



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE  
WITH THE PEDIATRIC SUBCOMMITTEE  
OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

Monday, February 2, 2004

8:00 a.m.

Holiday Inn Bethesda  
Versailles I and II  
8120 Wisconsin Avenue  
Bethesda, Maryland

1           In conclusion, use of SSRIs and atypical  
2 antidepressants is substantial in children and  
3 adolescents, and appears to be increasing rapidly  
4 every year. Pediatric specialists, pediatricians,  
5 and primary care providers continue to be the  
6 leading prescribers of these products, and over the  
7 past five years, the proportion of pediatricians  
8 prescribing these products has nearly doubled.

9           Finally, diagnoses related to the use of  
10 these antidepressants are slightly different among  
11 the younger pediatric population who are being  
12 treated for mood and anxiety disorders, and the  
13 adolescent population who are being treated mostly  
14 for mood disorders.

15           Thank you.

16           DR. RUDORFER: Thank you very much.

17           This morning we heard from Dr. Murphy  
18 about the mandated adverse event review associated  
19 with one-year post-exclusivity for some  
20 medications. Now, I am pleased to welcome Dr.  
21 Solomon Iyasu from the Division of Pediatric Drug  
22 Development who will give us a review of that  
23 information for paroxetine and citalopram.

24           One-Year Post-Exclusivity Mandated Adverse  
25           Event Review for Paroxetine and Citalopram

1 described in the adverse event reports may actually  
2 reflect to the underlying disease, because many of  
3 these events are also unexpected in other natural  
4 progression of the disease or part of the disease  
5 picture.

6           It may also be a drug effect or other  
7 concomitant medication, or it may actually be lack  
8 of effectiveness of the drug, and it is very  
9 difficult from these reports to sort out what is  
10 going on.

11           Therefore, evaluation of the controlled  
12 trials is necessary to sort out causality in terms  
13 of the observed adverse events.

14           [Slide.]

15           I am going to continue with the next drug,  
16 which is citalopram, but I would like to  
17 acknowledge the following individuals for their  
18 contribution for their review.

19           [Slide.]

20           Next, I will cover, as mandated by BPCA,  
21 citalopram, and will be talking about the adverse  
22 events in detail.

23           [Slide.]

24           To give you some background again about  
25 citalopram, it's an antidepressant belonging to

1 SSRIs, and marketed by Forest Pharmaceuticals.

2 Its current approved adult indication is  
3 for major depressive disorder. The adult dose  
4 ranges from 20 to 40 mg/day. There are no approved  
5 pediatric indications.

6 The original market approval was July 17,  
7 1998, and exclusivity was granted July 9, 2002.

8 [Slide.]

9 Again, to mention some of the relevant  
10 safety labeling which already exists, Pregnancy  
11 Category C, as I mentioned before, and also a  
12 caution against the use in nursing mothers.

13 There is also a Precaution section that  
14 mentions, similar to what is observed for Paxil,  
15 suicide risk inherent in depression and also the  
16 danger of activation of mania and hypomania.

17 Also, additional events mentioned in the  
18 precautions, any psychoactive agent may impair  
19 intellectual or psychomotor functions, and  
20 therefore, care should be exercised in prescribing  
21 these medications when individuals have to operate  
22 machinery or other things that may require  
23 intellectual and motor functions.

24 Seizures is another precaution that is  
25 mentioned especially in those with history of

1 seizure.

2 [Slide.]

3 Additional safety information in the  
4 Adverse Reaction section is about agitation with  
5 the use of citalopram, and also additional  
6 premarketing reports which are frequent, impaired  
7 concentration, depression, suicide attempt, and  
8 confusion; and infrequently reported in premarket  
9 reports are aggressive reaction, psychotic  
10 reaction, delusion, paranoid reaction, emotional  
11 lability, and panic reaction.

12 [Slide.]

13 To give you just a summary of the drug use  
14 pattern, it is the fourth most commonly used SSRI  
15 in children. Again, use had been increasing in  
16 recent years. Pediatric patients account for  
17 approximately 3.3 percent of the total U.S.  
18 prescriptions of Celexa.

19 Pediatric diagnoses most often linked with  
20 its use are depressive disorders,  
21 obsessive-compulsive disorder, and attention  
22 deficit order.

