Trends-in-Medicine

February 2005
By Lynne Peterson and D. Woods

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

SHIRE PHARMACEUTICALS' ADDERALL XR FOR ADHD: OFF THE MARKET IN CANADA

On Thursday, February 10, 2005, Health Canada ordered Shire's Adderall XR, a drug used to treat ADHD (attention-deficit/hyperactivity disorder) off the Canadian market, citing concerns about an association with "sudden deaths, heart-related deaths, and strokes in children and adults taking usual recommended doses." Health Canada pointed to reports of 20 sudden deaths worldwide in patients taking either Shire's Adderall or Shire's Adderall XR (an extended-release form of Adderall, which ***is sold*** in Canada). Adderall (a mixed salt of a single amphetamine product) ***is not sold*** in Canada, but the extended-release formulation, Adderall XR, ***was sold*** in Canada.

Health Canada asserted that these deaths – 14 in children and six in adults – were not associated with overdose, misuse, or abuse. The agency also cited 12 reports of stroke, including two in children. None of the reported deaths or strokes occurred in Canada.

However, the reaction in the U.S. has been mild, and the FDA is ***not*** pulling Adderall or any ADHD drug from the U.S. market. The FDA knew about Health Canada's decision before it was made public and discussed it with Canadian authorities. Dr. Russell Katz, Director of the FDA's Division of Neuropharmacologic Drugs, CDER, said, "We've been in discussions with Canada for at least a few days, so we had time to discuss it with them…We are very comfortable here with our decisions on the data in front of us. We've thought a lot about this…In light of Canada's action, we looked again, and we are still comfortable."

The FDA issued this notice to consumers: "SUD (sudden unexplained death) has been associated with amphetamine abuse and reported in children with underlying cardiac abnormalities taking recommended doses of amphetamines, including Adderall and Adderall XR. In addition, a very small number of cases of SUD have been reported in children without structural cardiac abnormalities taking Adderall. At this time, FDA cannot conclude that recommended doses of Adderall can cause SUD, but is continuing to carefully evaluate these data…As a precaution, FDA recommends that Adderall products not be used in children or adults with structural cardiac abnormalities."

Canada has historically taken a conservative approach to ADHD drugs:

- Novartis's Ritalin was approved in the U.S. for ADHD in 1956, but was not approved in Canada until much later. An estimated 1.5 million prescriptions were written in 2003 in Canada for all ADHD formulations.

- Shire's Adderall (a mixed salt of a single amphetamine product) was approved in the U.S. in 1994 to treat ADHD (attention-deficit/hyperactivity disorder), but that immediate-release formulation was never marketed in Canada.
- Lilly's Strattera (atomoxetine) was approved in the U.S. in 2002, but not until January 2005 in Canada, and it was not due to be launched in Canada until March 2005.

So far, consumer groups have not jumped on this issue or called on the FDA to follow Canada's example. Dr. Sidney Wolfe of Public Citizen said his group is looking into the problem but, on the surface, he did not appear alarmed. He said, "It turns out that other drugs for ADHD, like Ritalin, also have been associated with things like this…So, the question is, after adjusting for how much they are used, is there any difference? We are looking at that now. I don't know if Canada did that or not. They should have. Adderall is just a mixture of amphetamines, which is chemically different from Ritalin, but both have amphetamine-like properties. When you look at the FDA database, like we did, there are a fairly significant number of deaths in young people taking both drugs. We have not yet adjusted for prescribing." An official of a patient support group commented that they have taken note of Canada's action but also are not alarmed. He said, "We don't want to minimize the issue, but the long-track record with these drugs makes us relatively comfortable with them."

The media also have not been paying much attention to this story – yet. That may pick up, but the day the story broke, it simply wasn't on the radar screen of many reporters, even healthcare reporters. The big news that day was the Pope's health and the announcement that Prince Charles will wed Camilla Parker-Bowles. The story has been reported, but the general media reaction has been that if the FDA is not worried, they aren't. An FDA official commented, "I'm sensing that the reporting – and I'm also hoping – is going to be fairly sober and not sensationalized."

