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Quick Pulse

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PARKINSON'S DISEASE DRUG PERGOLIDE VOLUNTARILY WITHDRAWN FROM MARKET

The FDA announced that manufacturers have agreed to a voluntary withdrawal of pergolide because of reports of heart valve damage. Pergolide is an ergot-derived dopamine agonist (DA) sold by Valeant Pharmaceuticals as Permax and generically by Teva Pharmaceuticals, Ivax, and Parr. It is used with levodopa and carbidopa to manage the symptoms (tremors and slowness of movement) of Parkinson's disease.

Dr. Robert Temple, Director of the FDA's Office of Drug Evaluation, said that pergolide is being taken off the market because of a high incidence of heart valve damage in pergolide users. The drug causes mitral, aortic, or tricuspid regurgitation. In essence, the valve becomes "leaky." Symptoms include shortness of breath, fatigue, and heart palpitations. At least 14 pergolide users have had to have a heart valve replaced, and that number is thought to be a "substantial underestimate" of affected patients. No deaths have been reported, but mitral or aortic regurgitation can be a serious and life-threatening condition.

The recall and FDA Public Health Advisory come after two studies were published in January 2007 in the ***New England Journal of Medicine***. Dr. Temple called the studies "high-quality reports." Those studies, which confirmed earlier findings, reported that pergolide increased the risk of cardiac valve regurgitation at least five-fold, with valve problems occurring in 23% of pergolide patients vs. 6% in patients not on the drug.

Another ergot-derived dopamine agonist, Pfizer's Dostinex (cabergoline), also was found to be associated with a risk of heart valve damage. Dr. Temple explained, "(Cabergoline) is used in this country for a different purpose (hyperprolactinemic disorder) at a much, much lower dose, so we are not particularly worried about it. The European study in the ***New England Journal of Medicine*** showed cabergoline used at a dose less than 3 mg hardly had any risk at all, and the use in hyperprolactinemia is a still lower dose – less than 1 mg."

The two studies that contributed to the FDA action were:

- A German study that reviewed data from a U.K. database of 11,417 patients treated with anti-Parkinson's drugs from 1988 to 2005. Each patient with newly diagnosed cardiac valve regurgitation was matched with ≤25 controls. Of 31 patients with newly diagnosed cardiac valve regurgitation, six were taking Permax, six were taking Dostinex, and 19 had not been exposed to any dopamine agonist within the previous year. The valve regurgitation incidence rate was 7.1 with Permax and 4.9 with Dostinex.
- An Italian echocardiographic study which found that clinically significant regurgitation in all three heart valves occurred in patients taking Permax or Dostinex.

Italian Echo Study Results

Measurement	Permax n=64	Dostinex n=49	Non-ergot-derived dopamine agonists n=42	Control n=90
Clinically important regurgitation (moderate-to-severe, Grades 3-4) in any valve	23.4%	28.6%	N/A	5.6%
Relative risk of moderate-to-severe regurgitation				
Mitral regurgitation	6.3 (p=0.008)	4.6 (p=0.09)	N/A	N/A
Aortic regurgitation	4.2 (p=0.01)	7.3 (p<.001)	N/A	N/A
Tricuspid regurgitation	6.3 (Nss, 0.16)	5.5 (Nss, 0.12)	N/A	N/A

The first dopamine agonist to be approved was bromocriptine, which is now generic. Pergolide gained FDA approval in 1988, and the valvulopathy issue with pergolide emerged four years later. In 2003, a warning was added to the pergolide label, and Lilly, which marketed it at the time, issued a Dear Doctor letter. Then, in 2006, after small studies found a high rate of heart valve problems in pergolide patients, the FDA strengthened the warning, adding a black box to the pergolide label.

Dr. Temple estimated that 12,000–25,000 Americans currently take pergolide. The exact number isn't known because it isn't clear how many patients get the drug through mail order. Dr. Temple said, "We concluded that it (pergolide) really didn't have a place in therapy any more. Its use is quite modest now…There was pretty much general agreement that the time for this (drug to be withdrawn) had come."

Dr. Sid Wolfe of Public Citizen was critical of the FDA for not acting sooner. He asked, "Why didn't you do this several years ago…Why weren't the cases of valvular heart disease caused by this drug over the last 2, 3, 4 years prevented by taking action earlier?" Dr. Temple responded, "One new thing is that we now have very good evidence that other dopamine agonists don't do this, and that was relatively important…I'd say we've been gradually ratcheting up the level of concern… Use has been declining with the black box…The point where we decide to take away a therapeutic modality is always a matter of judgment, and we reached that point now and hadn't reached it before."

Patients on pergolide are being advised not to stop pergolide abruptly, but instead to consult their doctor and either switch to another drug or gradually reduce the amount of pergolide used. Abruptly stopping pergolide can be dangerous. Dr. Temple said, "Our conclusion is that pergolide has no demonstrated advantage over other therapies. We believe almost all patients can be converted to another drug."

There are two other dopamine agonists with FDA approval: GlaxoSmithKline's Requip (ropinirole) and Boehringer Ingelheim/Pfizer's Mirapex (pramipexole). FDA officials said neither of these drugs has been found to cause heart valve problems. Dr. Temple said, "The other drugs look pretty good. They are not totally free of problems…Some might be associated with compulsive gambling, etc… The other drugs have problems, but we don't think that they are of this magnitude."

Dr. John Feeney III, Acting Deputy Director of the FDA's Division of Neurology Products in the Centers for Drug Evaluation and Research (CDER), added that there are also non-dopamine agonist options for patients, "We believe the dopamine agonists are a valuable part of the armamentarium for treating Parkinson's disease, but there are other alternative dopamine agonists, and even beyond those there are other available therapies for Parkinson's disease patients."

The FDA plans to work with pergolide manufacturers to continue to make the drug available for the few patients who cannot change to another drug. Dr. Temple said, "We are asking for withdrawal to the wholesale level which will leave some drug available to allow people to make arrangements to switch (to another agent) or withdraw…And we are working with manufacturers to see if we can have drug available under an IND (Investigational New Drug Application) for patients who find they simply cannot get along without this drug. We don't have such an arrangement yet, but we will try to do that."

How many patients can't change to another drug? Dr. Temple said the number is thought to be very small, "We don't really know in any rigorous way how common that is, but some of the people we know, who are experts in movement disorders, do report every once in a while there is someone they are unable to transition – symptoms that are impossible to control and they are worse off than before. Why that would be, no one can answer…We think there may be such people…but we don't think there will be many such people."

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