December 8, 1999

NeuroScience DIVISION

Nulli Secundus

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.

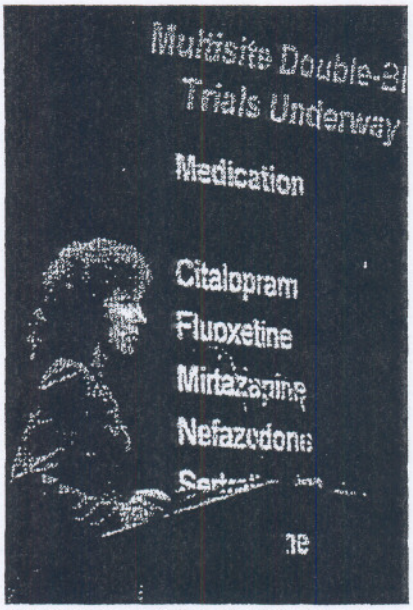
Dr. Wagner spoke to Neuroscience consultants at the launch meeting in Los Angeles. Dr. Wagner is Director of the Division of Child and Adolescent Psychiatry and the Vice Chair of the Department of Psychiatry and Behavioral Sciences at the University of Texas Medical Branch. Her message about major depression 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 Warminski)

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

WB 128683

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.

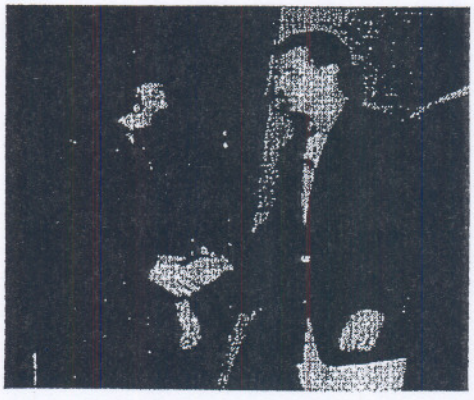
Does depression run in families?

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 Warminski

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.

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ONCE-DAILY
PAXIL®
PAROXETINE HCl

WB 128686

Neuroscience Division News, December 8, 1999.
Remember to check the "Product Pages" for more on *Paxil* and *Requip*.

Martin B. Keller, M.D.
Mary E. Zucker Professor & Chairman
Department of Psychiatry & Human Behavior

Psychiatrist-in-Chief
Butler Hospital
Executive Psychiatrist-in-Chief
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To: Barry Brandt X6103
FR: Sladen 37 pgs

February 11, 1999

Sally Laden
STI
898 Cahill Court
Cheshire, CT 06410

Dear Sally,

You did a superb job with this. Thank you very much. It is excellent.

Enclosed are rather minor changes from me, Neal and Mike and a cover memo from me to all co-authors. If it's agreeable to you, I would ask you to take my cover memo and send the revision, which incorporates the comments I am sending you, directly to all co-authors - even before I see again so that they may review this as quickly as possible.

Please let me know if you would like to discuss or handle differently.

Thanks,

Marty

cc: Jim McCafferty

Please copy for:
Bonnie
Scott
Chris
Tom

Hey Crugs!
Here is a copy of the adolescent study slated for submission to JAMA. -Sg

WB 202495

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SCIENTIFIC THERAPEUTICS
INFORMATION, INC.

February 6, 2001

Martin B. Keller, MD
Department of Psychiatry and Human Behavior
Brown University School of Medicine
345 Blackstone Blvd
Providence, RI 02906

Dear Dr Keller,

We are pleased to enclose all of the materials you will need to resubmit your manuscript "Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial" to the *Journal of the American Academy of Child and Adolescent Psychiatry.*

Enclosed in this package are the following items:

- Two copies of the revised paper with changes highlighted (submit 1 to the journal, keep 1 for your files),
- Four copies of the revised paper without the highlighting (submit 3 to the journal, keep 1 for your files)
- Two diskettes of the manuscript in Microsoft Word 97 format. Each diskette contains the revised manuscript without highlighting (submit 1 diskette to the journal, keep the other your files in the event further revisions are needed)
- Two copies of the responses to the reviewers' comments (submit 1 copy to the journal, keep 1 copy for your files). A diskette of these responses is also enclosed in the event you wish to make changes to this document before sending to the journal
- A draft cover letter to Dr Dulcan, Editor of JAACAP. Please retype on your letterhead and revise as you wish.

Please note the figures have not changed, therefore, the journal should be able to use the EPS file sent to you on January 15.

On behalf of Sally Laden, it has been a pleasure working with you on this project. Please keep us apprised of the status of this paper at the journal. Thank you and please do not hesitate to contact us if you have any questions or need additional assistance.

Sincerely,

Caroline Pretre
Copyediting Assistant

cc: J. Romankiewicz, M. Philips, S. Laden, J. McCafferty, B. Brand; .1301
encl

08/16/01

To:	All Sales Representatives Selling *Paxil*	cc:	RVPs TSMs *Paxil* DSMs RMSs
From:	Zachary Hawkins *Paxil* Product Management		
Study Title	"Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial"		
Author(s)	Martin B. Keller, M.D.		
Journal	*J. AM.ACAD. CHILD ADOLESC. PSYCHIATRY* 2001		
Date Vol Pages	2001, July, Vol. 40:7: 762-772		
Significance of article	**This "cutting-edge," landmark study is the first to compare efficacy of an SSRI and a TCA with placebo in the treatment of major depression in adolescents. *Paxil* demonstrates REMARKABLE Efficacy and Safety in the treatment of adolescent depression.**		

