Commentaries

Warning On Treating Depression

I am a paid consultant to a law firm representing patients who took metoclopramide (Reglan) for long periods of time and developed **tardive dyskinesia (TD)**. Many doctors who prescribe this drug have considered it a very benign, very helpful drug for treating gastrointestinal (GI) problems. It is particularly helpful for gastroparesis, but also for nausea, and a wide variety of non-specific GI complaints that seem to disappear magically with the drug, and re-appear when it is removed. In most cases the drug may be used safely for months, or even years, but a small percentage of patients develop TD.

Although many doctors think of TD as a disorder in which people have involuntary movements of their tongue, lips and jaw, so that they appear to be chewing gum when they are not, TD is actually a collection of syndromes that include choreic movements, choreoathetoid movements, dystonia, akathisia (inability to remain still due to uncomfortable restlessness) and tics. The problems are usually small, often not even noticed by a patient, but by the time they reach a neurologist, they are not. TD can be permanent, and the treatments are of variable efficacy, with real side effects.

The package insert for metoclopramide states that the drug should not be used for more than 12 weeks at a time. In the last year the FDA added a black box warning for the package insert; and about three years ago I attended an FDA meeting where they were judging a combination drug to be used for migraine, which included metoclopramide and a non-steroidal anti-inflammatory drug, which is approved in the UK, and they deemed it too unsafe, despite the restriction that the drug be used no more than six times per month. Thus the FDA allows the drug to be use qid for 3 months, but not six times/month.

Since metoclopramide is a generic drug, few doctors know about the black box warning. So, in the real world, Dr X sees a patient who has been complaining about some peculiar GI-type discomfort for the past few years, has had innumerable negative scans, endoscopies and GI consults, gets placed on metoclopramide and suddenly experiences his first relief in years and feels like a new person; and every attempt to stop it, results in symptom recurrence. At this point, our crazy medico-legal system strikes. It is a requirement that the doctor note in the chart that the patient was counseled about the possibility of TD, and that the patient was examined for it as well. But this doesn't happen very often: hence the lawsuits on behalf of some very damaged patients who took the drug for too long.

However, I'm actually not concerned about metoclopramide in this column. My real interest is in aripiprazole, because I see this train now just leaving the station. Aripiprazole (Abilify) is an antipsychotic drug recently approved for treating depression, and advertised heavily on television. In the "old days" depression was treated by psychiatrists, but with the development of the **selective serotonin reuptake inhibitors (SSRI)**s, which were quite safe and easy to use because they usually do not require titration, **primary care providers (PCP)**s took over the treatment of most patients with depression. In recent years, some companies have launched campaigns to involve PCPs in treating **bipolar disease (BPD)** with antipsychotic drugs as well, which are easier to use, and probably safer than lithium. I am not sure how successful this effort has been, with BPD being a bit more complex to understand than depression, but I am sure, based on the extensive lists of medications my patients are taking by the time they see me, that PCPs treat depression.

Aripiprazole is a so-called "atypical" antipsychotic drug. These are thought to have a much lower propensity to induce movement disorder side effects than the "typical" neuroleptics. While I do believe that this is true, the best studies, involving thousands of subjects, designed and performed by the world's leading experts, have shown that this is not the case. No one understands why in practice these drugs seem to be "relatively" free of movement disorder side effects, but not in large studies. In any case, they are not completely free of them.

In the case of aripiprazole, I have an article in press describing only the third case of a tardive syndrome induced by the drug in a neuroleptic-naïve patient. That is, the patient had never been on any antipsychotic drug before aripiprazole, so that no other antipsychotic could be implicated. In addition, she was taking the same very low dose that is recommended for depression. Most PCPs are not aware of this risk and because it is a "new" antidepressant, they will think it is like the SSRIs.

I fear that five years from now we are going to see the media ads we now see soliciting for metoclopramide-induced TD cases, substituting aripiprazole for metoclopramide, and the PCPs are the ones who will be sued. The psychiatrists generally are aware of movement disorder side effects, mention it to their patients, and chart their warning and then the absence of TD in follow-ups. They don't always do this, unfortunately, putting themselves at risk for the lawsuits that are going to come. PCPs almost never do this.

I hope that my concerns for the TD risk are overblown. I hope that only three TD cases in neuroleptic-naïve patients have been reported because it is so rare for this drug to cause TD, but I doubt it. I suspect that no one has reported it because the doctors who use the drug have been psychiatrists and they don't think it's such an unusual observation that it deserves reporting. I suspect that the doctor doesn't generally recognize TD, and the patient doesn't generally complain. I think that having PCPs start to use aripiprazole as they use the SSRIs is an invitation to malpractice pig heaven.

– Joseph H. Friedman, MD

Disclosure of Financial Interests

Joseph Friedman, MD, and spouse/significant other. Consultant: Acadia Pharmacy, Ovation, Transoral; Grant Research Support: Cephalon, Teva, Novartis, Boehringer-Ingelheim, Sepracor, Glaxo; Speakers' Bureau: Astra Zeneca, Teva, Novartis, Boehringer-Ingelheim, GlaxoAcadia, Sepracor, Glaxo Smith Kline, Neurogen, and EMD Serono.

Conflicts: In addition to the potential conflicts posed by my ties to industry that are listed, during the years 2001-2009 I was a paid consultant for: Eli Lilly, Bristol Myers Squibb, Janssen, Ovation, Pfizer, makers of each of the atypicals in use or being tested.