My Mother's Levetiracetam

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My mother has survived metastatic breast cancer for >25 years with at least 7 major metastases in multiple organs, including her brain. She had a lesion in her left parietal lobe with confusion, weakness in her legs, and tremors in her hands. After surgeons removed the lesion she was reasonably symptom free for ~2 years, when she had a seizure. Magnetic resonance imaging revealed a cyst that had developed in the area where she had surgery. Drainage and removal of the cyst resulted in resolution of most of her neurological symptoms with continued, but much attenuated, tremors. A few weeks later, she became more confused and was diagnosed with a postoperative subdural hematoma. After another surgical procedure to drain the hematoma, she felt remarkably better for ~2 days and was started on levetiracetam. Shortly thereafter she began sleeping 20 hours/day. When she was awake she would feel dysphoric and fatigued and want to go back to sleep. On better days, she would sleep 10–14 hours a day, including naps. On worse days, she could barely stay awake at all. Her quality of life decreased and she could barely do her beloved painting or attend her art classes. At times, she would go for months without painting as her world diminished.

I urged her to tell her doctors that she was having a difficult time. In the past she had been quite assertive about her medical needs. It is important to acknowledge that my mother's care has been nothing short of stellar over the years. When she was first diagnosed, she had 32 out of 33 lymph nodes positive for cancerous cells and yet she has survived. However, in her fatigue and slight confusion, she had a difficult time telling her doctors how miserable she was. I spoke with several of her doctors and expressed my concern about her quality of life and wondered if the levetiracetam could be contributing to her fatigue. (They were clearly unimpressed that I am a psychiatrist.) Her doctors listened patiently and countered with the argument that since she was free of seizures, her medications were working. They felt that while it was possible that the levetiracetam was a cause of her dysphoria and hypersomnia, it was unlikely. Alternative causes could be residual neurological symptoms from the surgery, the loss of brain tissue, and any one of the multiple other medications she was taking. They saw their mission as keeping her seizure free and posited that even if the levetiracetam was a possible cause, it was not worth the risk of stopping the levetiracetam or switching to an alternative anticonvulsant.

I was stuck in the middle. On one side was my mother who was seizure free, but feeling terrible. On the other side were her doctors who genuinely cared about her and her well-being, but were reluctant to consider entertaining the hypothesis that the levetiracetam could be causing some harm. I realized I could be wrong. If they stopped the levetiracetam upon my insistence and switched to something else, it was possible that my mother would get worse. On the other hand, if they stopped the levetiracetam and she got better, then everyone would be satisfied. I failed to convince the doctors about

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the benefits of an empirical trial of stopping the levetiracetam, so I decided to do my homework.

I asked my neurology colleagues if they had seen any problems with levetiracetam. They informed me that they had seen several cases in which levetiracetam caused profound dysphoria and fatigue, with hypersomnia that resolved with discontinuation of the medication. I thought, what should I do with this information? Insist on a consult with my colleagues who confirmed my suspicions and my hypothesis? Would my mother's excellent doctors be insulted and feel that I was meddling in their clinical decisions? That might be worth it, but my mother lives in a different city and it would be quite difficult to have her see my local colleagues.

Perhaps objective data would help. I examined the package insert and searched the literature. The package insert[1] states the following:

> .... In controlled trials of adult patients with epilepsy experiencing partial onset seizures, 14.8% of KEPPRA-treated patients reported somnolence, compared to 8.4% of placebo patients... The somnolence was considered serious in 0.3% of the treated patients, compared to 0% in the placebo group. About 3% of KEPPRA-treated patients discontinued treatment due to somnolence, compared to 0.7% of placebo patients. In 1.4% of treated patients and in 0.9% of placebo patients the dose was reduced, while 0.3% of the treated patients were hospitalized due to somnolence... Somnolence, asthenia, and coordination difficulties occurred most frequently within the first 4 weeks of treatment... A total of 13.3% of KEPPRA patients experienced other behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability, etc.) compared to 6.2% of placebo patients. Approximately half of these patients reported these events within the first 4 weeks.

The published literature included a scholarly case report[2] of hypersomnia with decreased multiple sleep latency (2 minutes) and excessive sleep (12 hours) that resolved when levetiracetam was discontinued, with reasonable caveats about concluding that a cause-effect relationship exists. Remarkably, in this case report, fatigue started in February 2001 and levetiracetam was not stopped until June 2002.

I told my mother's doctors what I had found. After ~2 years, they finally agreed that if she were seizure-free for a year, they would consider tapering her off of the levetiracetam. The trial begins this week.....but it has been a long haul to get to this point. It was difficult for excellent doctors to hear and act on my concerns. Being on the other side taught me to listen even more carefully to complaints about side effects and consider alternatives if reasonable alternatives exist. ***CNS***

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