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

May 1, 1997

Lilly has initiated a new campaign focused on discontinuation symptoms associated with cessation of SSRI therapy. Two local 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 reports2. 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 reports3. 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 paper4 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.5 states "the prevalence of symptoms 0% for fluoxetine ... and 28% for paroxetine".
4) Establish benefits of Paxil's optimal half life vs. Prozac's long half life and active metabolites.

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


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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