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Desvenlafaxine: The Newest Antidepressant

LATEST ANTIDEPRESSANT AVAILABLE IN THE UNITED STATES DESVENLAFAXINE

After many years of trying Wyeth has received approval and is currently marketing the newest antidepressant in the United States, desvenlafaxine. What you need to know about this medicine. Welcome to The Clinician's Round Table. I am Dr. Leslie Lundt, your host, and with me today is Dr. Philip Ninan. Dr. Ninan is the Vice-President for Neuroscience in Global Medical Affairs for Wyeth Pharmaceuticals. Dr. Ninan has an international reputation for excellence in research in the neurobiology and treatment of anxiety and depressive disorders.

DR. LESLIE LUNDT:

Welcome to ReachMD, Phil.

DR. PHILIP NINAN:

Thank you Leslie, it is a real pleasure to be with you.

DR. LESLIE LUNDT:

Phil, the history of desvenlafaxine is pretty interesting in itself. I wanted to listen.

DR. PHILIP NINAN:

Yes actually, not many people might be aware, but why it was voted last year as having the best pipeline in the neurosciences, and so we invest a lot of effort, people, and money in being able to come up with new medications both in Psychiatry and Neurology. And we have a broad portfolio in the area of anxiety and depression, particularly in the area of novel mechanisms that we would have and so there was a tremendous effort to be able come up with the next generation of medication, but as you know and several companies have learned, it's much easier to talk about these things than to be able to deliver it. So we had been looking at a number of different approaches, and it turned out that when we looked at a whole host of issues, so when we start looking at medication in the pipeline, there are initial studies that look at pharmacokinetics and pharmacodynamics. There are issues in terms of formulation. The whole biodistribution business, how it has absorbed, distributed, metabolized, and eliminated. Whether age and gender matter, whether it affects the liver, the kidney, those kind of issues and then of course we are very sensitive to the issues related to the heart and so what you do when you have a drug is you run them through all of these preliminary trials and the test tube and in animals and many, many drugs at that point fail, or we make choices, I mean no body would come up with the drugs these days that would have a major impact on you know have to go in a major way through one of the cytochrome P450 enzyme systems, because people are much more sensitized to it. We would not come up with the drug that would have an effect say on the QTC of the heart and so among all the things that were done desvenlafaxine landed up coming out looking actually very clean and so they said, "Well, lets go ahead and develop it" and so that is how desvenlafaxine was chosen out of whole portfolio studies of compounds that we had to be developed.

DR. LESLIE LUNDT:

And how long did it take, you know most of us were end users of these products and we are really not privy to the life cycle of these compounds. Roughly, how long from first identifying desvenlafaxine to having it on the shelf?

DR. PHILIP NINAN:

It can take a decade or more. Because you actually give it even to an animal, you do all these basic test and then you give it to animals, and then you give it to humans, and actually the longest period of development actually happens in the human part, particularly in the phase 3 trials because you have to have a whole portfolio of studies that meet very specific criteria for the FDA to be able to demonstrate efficacy as well as safety. Now when the new drug application went in, this is amazing to me, the number of pages that the new drug application had to FDA was 280,000 pages.

DR. LESLIE LUNDT:

280,000!

DR. PHILIP NINAN:

That's right and then of course we have back and forth with the FDA. They have number of questions about they actually read this thing and they study it and they think about it, they relate one bit to another and all this stuff and then they ask us a whole bunch of questions. And so by the time we finally finished all of this back and forth, we have more than half a million pages that was part of the application for this and that is the amount of effort that goes in to the getting a medication on the market.

DR. LESLIE LUNDT:

Wow!. Lets talk specifics for those that may not be familiar with desvenlafaxine. What is the research now to support the use of it in the treatment of major depression?

DR. PHILIP NINAN:

Well if you look at it in terms of the studies that were done in patients with major depression. There was portfolio of 9 studies that were done that looked at a range of doses. We looked initially at doses that turned out to be much higher than was necessary so the initial studies were 200 to 400 mg and then later on we found that even 50 mg was going to be effective and in fact we waited, you know we had got what is call the approvable letter much earlier on, but we decided to wait until we got some of our final clinical data, because we thought that would really have an impact on us being able to tell clinician how best to use the medications and so that's where we came up with 50 mg, which is the lowest dose pill once a day was going to be an effective dose and that was the starting dose of the effective dose and it was actually quite well tolerated when you look at it in the standards of antidepressants so if you look at one measure, which is the number of people who discontinued the medication because of unacceptable side effects, it was very similar to that in the placebo group and so we had a profile where once a day medication, the starting dose of the effective dose, its tolerability profile is very positive because when we are looking at the benefits that we wanted to be able to provide the ease of use of a medication is now increasingly becoming important because primary care physician, healthcare providers have whole a lot of things that they had to pay attention to. And anything that makes it easier for them to use and makes it easier for patient's to adhere to can make a big difference.

DR. LESLIE LUNDT:

If you are new to our channel, you are listening to The Clinician's Round Table on ReachMD XM157, The Channel for Medical Professionals. I am Dr. Leslie Lundt your host, and with me today is Dr. Philip Ninan. We are discussing the latest antidepressant available in the United States, desvenlafaxine.

