December 8, 1999

NulliSecundus

NEUROSCIENCE
DIVISION

Breakthroughs in the Treatment of Child and Adolescent Depression & Anxiety

Children grow out of shoes and clothes, but the odds say it is unlikely they will outgrow depression. A depressed child is twice as likely to be a depressed adult, according to Dr. Karen Wagner, a leading child psychiatrist.

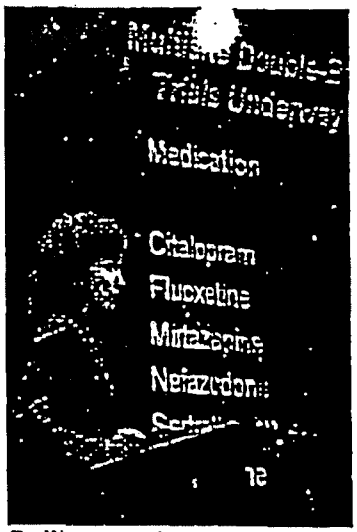
Dr. Wagner spoke to Neuroscience consultants at the launch meeting in Los Angeles. Dr. Wagner is Director of the Division of Child and Adolescent Psychiatry and the Vice Chair of the Department of Psychiatry and Behavioral Sciences at the University of Texas Medical Branch. Her message about major depression was that "it is a lethal disorder and it requires treatment."

Threat of suicide

Dr. Wagner pointed out that depression in adolescents can lead to suicide for 2.5% of those diagnosed with depression. Left untreated, the percentage rises to 8% as they become adults. Obviously, therapy is needed and *Paxil* is one of the few pharmaceutical approaches that has safety and efficacy data to support its use in this patient population. And more data is on its way.

Depression results in suicide for 2.5% of cases (from *Paxil* Web site)

As many of you know, SB is preparing an indication for adolescent depression for *Paxil* next year! SB's clinical study demonstrating the success of *Paxil* in treating depression among adolescents will be published in a peer reviewed journal during first quarter 2000.



Dr. Wagner at the Neuroscience Division launch meeting (photo by Ed Wamsnski)

SB's advantage

Dr. Wagner said the window of opportunity is before SB. Several other competing SSRIs and other compounds have studies ongoing. But *Paxil* and *Prozac* are the only two SSRIs that have any published data to date and many physicians have already found success in treating adolescent patients with *Paxil*.

Episodes of depression typically last nine months, according to Dr. Wagner. This disruption is equivalent to a whole school year and it may be time that can never be recovered for the patient. Families with a history of depression have to be especially vigilant for these signs:

- Irritable mood, complaining about everything.
- Diminished interest in activities
- Loss of weight
- Sleep disturbance; exhausted when it's time to get up
- Naps after school
- Feelings of worthlessness or guilt "I'm stupid. Nobody likes me"
- Declining grades
- Suicidal tendencies

Failure of tricyclics

Treating depression in children and adolescents is critical, but there are not many options. Dr. Wagner said the tricyclics are almost useless in children.

"Tricyclic antidepressants, in all the studies that have been done, have not been shown to work with children or adolescents. They *don't* work! Where they fit in is really at the bottom of the list. They *just don't* work!"

To date, only two rigorous studies have been done in children and adolescents. Dr. Wagner said we can't say that what works in adults will work in children because of the great difference in metabolism, among other things. The only way to be sure is to compare against placebo, as in the two studies completed: one with fluoxetine and one with paroxetine.

The fluoxetine study was a fixed 20 mg dose for children and adolescents with major depression. The eight week study at one site was conducted in 96 patients, in which 48 received medication and 48 received placebo. The results? 56% of the fluoxetine group improved. In placebo, 36% improved. This was the first published study to show that an SSRI worked in youth.

Does depression run in families?

There is a very strong genetic component to depression. In a study of 91 families in which one or both parents had depression, the risk for children is:

- Eight times higher to suffer depression
- Three times higher of having an anxiety disorder
- Five times more likely to have conduct problems
- Five times the risk of being a depressed adult

Large paroxetine study

The paroxetine study measured treatment of adolescent depression. It is the largest study to date, involving 275 adolescents at 12 sites for eight weeks. In the study, one of three treatments was possible: imipramine (tricyclic), paroxetine, or placebo.

Chris Hanson thanks Dr. Wagner in Los Angeles (photo by Ed Warminski)

Results:

- 66% of paroxetine group improved
- 52% imipramine improved
- 48% of placebo improved.

The paroxetine results were statistically significant. The imipramine result was not, showing that tricyclics are no better than placebo in treating depression in youth.

Since so many received paroxetine, Dr. Wagner said another important finding was with side effects. While both drugs caused some headaches, dizziness and tremor, in the paroxetine group, only 7% experienced cardiovascular side effects, as compared with imipramine, in which 43% of the group had problems with blood pressure, EKGs or conduction problems.

