Abnormal Involuntary Movements Scale (AIMS)10 as the measure of reduction in abnormal movements. However, each of these studies was a single-site trial, had a relatively small sample (from 8 to 37 subjects), took place before the introduction of atypical antipsychotic medications, and except for one trial,9 used a short treatment duration.

This article presents results from a 9-site Department of Veterans Affairs Cooperative Studies Program trial of up to 2 years of treatment with \( d \)-vitamin E (1600 IU/d) vs placebo. The trial enrolled eligible veterans who had TD for 10 years or less and were receiving typical neuroleptics or risperidone.

The primary goal of this study was to establish whether vitamin E is a safe and efficacious treatment for widespread and long-term use for TD.
SUBJECTS AND METHODS

The institutional review boards at the 9 Veterans Affairs medical centers that served as sites (see the box at the end of the article) approved the study. Before the study, all personnel attended a startup meeting to review procedures and establish interrater reliability.

We based power and sample size calculations on a 2-sided significance test at the .05 level of the hypothesis that there was no difference in the mean AIMS score after 1 year of treatment, with 0.90 power, a common group SD of 3.4 AIMS points,9 a minimum clinically significant difference of 2 in group means, and a dropout rate of 30%. This calculation yielded a sample size of 177 subjects to produce 124 who would complete 1 year of treatment.

SUBJECTS

Site personnel identified subjects from clinical referrals or by screening subjects taking neuroleptics. If the subject provided written informed consent, the research assistant (RA) screened the subject for the first set of entry criteria and performed the initial AIMS assessment. If the subject was still eligible, the participating investigator (PI) collected a medical history and blood sample, and performed a physical examination to screen for the remaining entry criteria.

To be included in the study, subjects had to satisfy all the following criteria: (1) meet Research Diagnostic Criteria for TD at both screening and baseline; (2) have had dyskinetic movements for a minimum of 3 months; (3) have been taking a minimum 3-month cumulative course of neuroleptic treatment; (4) be older than 18 years; (5) have a primary Axis I diagnosis of a nonorganic psychosis11 (eg, schizophrenia, schizoaffective disorder, unipolar disorder, bipolar disorder, or a delusional disorder); (6) be receiving treatment with a typical neuroleptic or risperidone; (7) be taking stable doses of all oral antipsychotic and other psychotropic medications for at least 4 weeks prior to enrollment (at least 12 weeks for depot neuroleptics); (8) provide written informed consent; and (9) agree to not take vitamin E supplementation during the study.

Subjects were excluded if they (1) had a medical illness likely to affect TD, its assessment, or the subject’s ability to complete the study; (2) were pregnant; (3) had drug dependence or significant abuse; (4) had TD for more than 10 years; (5) were allergic to vitamin E; (6) were receiving clozapine or deprenyl; (7) were receiving anticoagulant therapy; (8) had taken vitamin E supplements or participated in a vitamin E treatment study within the previous 6 months; (9) had taken supplements of vitamin A, vitamin C, or beta carotene; (10) were involuntarily hospitalized; (11) had a conservator; (12) had orofacial dyskinesia and poor dentition; (13) had Wilson disease; or (14) had a hematocrit value of less than 0.30.

STRATIFICATION AND RANDOMIZATION

The investigators stratified potential enrollees by site, age (19-39 years, 40-59 years, 60 years or older), and baseline TD severity (item 8 of the AIMS [mild, moderate, severe]). Central randomization occurred at the coordinating center using adaptive allocation12,13 with the “biased coin” method14 within site to make treatment assignments.

TREATMENT

Enrollment took place during the first year. Subjects received d-vitamin E (400 IU, 2 capsules by mouth twice daily, for a daily dose of 1600 IU) or matching placebo. Treatment and follow-up were designed for a minimum of 12 months, but, if willing, subjects could keep receiving double-blind treatment until the study ended. To address the possible benefits of vitamin E in its true clinical use, the study protocol allowed treating clinicians to adjust the dose of neuroleptics and switch therapies when clinically indicated. Site personnel recorded all concomitant medications and dose changes at each visit.

Continued on next page
ASSESSMENTS

Eligible subjects had their baseline visit 2 to 4 weeks after screening. At baseline, the RA performed the AIMS rating and if the subject still met Research Diagnostic Criteria for TD, the PI verified the subject’s eligibility before he or she was randomized to treatment. Additional assessments included (1) performing other ratings of movement disorders and psychopathologic disorders, (2) establishing the subject's medications and any adverse events during the prior 4 weeks, and (3) assaying plasma levels of vitamin E and the neuroleptics haloperidol, fluphenazine, and risperidone. Subsequent visits occurred every 4 weeks with a window of ±1 week (eg, the second visit occurred from 3 to 5 weeks after baseline).