Key Points

- The treatment of depression in adolescents is an area of burgeoning interest. Unfortunately, few well controlled, large scale, randomized clinical trials have been conducted in this population. (pg 762, col. 2, par 1)
- National Comorbidity Survey indicates lifetime prevalence rate of 15.3% for adolescent major depression, comparable with a 17% lifetime prevalence in adults. (pg 763 col 1 par 1)
- Comorbid anxiety disorders were present in 19% to 28% of subjects. (pg 765 col 1 par 1) **COMORBIDITY!**
- *Paxil* was significantly more effective than placebo with regard to achievement of both HAM-D total score $\leq$ 8, CGI score of 1 (very much improved) or 2 (much improved), and improvements in the depressed mood items of the HAM-D and the K-SADS-L
- Roughly two-thirds (63.3%) of the subjects on *Paxil*, 50% of Imipramine subjects, and 46% of placebo subjects achieved remission (a HAM-D total score of $\leq$ 8) at endpoint based on the LOCF Dataset. **(Table 2)** Among patients who completed 8 weeks of treatment, 76% of *Paxil* subjects, 64.3% of Imipramine subjects, and 57.6% of placebo subjects achieved remission. (OC Dataset) **FIG. 1**
- Nearly half of the subjects in the *Paxil* group remained at the initial starting dose of 20mg/day (48%). Mean dose at study endpoint for *Paxil* was 28.0 mg and for Imipramine was 205.8 mg. (pg 766 col 2 par 3)
- *Paxil* was generally well tolerated in this adolescent population,

and most adverse events were not serious. The most common adverse events occurred at rates that were similar to rates in the placebo group. (pg768 col 1 par 2)

- Adverse cardiovascular effects were not observed in subjects treated with *Paxil*. In contrast, tachycardia, postural hypotension, prolongation of QT intervals during imipramine therapy resulted in treatment discontinuation in one third (13.7%) of the 31.5% subjects who stopped treatment prematurely with the TCA.
- In conclusion, the findings of this study provide evidence of the efficacy and safety of *Paxil* in the treatment of adolescent depression. Here's another example of GlaxoSmithKline's commitment to Psychiatry by bringing forth "cutting edge" scientific data. *Paxil* is truly a REMARKABLE product that continues to demonstrate efficacy, even in this understudied population.

File (type an X in only one box)

Choose only one of these categories.

[X] **FYI** ***Article will be stamped****: This article is for pharmaceutical consultants' Information only. Do not use it with, or distribute to, physicians.*

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April 26, 2000

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RE: REVISION OF PAROXETINE ADOLESCENT DEPRESSION MANUSCRIPT

Dear Jim:

After an unanticipated delay due to a shift in priority assignments for the Paxil account, I am enclosing the revised manuscript. This version reflects both the *JAMA* reviewer comments and the comments of several authors who responded to our strategy letter earlier in the year. I attempted to make as many of the *JAMA* reviewer comments as practical. A summary of the more substantive points is listed below:

1. A more thorough discussion of the high placebo response rate in the Conclusion section.

2. A 'study limitations' paragraph has been added to the Conclusion that addresses the fact that the study was not designed to directly compare paroxetine and imipramine; that the HAMD score at baseline was low relative to adult studies; and that patients with externalizing disorders were eligible for enrollment.

3. The mean imipramine plasma concentrations at weeks 4 and 8 will be stated (SB: please provide this data), and it is stated that a more thorough discussion of this data will appear in a separate publication.

4. A new figure (Fig 3) showing the HAMD total score response vs time.

5. As noted by several reviewers, the definitions of remission and response overlap. Boris Birmaher suggested that the definitions be revised to delete mention of remission and simply describe response. This suggestion is reflected in the enclosed manuscript.

6. As suggested by Reviewer #2, the title is revised to delete the phrase 'But Not Imipramine.'

After hearing back from yourself and the 3 lead authors, I will address your comments, circulate the revised draft to all authors for their approval and signed release forms for *American Journal of Psychiatry*, and prepare a submission package for Dr Keller.

Thank you for your attention to this matter, and I apologize once again for the extended delay in returning this manuscript to you.

Sincerely,

Sally Laden

Sally K. Laden, MS
Associate Editorial Director

encl

cc: .1301

FAXED 12/7/99

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December 7, 1999

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RE: PUBLICATION STATUS - PAROXETINE ADOLESCENT DEPRESSION STUDY

Dear Dr McCafferty:

The purpose of this letter is to inform you of the publication status of this study and to outline next steps.

Dr Keller submitted the manuscript to *JAMA* in early August, 1999. The journal elected not to publish the paper and notified Dr Keller in November. In a conference call in November involving Drs Keller, Ryan, and Strober and Jim McCafferty, the action plan itemized below was agreed upon:

1. Sally Laden and Jim McCafferty will summarize the reviewers' extensive comments and draft a memo outlining the changes to be made.

2. This memo will be circulated to all authors for their review and approval.

3. The current draft will be revised and circulated to all authors for review and approval.

4. The revised manuscript will be submitted to *American Journal of Psychiatry*.

Resubmitting this manuscript is our top priority, and we will be asking for rapid review when we send materials to the authors.

Thank you for your attention to this matter. Please do not hesitate to contact me (203/272-9750), Jim MacCafferty (610/917-4705), or Marty Keller (401/455-6430) if you have questions or require additional information.

Sincerely,

Sally Laden

Sally K. Laden, MS
Associate Editorial Director

cc: Martin B. Keller, MD, Barry Brand, .1301