

## **International Warnings on Psychiatric and Other Drugs Causing Hostility, Aggression, Homicidal and Suicidal Behavior/Ideation**

### **1991**

Britain banned the use of Halcion (benzodiazepine, in the same class as Valium and Xanax), the world's largest sleeping pill at the time, because of its risks, including **hostility**. Halcion was **blamed for causing hallucinations, suicidal tendencies**, amnesia and **aggressive behavior, including homicide and assault**.<sup>1</sup>

### **1992**

The FDA required stronger warnings for the labeling of Halcion after serious concerns were raised about the drug provoking episodes of **violence and psychological disturbance**.<sup>2</sup> The FDA was aware that Halcion users had a much higher rate of **hostility** than any similar drug. Between 1981 and 1988, the FDA received from the manufacturer, Upjohn, 241 reports of the drug causing **psychosis**.<sup>3</sup> The labeling warned of "rebound insomnia and **hostility**."<sup>4</sup>

### **1993**

The FDA conducted an analysis of adverse drug reactions for Xanax (anti-anxiety drug/tranquilizer, in the same class as Halcion and Valium), reporting the drug could cause **bouts of rage and hostility**. The side effects were six times more common in Xanax than in Ativan.<sup>5</sup>

### **1995**

**October:** The U.S. Drug Enforcement Administration (DEA) that "**psychotic episodes, violent behavior and bizarre mannerisms** had been reported" with the use of Ritalin.<sup>6</sup>

**February:** The Australian Therapeutic Goods Administration issued an Adverse Drug Reactions Bulletin that SSRI antidepressants had been associated with *withdrawal* syndrome. The symptoms most commonly reported were dizziness, nausea, **anxiety**, headache, **agitation**, insomnia, increased sweating, tremor, vertigo, **hallucinations, and depersonalization**. There were a total of 51 different symptoms documented in the reports with a wide range of other neurological and "psychiatric" symptoms, including, confusion, delirium, mood swings, neurosis, nervousness, nightmares, and sensory disturbance.<sup>7</sup>

### **1999**

**August:** The Australian Therapeutic Goods Administration issued an Adverse Reaction Bulletin to warn Zyprexa could cause serious problems such as white cell disorders, convulsions and neuroleptic malignant syndrome (abnormally high body temperature causing tissue destruction that is potentially deadly).<sup>8</sup> This condition is associated with **confusion, agitation** and **altered mental status**.<sup>9</sup>

## 2002

**December 14:** GlaxoSmithKline (GSK) and the FDA strengthened Paxil's label in regard to **withdrawal effects**. However, the revised label used the drug industry-invented term "discontinuation" instead of withdrawal to avoid the negative connotation that antidepressants were addictive. Withdrawal symptoms included abnormal dreams, paresthesia (abnormal sensations; electric shock sensations), and dizziness, **agitation, anxiety**, nausea and sweating.<sup>10</sup>

## 2003

**July:** Health Canada's Health Products and Food Branch warned health care professionals, "Until further information is available, Paxil should not be used in...pediatric patients...**due to a possible increased risk of suicide-related adverse events in this patient population.**" Further, incidents of suicidal thoughts and self-harm were nearly twice as high on Paxil as on placebo (5.3% vs. 2.8%).<sup>11</sup>

**August 22:** Wyeth Pharmaceuticals, the makers of SSRI antidepressant Effexor, issued a warning to U.S. doctors that Effexor could cause **hostility, suicidal ideation and self-harm** in patients under the age of 18.<sup>12</sup> Wyeth issued the same warning to doctors in New Zealand.<sup>13</sup>

**September:** Wyeth sent a similar alert to Canadian doctors telling them Effexor had been linked with a possible increase in suicidal thinking in children.<sup>14</sup>

**September 23:** The Irish Medicines Board (IMB) announced that, based on the findings of recent Seraxat [Paxil] studies by GSK, use of the drug showed an increased rate of self-harm and potentially suicidal behavior in this age group.<sup>15</sup>

**October:** The Australian Therapeutic Goods Administration reported that new antidepressants Remeron, Avanza and Mirtazon could cause potentially serious reactions such as convulsions, blood clots, **anxiety, agitation**, blood disorders, **nightmares**, and **hallucinations**.<sup>16</sup>