23 [Slide.]

24 Since marketing, there were over 6,000  
25 reports which included also duplicates that were

1 reported to FDA, 79 percent of them were domestic.  
2 Less than 5 percent of the reports were in  
3 pediatric patients.

4 The top 20 pediatric adverse events were,  
5 looking at that, all adverse events related to in  
6 utero exposure were unlabeled, which actually  
7 happened to be in the top 20 for pediatric adverse  
8 events.

9 Adverse event reports for children  
10 involving direct exposure were generally similar to  
11 those reported for adults.

12 [Slide.]

13 After a manual review of the one-year  
14 post-exclusivity period, there were 42 unduplicated  
15 reports that were pediatric. Sixteen of them were  
16 in utero exposures, and resulted in unlabeled  
17 events and one death.

18 There were 26 children involving direct  
19 exposure, 8 unlabeled events, and no deaths in this  
20 group.

21 Looking at the outcomes, there were 16  
22 serious outcomes, 10 hospitalizations, 4  
23 life-threatening, and 2 was disability. For the  
24 direct exposure group, the dose range was typically  
25 5 to 60 mg/day. The median dose was about 20

1 mg/day in these reports.

2 [Slide.]

3 Again looking at the age distribution, in  
4 the in utero exposure, most of them female, as well  
5 as in the direct exposure group, and age  
6 distribution is 0 to 1 in 15 patients, and then  
7 most of the direct exposure group, in older  
8 children.

9 [Slide.]

10 Looking at the reasons for exposure to  
11 citalopram, there were 26 direct pediatric  
12 exposures and then 16 in utero exposures. I am  
13 going to just focus on the adverse events  
14 pertaining to psychiatric, but these are the  
15 reasons for why they were exposed.

16 [Slide.]

17 There were only 5 psychiatric events, in 5  
18 patients where there were psychiatric events, and  
19 these are broken down by labeled and unlabeled  
20 events.

21 In the labeled events are the cognitive  
22 impairment, aggression, agitation, mania, and  
23 delusions, suicidality, and psychotic reaction.

24 Unlabeled events are the violent/homicidal  
25 behavior, which were observed in 2 of the patients.

1 [Slide.]

2 Looking at these 5 patients with  
3 psychiatric events, there were 4 males and 1  
4 female. The age distribution as 6 to 11 years with  
5 2; 11 to 16, about 3 of them. Diagnosis in 4 of  
6 them was MDD, and 1 case was oppositional defiant  
7 disorder, ODD.

8 Concomitant medications were reported in 2  
9 patients, Prozac in 1, and another, Keppra and  
10 clonazepam. Symptom resolved once citalopram  
11 discontinued in 4 according to the reports.

12 [Slide.]

13 In closing, I would like to say there were  
14 few psychiatric events that were reported during  
15 this one-year post-exclusivity period, unable  
16 really to determine causality due to limitations of  
17 the AERS database, therefore, we will continue to  
18 monitor these adverse events in children.

19 I would like to reiterate the same  
20 limitations that I mentioned before with respect to  
21 paroxetine when I talked about limitations of the  
22 AERS database.

23 Thank you very much for your attention.

24 DR. RUDORFER: Thank you.

25 Dr. Andrew Mosholder will now speak on the

1 Office of Drug Safety Data Resources for the Study  
2 of Suicidal Events.

3 Andy.

4 Office of Drug Safety Data Resources for  
5 the Study of Suicidal Events

6 DR. MOSHOLDER: Thank you very much.

7 I am very pleased to be here this  
8 afternoon. I am going to talk about how we looked  
9 at some of our Office of Drug Safety data resources  
10 to see if they would be relevant to exploration of  
11 this issue.

12 [Slide.]

13 It is very much a team effort and I want  
14 to start by acknowledging my colleagues who  
15 assisted me.

16 [Slide.]

17 The objective of my brief presentation  
18 will be to describe the data resources we have  
19 available in the Office of Drug Safety at FDA that  
20 are relevant to this issue, and, in particular,  
21 looked at two types of databases, the first being  
22 the postmarketing surveillance database that Dr.  
23 Iyasu just described, and also some  
24 population-based epidemiological databases.

25 Also, I will be describing the context of