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## Tardive Dyskinesia: Is Vitamin E Singing the Prostate Blues?

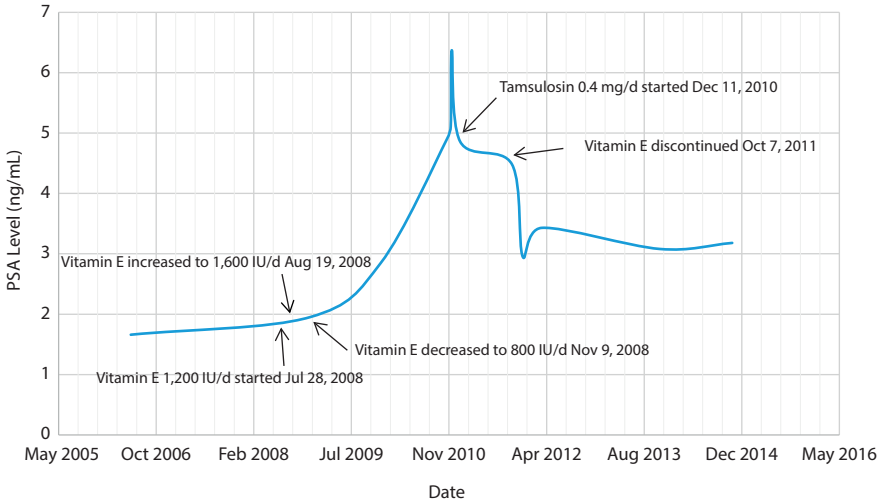
**To the Editor:** Tardive dyskinesia (TD) is a disorder characterized by various abnormal involuntary movements of the face, neck, trunk, and extremities that is precipitated by the use of antipsychotic medications.[1] In general, the incidence of TD has been reported to be 5% per year for typical antipsychotics and 1% per year for atypical antipsychotics.[2] This disorder is a devastating condition that until only recently had no US Food and Drug Administration—approved treatments. While prevention remains the best treatment option, several off-label medications, such as antioxidants, have demonstrated a therapeutic benefit in treating and preventing the progression of TD.[3] There are several hypotheses for the etiopathology of TD. We will focus on the neurodegenerative hypothesis, which suggests antipsychotics increase dopamine metabolism and turnover, leading to the formation of free radicals.[4] The neuronal damage caused by oxidative stress and free radicals may lead to the development of TD.[5] Antioxidants are reducing agents that have the capability to accept electrons from free radicals, therefore neutralizing and preventing them from causing damage.[6]

Vitamin E is one of many antioxidants used for the treatment of TD; however, there is insufficient evidence to either prove or disprove its efficacy.[4] Daily doses of up to 1,600 mg of vitamin E have been studied in patients with TD.[6] Vitamin E therapy is not without consequence, as its use may lead to significant harm. Two trials[7,8] concluded that treatment with vitamin E increased the risk of hemorrhagic stroke. Findings from another study[9] suggested that patients with vascular diseases or diabetes who took vitamin E 400 IU daily for 7 years had a 13% increased risk of heart failure. Furthermore, the Selenium and Vitamin E Cancer Prevention Trial (SELECT)[10] found a 17% relative increase in the incidence of prostate cancer in men taking only vitamin E supplementation, which started to emerge around year 3 of the study.

***Case report.*** Mr A is a 57-year-old man with a diagnosis of schizophrenia and TD who resides at a long-term state psychiatric facility. On July 28, 2008, vitamin E 1,200 IU daily was initiated for treatment of TD. The dose of vitamin E changed during the first few months of treatment. Twenty-two days after starting vitamin E, the dose was increased to 1,600 IU daily. On November 9, 2008, it was decreased to 800 IU daily. This dose was continued for the remainder of the treatment period. On November 6, 2010, a mildly elevated prostate-specific antigen (PSA) level of 4.89 ng/mL was discovered. After another month, the PSA level had reached 6.37 ng/mL, which resulted in the general practitioner's prescribing tamsulosin 0.4 mg daily 8 days later. After initiation of tamsulosin, an $\alpha_{1a}$-adrenergic receptor antagonist, the PSA level dipped but remained elevated until vitamin E was discontinued on October 7, 2011 (Figure 1). Less than 2 months after discontinuation of vitamin E, Mr A's PSA level was found to be within normal limits and remained stable for approximately 3 years. There were no other medication changes that occurred during this period that would have accounted for the changes in the total PSA level.

An elevated total PSA level is not a diagnosis for prostate cancer; however, there is a strong correlation between the PSA level and the presence of prostate cancer and future development.[11] When PSA levels are mildly elevated (4–10 ng/mL), some clinicians use the percentage or ratio of free PSA/total PSA level as a guide to determine the cause of the elevated PSA level.[12] There is evidence that the ratio of free PSA/total PSA level based on age is linked to the probability of finding prostate cancer on a needle biopsy.[12] If we had obtained both the total and free PSA levels, we may have been able to further assess Mr A's risk for prostate cancer. Additionally, changes in total PSA levels can be analyzed over time by calculating the PSA velocity (PSAV), which can assist in the detection of prostate cancer.[13] A prostate biopsy has been suggested for a PSAV >0.4 ng/mL/year because this carries a significantly higher risk of prostate cancer, whereas elevations due to prostate manipulation, natural variance of PSA values, and ejaculation would be unlikely.[13] In addition, benign prostatic hyperplasia has been shown to accompany very small changes in PSA levels annually (approximately 0.1 ng/mL/year).[13] During the first 2 years of vitamin E therapy, before tamsulosin was started, Mr A's PSAV was 1.9 ng/mL/year. Rather than completing further testing, the

**Figure 1. Prostate-Specific Antigen (PSA) Versus Time**

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general practitioner thought it prudent to discontinue vitamin E based on changes in the total PSA level over time. The first 3 years after vitamin E therapy was discontinued, Mr A's PSAV was 0.2 ng/mL/year.

The findings of this case report and the SELECT trial[10] suggest that long-term vitamin E therapy may increase the risk of developing prostate cancer. This finding incites concern, primarily because a much higher dose of vitamin E is many times used to treat TD. Health care providers should include patients in the decision-making process when assessing the risks and benefits of vitamin E therapy. Further research is warranted in this area before any definitive conclusions or recommendations can be made.

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**O. Greg Deardorff, PharmD, BCPP**[a]
odeardor@gmail.com
**Nicole A. Burns, PharmD**[a]
**David R. Hunter, MD**[a]

[a]Fulton State Hospital Pharmacy, Fulton, Missouri

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