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SB
SmithKline Beecham
Pharmaceuticals

VIII

file:
discontinuation
syndrome

May 1, 1997

Memo To: Paxil Selling Team
From: Bill Kinnier and Barry Brand
Subject: Discontinuation Syndrome

Lilly has initiated a new campaign focused on discontinuation symptoms associated with cessation of SSRI therapy. Two focal components to their campaign include:

- 1) Journal of Clinical Psychiatry Supplement - A retrospective review of case reports and clinical studies which show higher discontinuation rates with Paxil than either Prozac or Zoloft, a biased and selective representation of the data. (Attached, please find a copy of the supplement preview).
- 2) Clinical study to be presented at APA (American Psychiatric Association) on May 18 in San Diego, CA. Patients on chronic therapy for Prozac, Zoloft or Paxil were discontinued for 5 - 8 days. Adverse events were compared. A higher incidence of discontinuation symptoms were reported for Paxil than Prozac and Zoloft.

Is there merit to this campaign? No, Lilly is trying to hide the disadvantages of a long half life and active metabolites. In addition, they limited the evaluation period to 5 - 8 days. We know from other studies (i.e. Kreider) that Prozac is associated with discontinuation symptoms, but they are delayed in onset and may have longer duration based on case reports^{4,7}. A competitive response flashcard/reprint holder is being developed and will be available in the next few weeks.

SB Response

- 1) Acknowledge that the discontinuation symptoms exist for Paxil as they do for Prozac, Zoloft, Luvox, Serzone, Effexor and TCAs. This is due to a drop in serotonin levels from stopping the SSRI. That is why it is reported for all SSRIs (attached are a list of some of the references).
- 2) Educate physicians that discontinuation symptoms tend to be mild and transient. They may include one or more of the following: Nervousness, Dizziness, Diarrhea, Nausea, Headache. These symptoms tend to resolve in 5 days for Paxil and may be extended for Prozac based on case reports^{4,7}. Symptoms may be more frequently reported for the anxious and agitated patient.
- 3) Use Kreider reprint to document comparable incidence of discontinuation symptoms with Prozac. The Kreider paper² established that it wasn't necessary to wash out Prozac before switching to Paxil. This paper demonstrates the incidence of discontinuation related symptoms for Prozac (p.144 Table 3, Nervousness: Prozac 15.1% ; Diarrhea: Prozac 9.2%). In contrast, Lilly's J. Clin. Psych.³ states "the prevalence of symptoms 0% for fluoxetine ...and 20% for paroxetine".

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4) Establish benefits of Paxil's optimal half life vs. Prozac's long half life and active metabolites:

<u>Clinical Consideration</u>	<u>Features of 1 Day Half-life</u>	<u>Features of Multiday Half-life</u>
• Dosing	Once Daily Dosing	Once Daily Dosing
• Titration	Predictive pharmacokinetics simplify titration (10 Days to reach steady state with no active metabolites)	Confounding pharmacokinetics complicate titration (ill-defined steady state with active metabolite)
• Pregnancy	Minimized Fetal Exposure Period	Extended Fetal Exposure Period
• Treatment Emergent Adverse Event	Shortened Duration (5-10 Day Washout)	Prolonged Duration (20-45 Day Washout)
• Medication Switch	Less drug accumulation allows faster switches (5-10 Day Washout)	Drug accumulation delays switching (20-45 Day Washout)

Bottom Line: Paxil allows better clinical control

The Lilly study makes no attempt for fair balance by explaining the more serious, unmanageable downsides of a long half-life and active metabolites.

The truth of the matter is that the only discontinuation syndrome Lilly is worried about is the discontinuation of Prozac.

1. I Barr, W. Goodman and L. Price; *Am. J. Psych.* 151: 289, 1994.
2. M. Kreider, W. Bushnell, R. Oaks and D. Wheadon; *J. Clin. Psych.* 56: 142-145, 1995.
3. A. Schatzberg *et al.*; *J. Clin. Psych.* 58: 7-7, 1997.
4. J. Stoukides and C. Stoukides; *Am. J. Psych.* 148: 1263, 1991.
5. E. Lauterbach; *Neur.* 44: 963-964, 1994.
6. E. Einbinder; *Am. J. Psych.* 152: 1235, 1995.
7. C. Bertin; *J. Clin. Psych.* 57: 93-94, 1996.

Let's face it in the end. The only thing the anxious and agitated patient will be saying is



" Where's my Paxil !!!!! "

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