

## Cunnup, Jillyan

---

**From:** Buse, John  
**Sent:** Sunday, January 26, 2003 2:45 AM  
**To:** 'CAVAZZONI\_PATRIZIA@Lilly.com'  
**Subject:** RE: Manuscript # 1205R - PCS paper

Patrizia: Here is the manuscript that I wanted your advice on as well as my review from 10,000 feet. The critical parts are below. The full review is attached in a "printable form". Please destroy it after you are done. I feel in a way that I have been unduly harsh – that in some ways the psychiatric community has not quite gotten to the level of systematic review. If you think I should tone it down, feel free to suggest away. j

### Comments to Editor:

First, several disclaimers:

- a) I am not a psychiatrist. I am a diabetologist.
- b) One of the papers discussed in this manuscript (reference #11) is now a full manuscript of which I am an author.
- c) I am an unpaid collaborator with Lilly's psych division. The University of North Carolina, under contract, has received monies from about twenty different pharmaceutical companies that develop or market diabetes products for research studies, consulting work and speaking performed by me. I do not have direct control of those funds though they do benefit my group. These companies include at least three that manufacture products mentioned here - Lilly, Novartis and Pfizer.
- d) I have never seen a copy of your journal and thus do not have a clue as to what standard you hold your authors nor do I know who your audience is.

Perhaps each of those should disqualify me from evaluating this paper, but I am going to go for it anyway.

My major disappointment is that this is not really a systematic review, a meta-analysis, or anything scholarly. It is a fairly slipshod commentary on some papers and what is worse, some abstracts, which were compiled in an undefined manner. I do not know who the authors are (probably on purpose) and do not know if they have any substantial conflicts of interest (it seems that most of the people that I run into in this field do). This manuscript is up to the standards of a good B+/A- college paper. It does not meet the standards that I think are required to add to the medical literature. I think its publication will just muddy the waters further in a morass that is already almost impenetrable. I suspect there was nothing systematic about this review. The references are so similar to what has been compiled in a variety of documents that I have seen, that I think these were the papers and abstracts that these authors obtained from one or more sources and no systematic review was actually performed.

### Comments to Author:

The conclusion (from the abstract) is: "Nevertheless, an increased risk for diabetes mellitus appears to be present for patients receiving atypical antipsychotics, with the risk being higher for clozapine and olanzapine, but also present for risperidone, quetiapine, and ziprasidone." This statement is sandwiched between a disclaimer and a disclaimer, suggesting that the authors are at best uncertain about the conclusion, at least to the extent that they have to disclaim a great deal. Why therefore make such a statement? What could be the benefit? It just adds to the partisan nature of the debate between pharmaceutical companies without shedding new light on the subject.

The nature of the work performed that is being put up for consideration by the reader is world is basically that the author(s) gathered some papers and some abstracts (not in a particularly systematic way nor with 100% ascertainment of pharmacoepidemiologic studies) read them, made some tables and had some focused comments here and there about certain aspects of certain studies. Effectively there is a tallying of the conclusions of these papers (and even worse abstracts) without substantial systematic critical analysis of the techniques, confounders, and analysis plan. This is not a systematic review of the Cochrane variety nor a meta-analysis. It is adding opinion to a flawed and often unpublished literature.

CONFIDENTIAL SUBJECT TO PROTECTIVE ORDER: MDL 1596 (Zyprexa Litigation)

9/15/2004

300

**BUSEHC000087**

That said, I would not mind nearly as much if there was just a compiling of those papers and abstracts (perhaps with a bit more of a systematic search or reporting of the search method). Searching for pharmacoepidemiologic studies on MEDLINE is a non-trivial task. How was the search conducted? What search terms; who did it; were there predefined criteria for the studies that were appropriate for analysis in this paper; who made that determination; how was that determined? Similarly, the language used in methods about how the abstracts were ascertained are an insult to the serious conduct of this kind of scholarship ("The proceedings of several professional meetings conducted in the United States, Canada and Europe were also examined for the presence of poster presentations on this topic.") How was this done? Which meetings over what years? Why were those selected? Many of these studies have been reported more than once. In that case, how was the particular abstract selected? How were the details of the studies referenced ascertained from the abstracts? I suspect that the author(s) must have had other documentation of the presentations.