As a result of this large study, Dr. Wagner said: "We can say that paroxetine has both efficacy and safety data for treating depression in adolescents."

Side effects

Dr. Wagner said she sees the half-life of paroxetine as an advantage over fluoxetine. The shorter half-life reduces side effects. During the Q&A session, several consultants challenged this advantage, saying they heard

Photo by Warmanski

the opposite. Some physicians believe the quicker metabolism of young people necessitates a longer half-life.

Dr. Wagner pointed out that one of the big challenges in treating depression in children and adolescents is getting them to stay on their therapy. As soon as parents see side effects in their children, they stop them from taking the drugs.

There are two things to keep in mind in this regard. First of all, begin patients on low doses of 5 to 10 mg and work up to 20 mg over a 12-week course of therapy. In some cases, 40 mg may be necessary. A gradual build up reduces noticeable side effects. The other factor to help control side effects is using paroxetine with its shorter half-life.

Anxiety disorders

Dr. Wagner spent a large part of her talk on anxiety disorders, as well as depression. She said more data is needed. The problem is also very serious.

For adults, a top fear is speaking in public. For children, it is reading aloud in front of the class. Unlike children, though, adults can control a lot their life and avoid painful situations. For children with social anxiety disorder, this is a fate and others are too dreaded to be faced. Too painful to be called upon. "For a child with social anxiety disorder, *everyday* is like the first day of school," according to Dr. Wagner.

She said she looks to the future when studies with drugs like *Paxil* show how SSRI therapy can help children cope with situations in which they have almost no control.

Social Anxiety Disorder

Symptoms

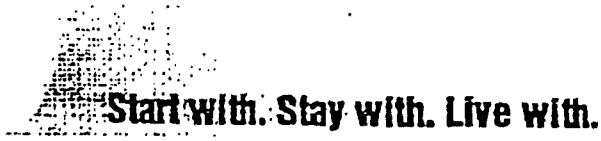
- Children are very shy
- No sports
- No music
- Little interaction.

Top Three Fears

- Reading out loud
- Athletic or music performance
- Joining in on a conversation

Prevalence

- About 3% to 4% of children have social anxiety disorder
- Affects boy and girls equally
- Onset is about 60% before the age 16..



Requip dosing

In the previous issues of the newsletter, we discussed the treatment strategy for Parkinson's disease and the importance of influencing a change in that treatment strategy. Dr. Ray Watts, Professor of Neurology and Director of the Movement Disorder Program at Emory University in Atlanta, has been a great source for most of this information. In his lecture at the launch meeting, he also discussed dosing.

Dosing is important for two reasons. First, we know from market research studies that the average dose of *Requip* is between 3 and 4 mgs per day which is significantly lower than the optimal therapeutic range as seen in clinical trials, which is 9 – 12 mgs per day. Second, we know that the titration schedule for *Requip* can be complicated.

Remember to check the "Product Pages" for more on *Paxil* and *Requip*.

Listening to the strategy for using the *Requip* detail aid (photo by Ed Warminski)

Efficacy depends on dosing

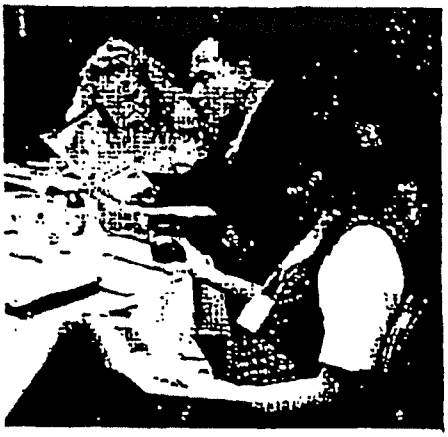
The dosing range is an important issue that you should address with physicians because efficacy is dependent on proper dosing. To achieve the efficacy results seen in the 5-year trial, it is imperative to dose *Requip* in the optimal therapeutic range. The dose response curve on page 13 in the sales aid shows that over 75% of patients responded at 9 mgs per day, whereas less than 50% of patients responded at the 3 and 4 mg per day doses. By educating your physicians on the optimal dosing for *Requip*, you will increase their success rates with *Requip*.

Titration schedule

The titration schedule for *Requip* can be complex, however we have tried to make it easier by providing a 3 mg starter kit and we will be coming out with a 6 mg starter kit in 2000. The titration schedule for *Requip* is beneficial in that it allows for a very wide dosing range which gives the physician great flexibility over the long-term. This ties in well with the new 5-year data because you can show the physicians that they will be able to maintain their patients over a significant amount of time on *Requip*.

Wide dosing range advantage

As the disease progresses, the physician has the option of increasing the *Requip* dose. Additionally, the wide range allows physicians to start patients slowly which should help physicians to successfully initiate *Requip* therapy.



At the *Requip* workshop in Los Angeles
(photo by Ed Warminski)

REQUIP™ ropinirole HCl

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