Parents and consumers have started to talk about the safety of ADHD drugs in Internet chat rooms, but, again, there appears to be some confusion but no panic. Writers seem to be tempering their comments with the recognition that ADHD drugs should be monitored carefully. Among the comments were:

- "Adderall XR has been the only med that has worked well with my son. Now I don't know what to do."
- "I, too, have my son on Adderall and don't want to switch him. I tried Strattera and Concerta (Johnson & Johnson, methylphenidate) which had a lot of side effects for him. I really believe any medicine you give is a risk, but what are you to do…I will talk to his psychiatrist at his next appointment, but if he says it's okay. I have no choice but to trust him. My instincts say to keep him on it because the strain to his body with the trying of new meds is probably worse."
- "If it was the drug Adderall, wouldn't the number be more than 20 or 12? I wonder if the deaths and strokes are for sure caused by Adderall. I would love to see some more research on the 20 and 12."
- "It also has me in a bit of a panic...Adderall XR is the only thing that has worked well for our son without side effects. I am going to be talking with his doctor today about our options."
- "We had our regular visit with our daughter's pediatrician this morning, and we asked him about the Adderall situation. He said he wasn't surprised by the announcement since, in his experience, Adderall seemed to have more side effects than Ritalin. He was much more comfortable with the more proven Ritalin (as well as Concerta). He also welcomes a complete review of all the ADHD drugs no matter what they are. Our daughter is on Concerta."
- "As far as the risk with Adderall, the deaths may have been due to a pre-disposed heart condition that was already there when the victims were taking the meds. However, a more thorough review is needed to see if Adderall enhanced the risk of heart failure or wasn't a contributing factor."
- "I am also disheartened by the potential negative findings of this drug, but I do have to wonder, given that this number of deaths may have occurred in this size population even without these drugs being used. This medication, started 3 weeks ago, has worked so well for DD. I will not jump to conclusions and abruptly stop the meds…We have an appointment on February 23rd, and we will be discussing all of this with the pediatrician."

In an interview with ***Trends-in-Medicine***, the FDA's Dr. Katz addressed many of the questions that have arisen since Health Canada pulled Adderall XR. Following are some of the key points he made:

- **The FDA takes seriously another country's decision to withdraw a drug currently on the U.S. market.** He said, "If another agency takes a drug off the market that we, too, had on the market, we would try to figure out whether they know something we don't know. We would try to figure out their reasons and see if we agree…We take it seriously."
- **It is difficult to determine the number of sudden deaths that would be expected to occur in this population (children with ADHD) either on treatment with ADHD drugs or not.** There are no long-term studies of this, and the FDA adverse event reporting system is voluntary and not complete. Dr. Katz said, "The numbers of sudden deaths in the adolescent population generally vary considerably from 1 in 100,000 person years to 8-9 per 100,000 person years to 1 in 400 person years. We are scouring the literature to see what is known. We don't believe there are very good numbers at all

of what the death rate is in patients with ADHD. Of course, they (ADHD patients) use other drugs. They have their own problems. It is possible the death rate is higher than the background rate, but that is not well documented."

➢ **It is also difficult to compare the adverse event rates among the various ADHD products.** Dr. Katz said, "There are many vagaries in trying to compare rates. The reporting system is voluntary, so no one is required to report an adverse event to the government or the company…And there are many, many factors that go into reports being made – like marketing, distance from the time a drug was introduced to the market, etc. So, there are many assumptions that go into things, and many, many unknowns. If one drug had 10 times the (death) reporting rate, you might say, even given the vagaries, that there is still a big difference, but that was not the case…We also look at other drugs used (by these patients). We look at deaths in drugs to treat the same indication. We did that in this case, looking at the death rates with methylphenidates – which are similar pharmacologically but different. It was difficult to compare precisely one drug with another. When we did that, for the time period of 1999-2003, there were slight differences in the reporting rate – the number of sudden deaths vs. the number of patients who had been exposed – but very slight difference so that it was very difficult or impossible to differentiate. There were no statistically significant differences."

