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We Smell A Rat

Tests in rats shouldn't kill a promising new drug for RLS.

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Which group should the U.S. Food and Drug Administration care about more: humans or rats? That's not a trick question. The FDA's recent decision to reject the drug Horizant suggests that, at least in this case, it cares more about rats. And because of the FDA's decision, some people (not rats) with restless legs syndrome (RLS) will suffer more.

Here are the facts. Horizant is a next-generation version of gabapentin. It is just like the original gabapentin except that it is more easily transported through the intestinal wall. That is the crucial fact to know in order to understand how strange and destructive was the FDA's rejection of Horizant. In 1993, Pfizer launched gabapentin, with the brand name Neurontin, for treating seizures, postherpetic neuralgia, neuropathy, and other nerve pain. The FDA approved Neurontin even though, in animal testing, some male rats given ten times the highest human dose got a certain type of pancreatic cancer. Yet the rats still did fine. The tumors did not metastasize, were not locally invasive, and did not affect the rats' survival. Interestingly, neither mice nor female rats given gabapentin developed the tumors. And, most important, *neither did humans*. We have had seventeen years of experience with Neurontin with no reported increase in pancreatic cancer. The FDA even acknowledges this fact. That should be enough, right?

Not for the FDA. Not surprisingly, GlaxoSmithKline's and XenoPort's drug Horizant showed these same tumors in male rats given up to twenty-five times the highest human dose. Said the FDA: "[P]reclinical finding of pancreatic acinar cell tumors in rats was of sufficient concern to preclude approval of Horizant for RLS at this time."

It gets worse. XenoPort's CEO, Ron Barrett, stated that the FDA had never raised the issue in its many discussions with XenoPort. Moreover, Mr. Barrett, who has actually seen the FDA's rejection

letter, claimed, in a conference call to explain the FDA's decision, that the FDA had determined that Horizant was effective and associated with no clinical (human) safety problems. Said Barrett, "[T]his one came out of left field." Indeed, XenoPort's stock dropped a whopping 66 percent the next day.

Moreover, researchers have previously shown that the rat pancreatic exocrine tumors induced by gabapentin do not correspond to human tumors. Acinar cell carcinoma was very uncommon in humans before Neurontin launched, and it is still uncommon.

Remember that the whole purpose of testing new drugs in humans is to look for possible dangers. That is exactly why Horizant was tested in clinical trials. Is the FDA now going to admit that clinical trials aren't that useful? And if they aren't, why does it persist in requiring them?

Now, you might say that with Neurontin already on the market, rejecting Horizant is no big deal. But it is a big deal. Neurontin is short-acting and requires a high dose to produce a certain blood level, while Horizant requires less to achieve the same effect since it is more efficiently transported through the intestinal wall. In other words, Horizant is more convenient and effective because it can be dosed lower and/or less frequently than Neurontin's three-times-per-day regimen and still provide more stable levels in the blood. Ask almost any doctor what his biggest frustration is with patients and medicines, and he will likely tell you that it's hard to get patients to keep taking their pills. Easier dosing causes patients to better adhere to their therapy.

There are only two approved medications for restless legs syndrome. Unfortunately, they are associated with significant side effects and actually cause the symptoms to worsen. According to the National Institute of Neurological Disorders and Stroke, RLS is a neurological disorder characterized by unpleasant sensations in the legs and an uncontrollable urge to move them for relief. People with RLS report feelings of burning, creeping, or tugging, and they sometimes feel as if they have insects crawling inside their legs. The sensations range in severity from uncomfortable to painful. RLS is generally a life-long condition for which there is no cure. These sufferers can now thank the FDA for making them suffer for a lifetime.

Beyond the damage inflicted on people with RLS is the damage inflicted on drug companies. Drug companies are in the business to make money by curing or ameliorating disease. When the FDA gives them the green light to go beyond animal studies and do the more-expensive studies on humans, drug companies believe that they have some assurance that if the drug works on humans without untoward side effects, the FDA will approve the drug. But now the FDA has established a bad precedent. It can say, in effect, "We know we approved this next phase of testing, but we've changed our minds. We're worried about the effect on rats that we ignored earlier." This creates enormous uncertainty for drug companies. If they see this decision on Horizant as a precedent, they will be less likely to invest in new medicines. And that will hurt all of us.

Seventeen years of human data in millions of patients showing that gabapentin doesn't cause pancreatic cancer in humans were trumped by a two-year study in 200 rats given extremely high doses. The real danger to our health comes from such myopic views of safety and a hyperconservative, opaque, and capricious FDA keeping useful medicines out of the hands of American doctors and patients. The FDA needs to be reminded that it is reviewing drugs for humans, not for rodents.

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