**December:** The UK Medicines Control Agency issued new guidelines advising against prescribing SSRIs to anyone under 18 because of an **increased risk of suicide**.<sup>17</sup>

## 2004

**March 22:** The FDA Public Health Advisory was issued, stating: "**Anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia [severe restlessness], hypomania [abnormal excitement, mild mania] and mania [psychosis]** have been reported in adult and pediatric patients being treated with [Paxil-like] antidepressants...both psychiatric and non-psychiatric."<sup>18</sup>

**March 22:** Medsafe, New Zealand's drug regulatory agency, sent a letter to prescribers regarding the use of Selective Serotonin Reuptake Inhibitors (SSRIs) in children and adolescents. The letter detailed concerns that had arisen over the past year relating to the possible risk of **suicidal ideation and behaviors**, citing FDA findings.<sup>19</sup>

**September 21:** The British Healthcare Products Regulatory Authority advised that it had issued guidelines that children should not be given most SSRI antidepressants because of an increased rate of harmful outcomes, **including hostility**.<sup>20</sup>

**October 15:** The FDA ordered pharmaceutical companies to add a "black box" to SSRI antidepressant packaging, warning that the drugs could cause **suicidal thoughts and actions in children and teenagers**. It also directed the manufacturers to print and distribute medication guides with every antidepressant prescription and to inform patients of the risks.<sup>21</sup>

**October 19:** The New Zealand Medicines Adverse Reactions Committee (Medsafe) recommended that **SSRI, Tricyclic and MAOI** antidepressants not be administered to patients under 18 years of age and were contraindicated in children under 13 years of age because of the potential increased risk of **suicide**.<sup>22</sup>

**December:** The Australian Therapeutic Goods Administration published an Adverse Drug Reactions Bulletin recommending caution in prescribing SSRIs to children and adolescents should be carefully monitored for the emergence of suicidal ideation, citing a recent study involving Prozac that showed an increase **suicide, self-harm, aggression and violence**.<sup>23</sup>

**December:** The European Medicines Agency's scientific unit, Committee for Medicinal Products for Human Use (CHMP) warned that Seroxit/Paxil could cause **suicide-related behavior in children and adolescents.** <sup>24</sup>

## **2005**

**April 25:** The European Medicines Agency's scientific committee concluded that all SSRI and SNRI antidepressants were associated with increased **suicide-related behavior and hostility** in young people. <sup>25</sup>

**June 28:** The FDA announced its intention to make labeling changes for Concerta and other methylphenidate (Ritalin) stimulants to warn of "psychiatric events such as **visual hallucinations, suicidal ideation, psychotic behavior, as well as aggression or violent behavior.**" <sup>26</sup>

**June 30:** The FDA issued an "Alert for Healthcare Professionals" about the antidepressant Cymbalta, concluding that **suicidal thinking or behavior** may increase in pediatric patients treated with any type of antidepressant, especially early in treatment. <sup>27</sup>

**June 30:** The FDA issued a Public Health Advisory entitled "Suicidality in Adults Being Treated with Antidepressant Medications," that stated that several recent scientific publications suggested the possibility of an **increased risk of suicidal behavior in adults taking antidepressants.** <sup>28</sup>

**July 1:** An FDA "Talk Paper," entitled "FDA Reviews Data for Antidepressant Use in Adults," said the FDA had asked antidepressant manufacturers to provide information from their clinical trials on possible **increased suicidal behavior in adults.** <sup>29</sup>

**August 4:** The Australian Therapeutic Goods Administration published an Adverse Drug Reactions Bulletin reporting evidence supporting an association between SSRI use and "**new onset of suicidality**" in **adults.** It usually developed shortly after commencing the drugs or after an increase in dosage that could cause **akathisia, agitation, nervousness and anxiety.** Similar symptoms could also occur during *withdrawal.* <sup>30</sup>

**August 19:** The Commission of the European Communities issued the strongest warning yet against child antidepressant use as the drugs caused **suicidal behavior including suicide attempts and suicidal ideation, aggression, hostility (predominantly aggression, oppositional behavior and anger) and/or related behavior.** <sup>31</sup>