Several clinical assessments were used in the study. The AIMS, performed by the RA at every visit to gather data for the study’s primary outcome and by the PI at baseline and selected visits to check the RA’s ratings, measured dyskinetic movements. The Barnes Akathisia Scale, done by the RA at baseline and at all subsequent visits, assessed akathisia. The Modified Simpson-Angus (for Extrapyramidal Symptoms) Scale, conducted by the RA at baseline and all subsequent visits, rated drug-induced parkinsonism. The Brief Psychiatric Rating Scale, performed by the PI at selected visits, measured psychopathologic disorders. The Global Assessment of Functioning Scale (GAF), performed by the RA at baseline and at 24 and 52 weeks of treatment, assessed the subject’s level of functioning.

We also used electromechanical assessments of dyskinesia (collected by the RA at baseline and all subsequent visits) to provide continuous assessment of TD and to measure force instability to quantify hand and jaw dyskinesia. The subject was instructed to provide a constant level of force either by flexing the finger muscles against a rigid beam (hand dyskinesia) or by biting down on a transducer placed in the mouth (jaw dyskinesia). Dyskinesia appears as an irregular pattern of muscle contraction transduced as variable force levels over time. Caligiuri et al described the procedures used to derive the statistic of interest (larger of the coefficients of variation for the left and right hands) for both unfiltered and filtered hand force instability. For accelerometeric analysis of the jaw, we calculated the range for each of 3 trials, and used the largest of the 3 ranges.

In direct contrast to results from prior studies, this study found no effects of vitamin E on clinical ratings of TD (AIMS ratings). In addition, vitamin E had no effect on electromechanical ratings of TD or assessments of akathisia (Barnes Akathisia Scale scores), drug-induced parkinsonism (Modified Simpson-Angus [for Extrapyramidal Symptoms] Scale ratings), or clinical psychiatric status (Brief Psychiatric Rating Scale or GAF scores). The negative finding from this trial highlights the importance of performing large-scale, long-term, multicenter trials, given positive findings from smaller trials.

comment

Although it is clear this study found no effect from vitamin E, it is worthwhile to propose reasons for how this could occur given the generally positive results from prior trials. These explanations (the major limitations of the study) stem from 2 sources—differences in study design and population differences between trials.

In the present study (1) used a longer duration of treatment (up
to 2 years vs a maximum of 36 weeks), (2) used a higher dose of vitamin E (1600 IU/d vs 800-1200 IU/d), (3) most likely enrolled subjects with less fluctuation in TD as subjects had to meet Research Diagnostic Criteria for TD on 2 separate occasions, (4) studied a larger sample (158 subjects vs a maximum of 38), (5) involved multiple sites, and (6) allowed clinicians to change neuroleptics and doses (to permit a more naturalistic examination of the utility of vitamin E).

However, as noted in an editorial written by 2 investigators from the present study,22 we suggest that the discrepancy is more likely due to differences in the reference populations.

The present study started about 6 years after the last prior trial. Although most subjects in prior and the present studies had schizophrenia or schizoaffective disorder, during this time changes in prescribing patterns took place, including the use of atypical antipsychotic and anticholinergic medications and a decreased neuroleptic dose, which led to the population differences.

All prior trials occurred before the introduction of the atypical antipsychotic drugs risperidone and olanzapine. These agents have become widely prescribed in recent years; in fact, 36% of the 150 subjects in the present study with at least 1 postbaseline visit were treated with risperidone or olanzapine. The number of subjects taking risperidone and olanzapine at baseline were 37 and 0, respectively, and 18 subjects were switched to either of these agents during treatment. A preliminary study found subjects treated with olanzapine had a significantly lower incidence of TD compared with those taking haloperidol.23 However, in the present study the distribution of subjects treated with atypical agents was similar in the vitamin E and placebo groups at baseline (21% and 26% receiving risperidone, respectively; 0% each for olanzapine) and during treatment (for risperidone, 34% and 41%; for olanzapine, 4% and 1%). Subjects in prior trials were generally treated with higher doses of typical neuroleptics compared with those in the present study. In addition, about 26% of the subjects in the present study had anticholinergic medica-