Finally greater justification for compiling the data from abstracts needs to be provided. Is the field so desperate for this kind of information that abstracts can really rise to the level that they are fair game for systematic review and analysis? In fact, they are really a distraction to this paper.

Finally, I am most disappointed that the authors did not make any systematic effort to expose the flaws of essentially each of these studies. I do not know what the expertise of the authors is. I would suggest that with the help of a biostatistician and an evidence-based medicine guru or a meta-analyte (often found in divisions of general internal medicine or departments/schools of public health), they could with only modest additional effort make this a more scholarly treatment.

There is fairly extensive discussion of each of many potential issues that is in many ways quite helpful. However, there is no systematic gutting of each study, just a compilation of issues, with some specific points made about certain studies. There is not one whose methodology is sufficient, where confounders were specifically evaluated and in which there were large differences between agents to drive clinical decision-making.

Particular attention to the analysis plans of these studies needs to be taken.

There are so many simultaneously occurring secular trends that confound these kinds of studies - rapidly increasing incidence of diabetes (>50% increase in the last 5-7 years), new diagnostic criteria for diabetes, earlier diagnosis. These are not all systematically examined in any report and some are not adequately controlled for in any report. As an example, there seems to be an association of schizophrenia with diabetes (as pointed out by the authors) - many of the studies do not select based on diagnosis but based on drug. Thus if a drug A compared to drug B was being used for another indication with greater frequency - e.g. agitation or delirium - it might affect the prevalence if the real driver of the prevalence of diabetes is the underlying psychiatric diagnosis.

There are known differences in risk of diabetes based on many factors (some mentioned by the authors, other not) - age, race, sex, physical activity, obesity, family history, cardiovascular disease and CVD risk factors, socioeconomic status, fatty liver, etc, etc. There is no effort to systematically comment on those risk factors that were examined and how there may have been bias in drug assignment based on the prescribing physicians assessments. As an example, in more recent studies, if there is a greater concern that clozapine may cause diabetes, would not physicians tend to not prescribe that drug in patients perceived to be at high risk perhaps increasing the apparent risk for some other drug that might be viewed as the most reasonable substitute for clozapine.

How are issues of drug switching and combination therapy handled in each analysis? There is no

CONFIDENTIAL SUBJECT TO PROTECTIVE ORDER: MDL 1596 (Zyprexa Litigation)

9/15/2004

301

**BUSEHC000088**

comment, for instance, that, in one of these studies, patients who develop diabetes on olanzapine and risperidone are assigned to the olanzapine group as a matter of protocol.

As another example, if there was a perception that there was even a small perceived difference in efficacy or a greater failure rate with one drug than another, is it not possible that differences in diabetes risk associated with one drug are related to disease severity?

I would feel much more comfortable with a critical review which pointed out that the issue of whether one atypical antipsychotic is associated with a higher risk of diabetes than another cannot possibly be answered by the available data. Effectively, the authors state as much, they just go beyond that conclusion on several occasions to make their best guess of what appropriate clinical decision making would be based on what stack of flawed data is higher. I would feel much more comfortable with a statement that it is possible that there are particular agents that are associated with modestly higher absolute risk of diabetes, but that the risk of diabetes in patients with schizophrenia is much greater than any apparent difference between drugs. Based on the fact that over half of what the authors seem to believe are the least biased and most high quality studies show no difference between agents, it seems silly to then state that clozapine and olanzapine seem to have a real issue and maybe the others do to.

