



Sent by Mistake

Brown University
Department of Psychiatry and Human Behavior
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| | | |
|-----|-----------------------|---------------------|
| TO: | <u>Sally Laden</u> | <u>203-272-6917</u> |
| | <u>Jim McCafferty</u> | <u>610-917-4133</u> |
| CC: | <u></u> | <u></u> |

From: Martin B. Keller, MD (E. Zaleski) Pages including cover: 6

Date: February ¹⁴~~15~~, 2002

Dr. Keller has asked that I forward this to you for your review and action.

If you have any questions, please contact me between now and February 15 at (401) 444-1939.

Additionally, for Sally Laden, I am in need of a copy of the previous response to the response to the letter to the editor of the JAACAP. Materials were faxed to you I believe and currently I don't have access to a copy of Dr.Keller's article or the response to it. I have to get those materials to Jim McCafferty so he can also work on that response.

Thank you both for your help and again, do not hesitate to call with any questions.

Ed Zaleski
Secretary - Department of Psychiatry and Human Behavior

Confidentiality Note:
This facsimile contains privileged and confidential information solely for the use of the party mentioned above. If the reader of this facsimile is not the intended recipient or the employee responsible for delivering this facsimile to the intended recipient, you are hereby notified that dissemination or copying of this facsimile is strictly prohibited. If you have received this facsimile in error, please notify us immediately by phone (collect) and return the original facsimile via U.S. Postal Service. Thank you.

Butler Hospital, 345 Blackstone Boulevard, Providence, RI 02906

PAR001375827



"Ryan, Neal"
<Ryannd@MSX.UPMC.
EDU>

06-Nov-2002 15:30

To: "Martin Keller (Home Fax)" , "Sally Laden (SallyL, "Mike Strober
(mstrober, James.P.McCafferty, "Martin Keller (martin_keller, "Martin
Keller (Business Fax)"

cc:

Subject: paxil response to juredini article.doc

Please critique and get back to me ASAP. I'm traveling thu-fri of this week and then wed-fri of next week so time is tight here.

Neal

DRAFT 01

Mina K. Dulcan, Editor
Journal of the American Academy of Child and Adolescent Psychiatry
Editorial Office
Children's Memorial Hospital
2300 Children's Plaza, #156
Chicago, IL 60614-3394

Re: letter of Drs. Jureidini and Tonkin

Dear Dr. Dulcan,

In response to the letter of Drs. Jureidini and Tonkin commenting on our study of paroxetine in adolescent depression (1), we would first like to address the overt issues that they raise and then respond to a covert argument they made.

It seems that they argue that (a) we were insufficiently clear distinguishing between our primary outcome measures and our secondary outcome measures and (b) our assessment that this study found paroxetine effective was incorrect. We feel that we were quite clear in which were primary outcome measures and which were secondary since this is explicitly and clearly elucidated in the abstract of the paper. Therefore, since our two primary outcome measures did not reach a $p < 0.05$ level of statistical significance, the more complex question that remains is whether or not we fairly interpreted the pattern of significant p values across a range of secondary endpoints as indicating that paroxetine is better than placebo for adolescent depression.

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This study was designed at a time when there were no randomized controlled trials showing antidepressant (TCA or SSRI) superiority to placebo so we had no prior data from which to astutely pick our outcome measures. In retrospect, the field has moved strongly away from using the Hamilton Depression Scale in adolescent treatment studies and has gone virtually uniformly to using the CDRS-R because of better and more reliably capturing aspects of depression in youth. Surely a national regulatory body charged with approving or not approving a medication for a particular use might well simply say that if a study doesn't show efficacy on the primary endpoint(s) it is a failed study and secondary outcome measures cannot then be used for approval. However, as scientists and clinicians we must adjudge whether or not the study overall found evidence of efficacy and we do not have the convenience of falling back upon such a simple rule. If we choose wrongly (in whichever direction) we don't treat depressed children as well as the data would permit. Since we found a clear pattern of significant p values across multiple secondary analyses (recovery as assessed by HAM-D < 8, Ham-D depressed mood item, and CGI score at endpoint) we thought and still think this provides significant evidence of efficacy of paroxetine compared to placebo in adolescent depression. Without established reliable measures that distinguish medication responder from non-responders at the time the study was designed, it is not surprising at all that the primary measures didn't reach significance while other measures did. It still provides a strong "signal" for efficacy.