➢ **More children have died on Adderall than on methylphenidate products, but the difference is not statistically significant.** Dr. Katz said, **"**On Adderall, 12 kids died, and seven died on methylphenidate products. There was slightly more use with methylphenidate products, but just a little more. So, the numbers are different, but not differences you can hang on, particularly because of the reporting system and the usage. We don't have direct information on how many adolescents use the drugs – just the number of prescriptions."

➢ **Most of the children on Adderall who died either had structural defects of the heart or had confounding problems.** Dr. Katz explained, "We couldn't rule out any of the 12 (Adderall) deaths, but five had underlying heart structural defects, which themselves are an increased risk of sudden death. The other seven on Adderall pose significant problems in interpretation. For example, one adolescent was exercising in 110 degree temperature, and several had very elevated levels of amphetamines, suggesting they might have been overdoses."

➢ **The FDA plans to continue looking into the safety of ADHD drugs, and a public advisory panel meeting or additional epidemiological studies are a possibility.** Dr. Katz said, "We are discussing this internally. From the point of view of the data we have in front of us, we looked at it closely and are comfortable with it now…We need to think about what other additional analyses are needed. Given all the post-marketing data since 1999, we are pretty comfortable with our current position, but we are discussing whether folks think something else is necessary, whether an advisory committee meeting is worthwhile, or whether there are other epidemiological studies that might shed light on this…If we thought there was a significant public health risk, and the only way to more definitively address that risk is to do a study, there are things I suppose we could do, but I don't think we are at that stage yet."

➢ **The FDA is reviewing the safety of all ADHD drugs, not just Adderall XR.** Dr. Katz said, "All of them. When there is a potential signal for a particular drug, one of the things we do is go ahead and look at whether there is a signal across the other drugs typically approved for the same indication. We did that, and we didn't think there were material differences between the two classes."

➢ **Parents who have a concern about their child taking an ADHD drug should discuss it with the child's doctor.** Dr. Katz said, "I think they need to speak to the child's doctor. For many typical pharmacological effects, we think of amphetamines and methylphenidates as similar. Again, we concluded we don't think there is an increased risk of sudden death (with either). No doubt these announcements and Canada's action will raise questions in parents' minds, but we don't think there is much to be said that the two classes are different."

➢ **At this point, the FDA does not believe Adderall and Adderall XR are less safe than methylphenidate products such as Ritalin.** Dr. Katz said, "The only thing in the Adderall label that is not in the methylphenidate product labels is a warning about sudden death in patients with underlying cardiac defects. When you look at the two classes (amphetamines and methylphenidates), there were five structural defects with amphetamines and one with methylphenidate. That was based on post-marketing reports from 1999-2003. We may look at longer time periods and see if, with respect to cardiac defect, it is the same with both categories."

➢ **The FDA is unlikely to take any action with respect to ADHD products without warning and/or public comment.** Dr. Katz said, "If the Commissioner (Dr. Lester Crawford) made the decision this was an imminent public health hazard, there are things we can do. If we were contemplating that, we possibly would have an advisory committee meeting, and lay out all the data on the drugs, and ask what they think. We might discuss it publicly before we do something that drastic…We are trying to be more transparent. We obviously made the decision on what to do; we changed the Adderall XR label, and that's all we did. And I think that was appropriate. If someone (at FDA) had a different thought, or we looked at data from a larger period of time and saw something alarming, it is unlikely we would precipitously call the company and take it off the market. I'm not sure we have the authority to do that without an imminent public health hazard."

➢ **There is no correlation between how long a child took an ADHD drug and sudden death.** Dr. Katz explained, "The duration of treatment varies from one day to eight years, so there is no pattern."

➢ **The sudden deaths associated with ADHD drugs is not likely to make it more difficult for a company to get an ADHD drug approved in the future.** Dr. Katz said, "I don't think so. Would they have to expose more people longer? I haven't thought about it. The agency is generally thinking about long-term effects, but we are not convinced these cases are related to the drug, so it is not immediately obvious that it would (affect a new drug). Obviously, the database has to be robust, and we will look closely at this."

♦