John B. Buse, MD, PhD, CDE  
Associate Professor of Medicine  
Chief, Division of General Medicine and Clinical Epidemiology  
Director, Diabetes Care Center  
UNC School of Medicine  
Pager: 800-593-6916

Office:  
CB#7110, 5039 Old Clinic  
Chapel Hill, NC 27599  
Phone: 919-966-2276 ext 222 (Tonya)  
Fax: 919-966-2274

Clinic:  
5316 Highgate Drive  
Durham, NC 27713  
Phone: 919-484-1015  
Fax: 919-806-2181

-----Original Message-----

**From:** CAVAZZONI\_PATRIZIA@Lilly.com [mailto:CAVAZZONI\_PATRIZIA@Lilly.com]  
**Sent:** Friday, January 24, 2003 5:56 PM  
**To:** Buse, John  
**Subject:** RE: Manuscript # 1205R - PCS paper

John

Here's the info on the Editor

Editorial Offices  
Journal of Clinical Epidemiology  
J. Andre Knottnerus  
University of Maastricht  
Peter Debijeplein  
P.O. Box 616, 6200 MD  
Maastricht, The Netherlands

CONFIDENTIAL SUBJECT TO PROTECTIVE ORDER: MDL 1596 (Zyprexa Litigation)

9/15/2004

302

**BUSEHC000089**

011-31 43 388-2222

Let me know how it turns out

Patrizia

"Buse, John" <jbuse@med.unc.edu>

01/22/2003 10:08 PM

To: CAVAZZONI\_PATRIZIA@Lilly.com

cc:

Subject: RE: Manuscript # 1205R - PCS paper

I still have not heard from them. Was someone able to find J. André Knottnerus's telephone number? j

John B. Buse, MD, PhD, CDE  
Associate Professor of Medicine  
Chief, Division of General Medicine and Clinical Epidemiology  
Director, Diabetes Care Center  
UNC School of Medicine  
Pager: 800-593-6916

Office:  
CB#7110, 5039 Old Clinic  
Chapel Hill, NC 27599  
Phone: 919-966-2276 ext 222 (Tonya)  
Fax: 919-966-2274

Clinic:  
5316 Highgate Drive  
Durham, NC 27713  
Phone: 919-484-1015  
Fax: 919-806-2181

-----Original Message-----

**From:** CAVAZZONI\_PATRIZIA@Lilly.com [mailto:CAVAZZONI\_PATRIZIA@Lilly.com]

**Sent:** Thursday, January 09, 2003 11:07 AM

**To:** jbuse@med.unc.edu

**Subject:** RE: Manuscript # 1205R - PCS paper

John

Would you have any objection to my sending the following e-mail to the editor of the journal ? Would you prefer to send it in your name (in which case I would replace "one of the authors" with "the lead author". Let me know your preference, and of course feel free to edit.

CONFIDENTIAL SUBJECT TO PROTECTIVE ORDER: MDL 1596 (Zyprexa Litigation)

303

9/15/2004

**BUSEHC000090**

Patrizia

Dear Dr. Knottnerus:

I am one of the authors for manuscript no # 1205R. I am writing to ask if you could look into the delayed publication of this manuscript, which was accepted by the Journal of Clinical Epidemiology on June 12, 2002. My office had contacted you in November regarding this paper, and your quick response regarding its status was greatly appreciated. You had indicated that there were several problems resulting from the unfortunate death of the US co-editor and the subsequent move of the journal headquarters to Ottawa.

Per the instructions of Ms. Kim Luyten, we sent her the copy of the manuscript again on November 25th, as she could not find it in the journal records. However, we are unable to find it on Elsevier's Author Tracking Gateway as of this week (week of Jan 7, 2003), and upon enquiry with Ms. Luyten, were informed that there are several manuscripts before ours in the queue, and she has no idea where our manuscript stands. I am forwarding the e-mail history of these communications.

Based on the above, it seems that it could be several more months before this paper is published. We believe that the data presented in this paper sheds important light on the growing awareness of the association between schizophrenia, diabetes mellitus and the use of antipsychotics. Since this paper was accepted more than 6 months ago, and was delayed due to a series of unfortunate circumstances, my co-authors and I wonder if there is any way the publication date could be expedited to account for time lost as a result of these circumstances.

Thank you in advance for your attention to this matter. I look forward to hearing from you

Best wishes for the New Year,

Kim.Luyten@HAG.unimaas.nl

01/07/2003 02:43 AM

To: ROYCHOWDHURY\_SURAJA@LILLY.COM

cc:

Subject: RE: Manuscript # 1205R

Dear Suraja Roychowdhury,

I've already sent your final version to the publisher, unfortunately I don't know how long it takes before your manuscript will be published, since there were a lot of manuscripts before yours which weren't published yet.