Drs. Jureidini and Tonkin argue that the reviewers failed to understand and appropriately critique the paper (and by extension that the editor was not up to the task) and that the authors of the original paper swerved from their moral and scientific duty under the influence of the pharmaceutical industry. By extension, of course, they covertly argue that the reader who agrees with them is intellectually and morally superior while a reader who doesn't agree with their position shares the cognitive and/or moral failing of the rest of us. We say that this paper and body of scientific work is a matter for thoughtful and collegial discussion and say, in addition, that their emperor has no clothes.

Sincerely,

Martin B. Keller, M.D.

Neal D. Ryan, M.D.

WHOEVER ELSE WANTS TO OR SHOULD CO-AUTHOR THIS

PAR001375840

1. Keller MB, Ryan ND, Strober M, Klein RG, Kutcher SP, Birmaher B, Hagino OR, Koplewicz H, Carlson GA, Clarke GN, Emslie GJ, Feinberg D, Geller B, Kusumakar V, Papatheodorou G, Sack WH, Sweeney M, Wagner KD, Weller EB, Winters NC, Oakes R, McCafferty JP: Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry* 2001; 40(7):762-72

PAR001375841



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August 7, 2001

James McCafferty
Senior Scientist
GlaxoSmithKline
1250 S Collegeville Rd UP4410
PO Box 5089
Collegeville, PA 19426-0980

RE: PAXIL ADOLESCENT DEPRESSION PAPER

Dear Jim:

I am pleased to enclose a small supply of reprints of the paroxetine-imipramine adolescent depression paper that was recently published in *Journal of the American Academy of Child and Adolescent Psychiatry*. GSK funded the purchase of the reprints. A total of 300 went to Marty Keller, who is corresponding author on the paper, and the balance is being sent to Zach Hawkins for distribution to the Neuroscience sales force. Samples are also being sent to Rocco and Neil.

The paper looks excellent and demonstrates the commitment of GSK to the field of psychiatry. Thank you for your support.

Sincerely,

Sally K. Laden, MS
Associate Editorial Director

encl

cc: .1301

PAR001380128

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August 7, 2001

Martin B. Keller, MD
Chairman, Psychiatry and Human Behavior
Brown University
Butler Hospital
345 Blackstone Blvd
Providence, RI 02906

RE: REPRINTS OF ADOLESCENT DEPRESSION PAPER

Dear Marty:

Enclosed please find a supply of reprints of the adolescent depression study that was recently published in the *Journal of the American Academy of Child and Adolescent Psychiatry*. Purchase of the reprints was funded by the Paxil Product Management group at GSK.

Thank you for your patience and support as this difficult project was finally completed.

Sincerely,

Sally K. Laden, MS
Associate Editorial Director

encl

cc: Scott Sproull, James McCafferty .1301

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SCIENTIFIC THERAPEUTICS INFORMATION RELEASE FORM{PRIVATE }

Please check the appropriate box, sign, and FAX by November 6, 2000 to:

Sally K. Laden, MS
Scientific Therapeutics Information, Inc
505 Morris Avenue, Suite 300
Springfield, NJ 07081

FAX: 973-376-0611
Tel: 973-376-5655

By signing below, I, James McCafferty, MS, approve Draft 11 of the manuscript entitled "Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial" dated November 3, 2000, and agree that it can be released to Martin Keller, MD to submit for publication to *Journal of the American Academy of Child and Adolescent Psychiatry*. I understand that all copyrights to the article, once published, belong to the publisher and not to myself, STI, or SmithKline Beecham Pharmaceuticals.

PLEASE CHECK THE APPROPRIATE BOX:

- Manuscript approved without changes.
- Manuscript approved with changes indicated; no additional draft needed.
- Manuscript not approved; changes indicated, and additional draft required for approval.

Signature

Date

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