**September 29:** The FDA issued a Public Health Advisory for Strattera (atomoxetine), a drug used to treat "ADHD" that directed Eli Lilly to revise the labeling to include both a boxed warning and additional warning statements that alerted health care providers to an increased risk of **suicidal thinking** in children and adolescents being treated with the drug.<sup>32</sup>

**September 29:** The UK Medicines and Healthcare Products Regulatory Agency (MHRA) said it would ensure updated patient information for Strattera include a warning of **increased risk of suicide** in children taking it.<sup>33</sup>

**November:** The FDA's Safety Information and Adverse Event Reporting Program reported "**homicidal ideation**" as an adverse event of Effexor ER (extended release).<sup>34</sup>

## 2006

**February:** Health Canada approved a new warning label for Paxil to warn that those taking it may experience unusual feelings of **agitation, hostility or anxiety, or have impulsive or disturbing thoughts, such as thoughts of self-harm or harm to others.**" Health Canada required Paxil's product information to detail a list of "rare" side effects, including **delusions, hostility, psychosis, and psychotic depression.**<sup>35</sup>

**February 9:** Japan's National Health Ministry directed pharmacy companies to revise labeling to warn that antidepressants could cause **suicide.**<sup>36</sup>

**May 12:** The FDA and GSK warned doctors that Paxil could increase the risk of **suicide in young adults.** It was the first drug manufacturer warning that linked an SSRI antidepressant to suicide in adults.<sup>37</sup>

**May:** The FDA warned that use of **antipsychotic** drugs like Seroquel can lead to a potentially fatal disorder called Neuroleptic Malignant Syndrome, characterized by muscle rigidity and fever (also associated with **agitation,** confusion and altered mental status). AstraZeneca's Web site on Seroquel warned potential users about the risks of **suicide.**<sup>38</sup>

**June 14:** Japan's Health Ministry ordered GSK to change its package insert for Paxil to add the caution that the drug can cause the risk of **suicidal action** for young adults.<sup>39</sup>

**August 21:** FDA said "ADHD" stimulant manufacturers had to strengthen their warning labels that stimulants could cause suppression of growth, **psychosis, bipolar illness, aggression,** and 'serious' cardiovascular side effects, including misuse could lead to sudden death from heart attacks and strokes.

**October 18:** The Australian Therapeutic Goods Administration ordered manufacturers of "ADHD" drugs, Ritalin, Strattera and dexamphetamine to add stronger warnings to their information packaging after receiving 200 complaints about the drugs, including 123 reports of adverse reactions involving Ritalin, including **somnolence and depression**; 23 reports about Strattera, including **aggression**, and 60 reports about dexamphetamine, including **agitation**.<sup>40</sup>

**December 13:** The FDA held a hearing into the relationship between antidepressants and suicide in those 18-25 years of age ("young adults"). The Committee indicated that evidence existed to extend the black box warning from age 18 to 25.

## 2007

**April:** The Australian Therapeutics Administration warned that antipsychotic drugs could cause heart inflammation, muscle rigidity and neuroleptic malignant syndrome (associated with **confusion, agitation and altered mental status**).<sup>41</sup>

**February 23:** Health Canada advised consumers not to use a "sleep aid" called *Sleepees*, because it was found to contain an undeclared drug estazolam, which could be habit-forming even when used for as little as a few months. Estazolam belongs in the class of drugs known as benzodiazepines (minor tranquilizers like Valium and Xanax).<sup>42</sup> The side effects included dizziness, drowsiness, **confusion, depression**, loss of memory and **hallucinations**.

**April 5:** The Australian Therapeutic Goods Administration ordered the manufacturer of the sleeping pill, Stilnox, to upgrade its warning about mixing the drug with alcohol because of reports of bizarre behavior that included sleep walking, but also "**hallucinations** and amnesia."

**May 2:** The FDA officially extended the age group for the black box warning about antidepressant inducing **suicidal thinking and behavior** from 18 to 24.<sup>43</sup>

**November 7:** The Japan Health Ministry ordered pharmaceutical firms to include warnings about the **increased suicide risk** associated with taking antidepressant drugs in patients aged 24 or younger.