Sincerely yours,

Kim Luyten

-----Original Message-----

**From:** ROYCHOWDHURY\_SURAJA@LILLY.COM [mailto:ROYCHOWDHURY\_SURAJA@LILLY.COM]

**Sent:** maandag 6 januari 2003 20:40

**To:** Kim.Luyten@HAG.unimaas.nl

**Cc:** CARLSON\_CHRISTOPHER@LILLY.COM; CAVAZZONI\_PATRIZIA@LILLY.COM

**Subject:** RE: Manuscript # 1205R

CONFIDENTIAL SUBJECT TO PROTECTIVE ORDER: MDL 1596 (Zyprexa Litigation)

9/15/2004

304

BUSEHC000091

Dear Ms. Luyten:

Hope you are doing well. I am writing to enquire about the status of manuscript #1205R. As you can see from the attached e-mails, I had sent you the copy of the paper in November, per your request. If you recall, the paper was accepted on June 12th 2002. However, we still cannot track it at the Elsevier Author Gateway. I would really appreciate it if you could let us know when you would expect this paper to be published. Looking forward to your response,

Sincerely,

Suraja Roychowdhury

---

Suraja M. Roychowdhury, Ph.D., M.B.A.  
Sr. Scientific Communications Coordinator  
Zyprexa Product Team  
Eli Lilly and Company  
1 Corporate Center, DC 6314  
Indianapolis, IN 46285, USA.  
Tel: 317 433 0736  
Fax: 317 433 0448

Suraja Roychowdhury

11/25/2002 09:35 AM

To: Kim.Luyten@HAG.unimaas.nl  
cc: Christopher Carlson/AM/LLY@Lilly, Patrizia Cavazzoni/AM/LLY@Lilly  
Subject: RE: Manuscript # 1205R [Link](#)

Dear Ms. Luyten:

Thank you for your quick response. I am attaching the final version of manuscript number 1205R. There are 2 files : one with the text and one with the figures. Please let me know if there is anything else that I need to send you. I would also appreciate if you could let me know when the manuscript will be published.

Best regards,

Suraja Roychowdhury

---

Suraja M. Roychowdhury, Ph.D., M.B.A.  
Sr. Scientific Communications Coordinator  
Zyprexa Product Team  
Eli Lilly and Company  
1 Corporate Center, DC 6314  
Indianapolis, IN 46285, USA.  
Tel: 317 433 0736  
Fax: 317 277 5974

Kim.Luyten@HAG.unimaas.nl

11/25/2002 02:15 AM

To: ROYCHOWDHURY\_SURAJA@LILLY.COM  
cc:  
Subject: RE: Manuscript # 1205R

CONFIDENTIAL SUBJECT TO PROTECTIVE ORDER: MDL 1596 (Zyprexa Litigation)

305

9/15/2004

**BUSEHC000092**

Dear Dr. Buse,

Your manuscript has been accepted on June 12.  
Unfortunately we have never received your final version.  
Please send me your final version again by e-mail  
and I will send it to Elsevier this week.

Sincerely,

Kim Luyten

-----Original Message-----

**From:** Knottnerus Andre (HAG)

**Sent:** vrijdag 22 november 2002 17:48

**To:** 'ROYCHOWDHURY\_SURAJA@LILLY.COM'

**Cc:** Luyten Kim (HAG)

**Subject:** RE: Manuscript # 1205R

Dear colleague,

We will look at this. It maybe that a problem is caused by the logistic problems of the Yale editorial office after the death of the American co-editor, Dr. A.R. Feinstein and the period of transition of the office to Ottawa. Problems in mail handling may have been caused if mail has been sent to New Haven in June.

You will hear from us.

By the way, it is a bit strange to be contacted via the Lilly Product team. Dr Buse an co-authors can contact us directly next time.

Sincerely,

J. André Knottnerus

CONFIDENTIAL SUBJECT TO PROTECTIVE ORDER: MDL 1596 (Zyprexa Litigation)

306

9/15/2004

**BUSEHC000093**