### Table 2. Summary of Assessments at 1 Year of Treatment

<table>
<thead>
<tr>
<th>Demographic and Assessment Characteristics</th>
<th>Vitamin E Group (n = 73)</th>
<th>Placebo Group (n = 85)</th>
<th>t</th>
<th>P</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean ± SD Values</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIMS score†</td>
<td>9.5 ± 4.6</td>
<td>9.8 ± 3.2</td>
<td>0.9302</td>
<td>.36</td>
<td>-0.9 to 2.6</td>
</tr>
<tr>
<td>Hand force instability, %§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfiltered</td>
<td>3.4 ± 2.8</td>
<td>2.9 ± 1.7</td>
<td>0.9603</td>
<td>.35</td>
<td>-0.47 to 1.34</td>
</tr>
<tr>
<td>Filtered</td>
<td>2.9 ± 2.2</td>
<td>2.6 ± 1.6</td>
<td>0.5805</td>
<td>.57</td>
<td>-0.55 to 0.99</td>
</tr>
<tr>
<td>Accelerometric analysis for jaw, V</td>
<td>0.10 ± 0.11</td>
<td>0.09 ± 0.08</td>
<td>0.5474</td>
<td>.59</td>
<td>-0.03 to 0.06</td>
</tr>
<tr>
<td>BAS score</td>
<td>2.7 ± 3.5</td>
<td>2.4 ± 3.4</td>
<td>0.4712</td>
<td>.64</td>
<td>-1.0 to 1.6</td>
</tr>
<tr>
<td>SA-EPS score</td>
<td>6.0 ± 5.4</td>
<td>4.9 ± 5.6</td>
<td>0.9703</td>
<td>.33</td>
<td>-1.1 to 3.2</td>
</tr>
<tr>
<td>GAF score</td>
<td>56.4 ± 15.5</td>
<td>56.3 ± 14.0</td>
<td>0.0203</td>
<td>.99</td>
<td>-5.7 to 5.8</td>
</tr>
<tr>
<td>BPRS score</td>
<td>31.9 ± 8.9</td>
<td>30.7 ± 10.2</td>
<td>0.6101</td>
<td>.54</td>
<td>-2.6 to 4.9</td>
</tr>
<tr>
<td>Vitamin E level, µmol/L</td>
<td>57.1 ± 30.2</td>
<td>21.4 ± 5.1</td>
<td>6.6362</td>
<td>&lt;.001</td>
<td>10.8 to 20.1</td>
</tr>
</tbody>
</table>

*Abbreviations are explained in the footnote to Table 1.†Confidence interval (CI) on the difference in group means.§Other treatment comparisons of 1-year AIMS scores, some planned (for subgroups defined by baseline total AIMS score, AIMS severity item, age, duration of tardive dyskinesia, psychiatric diagnosis, length of psychiatric illness, and neuroleptic dose) and others after reviewing these results (percentage change from baseline and scores by treatment within site) were performed. With a .01 significance level owing to multiple testing, no differences were detected. Coefficient of variation.
tions discontinued during the course of treatment, while in prior trials anticholinergic treatment was continued throughout. Anticholinergics were discontinued evenly in the vitamin E and placebo groups (51% and 38% of enrollees, respectively).

These changes in prescribing practices probably resulted in the present study enrolling subjects with less variable and somewhat more refractory TD. The widespread use of atypical antipsychotics in the general population probably limited the availability of subjects with milder TD for this trial. A similar selection effect would have occurred by the general lowering of neuroleptic dose and discontinuation of anticholinergic medications, as subjects whose TD resolved due to these trends would not be eligible for this trial. Also, if treatment with vitamin E ameliorated TD, the present study may have selected a more refractory sample by excluding subjects who received mega-dose vitamin therapy or were in prior vitamin E trials.

In the present study, 97% of the enrolled subjects were men. While patient’s sex was not detailed in all prior studies, several were conducted at Veterans Affairs medical centers and, thus, involved mostly men. However, the results of these studies did not differ from those at non-Veterans Affairs sites.

The negative findings of this study do not necessarily refute the free radical hypothesis of TD. The differ-
ences cited may imply that the population in the present study was more refractory to vitamin E therapy. If oxidative damage did play a substantial role in the pathogenesis of TD, cases that are longer standing and persist despite treatment with atypical antipsychotic medications (with lower levels of dopamine D₂ receptor blockade and presumed lower effects on dopamine turnover) would be less likely to respond to antioxidant therapy. Another way to examine the role of oxidative damage would be through a study of antioxidant prophylaxis of TD to determine whether this would prevent free radical damage (rather than treat the suspected damage once it has occurred, the purpose of the present study).

The main conclusion of the present study is that vitamin E is not effective in treating TD in a population currently receiving neuroleptics. However, the clinical decision to use vitamin E should be viewed in the context of the course of TD, the nature of the neuroleptic treatment, and the safety of vitamin E and its other therapeutic or prophylactic effects. For subjects with TD who will be receiving long-term treatment with typical neuroleptics, clinicians may want to consider a trial of vitamin E. We believe, though, that the number of these subjects has and will continue to diminish over time given the increasing use of atypical neuroleptics.

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REFERENCES