Now Phil, so 50 mg is the starting dose, do we ever go higher?

DR. PHILIP NINAN:

We can go higher, as I said we started it up to 400 mg, but what we found was the difference over placebo the degree of benefit was no different at doses higher than 50. On the other hand, adverse events were much more likely at higher doses and so the FDA has put in our label that 50 mg is the effective dose and is the recommended dose and no additional benefit has been demonstrated at the doses higher, but if dose is higher you do have the greater potential for adverse events.

DR. LESLIE LUNDT:

Now thinking there is so many antidepressants in the market and I am thinking of primary care physician may be listening right now. When we would they think about desvenlafaxine what kind of patients, really are ideal for this drug?

DR. PHILIP NINAN:

Well when you look at the portfolio of antidepressants that we have particularly the new generation antidepressants, there is no conclusive evidence that can be drawn that says that one medicine is more effective than the other in the broad populations of patients with major depressive disorder. There might be some slight advantages in particular sub populations, but across the board you know the FDA is very cautious in making sure that no body can claim any kind of superiority so the efficacy is not an area. We are really looking at issues of tolerability, its metabolic profile. So for example Pristiq close to half of it is eliminated, unchanged in the urine, you know much of it goes through the liver, but not through the cytochrome P450 system predominantly goes through glucuronidation, which is a high-capacity system. There is a minor element less than 5% that goes to the 3A4. Its metabolism is also not through the 2D6 or whether you are a generic poor metabolizer or an extensive metabolizer doesn't

matter. The plasma levels of the drug are essentially the same in both those populations. Unlike venlafaxine where a 2D6 profile does have an impact, so if you are poor metabolizer then the parent compound is much higher because the 2D6 is an important pathway for its metabolism.

DR. LESLIE LUNDT:

For those that may not be familiar with desvenlafaxine, the venlafaxine part should be familiar and that of course is marketed under the trade name of Effexor, and there has been some suspicion that perhaps desvenlafaxine is come on the market because venlafaxine is going to come off patent soon, is that true?

DR. PHILIP NINAN:

Well venlafaxine is expected to lose patent some time in couple of years, but let me tell you that desvenlafaxine was actually developed initially not for depression, but for vasomotor symptoms associated with menopause and that was the indication that we had started our studies out with. We found that it was such a clean drug it had straight linear pharmacokinetics, it was well tolerated and it had all these signals that indicated that a broad population of patients would be able to take it and so they developed it also for major depressive disorder. We did get what is called an approvable letter for vasomotor symptoms of menopause, but they wanted us to do another study, which is being done. So I hope that when the results of those study become available that the FDA will make it available as an indication for desvenlafaxine.

DR. LESLIE LUNDT:

Now you mentioned earlier the increasing awareness of drug interactions. What is the drug interaction profile of desvenlafaxine?

DR. PHILIP NINAN:

Well it is actually relatively clean and that is one of the reasons why it was thought to be worth developing. So it really has very minor pathway through the 3A4 system, but the blood levels of venlafaxine get affected only to a minor degree when you have something that inhibits 3A4 or induces the 3A4. It doesn't go through the 2D6 as I mentioned earlier and it doesn't inhibit 2D6 beyond the very minor degree and it doesn't have an effect on any of the other pharmacokinetics enzyme systems. It is also not substrate for the other system that we increasingly becoming aware of which is the P-glycoprotein system, which is an efflux system that can take medicines out of cell and extrude it out into the lumen and that system is present in the blood brain barrier and so one of the things that it might do is it might take the medication from within the brain and get it outside the brain, and if you are interested in having the drug having effect on the brain then what happens is less likely to be able to continue to do that.

DR. LESLIE LUNDT:

Well thank you so much for being on this show today with us Phil.

DR. PHILIP NINAN:

Well listen it's a real pleasure and what I can say is that you know we have with desvenlafaxine or Pristiq, medicine that the starting dose is the effective dose, it's well tolerated in terms of discontinuation rates are equivalent to placebo and it has the fairly clean metabolic profile. So we are excited about being able to make that available to clinicians and patients and we hope that people find it useful.

DR. LESLIE LUNDT:

We have been discussing the ins and outs of the latest antidepressant Desvenlafaxine with our guest

today, Dr. Philip Ninan.

I am Leslie Lundt, you have been listening to the Clinician's Roundtable, on ReachMD XM157, The Channel for Medical Professionals. If you have comments or suggestions, please give us a ring at 888MD XM157. Thank you for listening.

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This is Dr. Mark Nolan Hill. This week we will be speaking with Dr. Arthur Matas at the University of Minnesota Medical School. We will be talking about global lessons towards reducing the organ shortage in the United States.

This is Dr. Mary Leuchars, join me this week as I speak with Dr. William Collins from the CDC Atlanta where we will be talking about new vaccines for malaria and with them the hope they carries for global eradication of this disease.

I am Dr. Goldstein inviting you to tune in to GI Insights this week as we discussed what GI doctors' need to know about Probiotics. Our guest will be Dr. Richard Fedorak at University of Alberta in Canada.

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