## 2008

**January 31:** The FDA put out a warning to healthcare professionals about the **risk of suicidal thoughts and behavior** with a class of drugs called anti-

epileptics, many of which are also "mood stabilizers" used to treat "bipolar," including Carbamazepine, Neurontin, Lamictal and Depakote. The FDA stated that an increased risk of suicidal behavior and suicidal ideation was observed as early as one week after starting the drugs and continued through 24 weeks.

**February 5:** The UK Government's Medicines and Healthcare Products Regulatory Agency said antidepressant manufacturers would be required to update the warnings on **suicidal thoughts and behavior**.

<sup>1</sup> "FDA Reverses Course, Seeks Probe of Halcion Maker," *Los Angeles Times*, 1 June 1996, "Federal report targets Upjohn for 'misconduct,'" *The Houston Chronicle*, 1 May 1994.

<sup>2</sup> "FDA Reverses Course, Seeks Probe of Halcion Maker," *Los Angeles Times*, 1 June 1996.

<sup>3</sup> "Halcion called 'Killer Drug,'" *The Dallas Morning Herald*, 8 Oct. 1992.

<sup>4</sup> "Halcion and Prozac," *Consumer Reports*, Jan. 1993.

<sup>5</sup> "Who Takes Xanax and Why?," *Consumer Reports*, Jan. 1993.

<sup>6</sup> "Methylphenidate (A Background Paper)," U.S. Drug Enforcement Administration, Oct. 1995, p. 16

<sup>7</sup> <http://www.tga.gov.au/docs/html/aadrb1tn/aadr9602.htm>

<sup>8</sup> <http://www.tga.gov.au/adr/aadrb/aadr9908.htm>

<sup>9</sup> <http://www.patient.co.uk/showdoc/40025090/>

<sup>10</sup> Peter Breggin, "Paxil Withdrawal Suit Resolved," Breggin website, 2002.

<sup>11</sup> "Important Drug Safety Information-Paxil," *Health Products and Food Branch Canada*, July 2003.

<sup>12</sup> Veronique Mandal, "Anti-depressant: Petition targets Wyeth's Effexor; Users want public to know side effects," *Windsor Star*, Sept. 12, 2003; Sharon Kirkey, "Drug may make youths suicidal, doctors warned; Number of children on psychiatric drugs soaring," *Windsor Star*, Sept. 12, 2003.

<sup>13</sup> "New advice on prescribing antidepressants," Media release, Ministry of Health, New Zealand, 21 Oct. 2004.

<sup>14</sup> Veronique Mandal, "Anti-depressant: Petition targets Wyeth's Effexor; Users want public to know side effects," *Windsor Star*, Sept. 12, 2003; Sharon Kirkey, "Drug may make youths suicidal, doctors warned; Number of children on psychiatric drugs soaring," *Windsor Star*, Sept. 12, 2003.

<sup>15</sup> "Seraxat (Paroxetine) Contraindicated for Children," *Irish Medicines Board*, Sept. 23, 2003.

<sup>16</sup> "Convulsions and Blood Dyscrasias with Mirtazapine," The Australian Therapeutic Goods Administration (TGA), *Adverse Drug Reactions Bulletin*, Vol 22, No. 5, Oct. 2003, p. 18.

<sup>17</sup> "The SSRI Saga," *Young Minds Magazine*, 2004.

<sup>18</sup> "Worsening Depression and Suicidality in Patients Being Treated with Antidepressant Medications," US Food and Drug Administration Public Health Advisory, 22 Mar. 2004.

<sup>19</sup> "Re: Updated information and advice about the use of antidepressant medicines," Medsafe (NZ), 19 Oct. 2004.

<sup>20</sup> "Antidepressant aggression concern," BBC News, 21 Sept. 2004.

<sup>21</sup> Labeling Change Request Letter for Antidepressant Medications – FDA Letter, 15 Oct. 2004; "FDA orders strong 'black box' warnings on antidepressants used by children," *Associated Press Worldstream*, 15 Oct. 2004.

<sup>22</sup> "New advice on prescribing antidepressants," Media release, Ministry of Health, New Zealand, 21 Oct. 2004.

<sup>23</sup> "Use of antidepressants in children and adolescents," The Australian Therapeutic Goods Administration (TGA) published an *Adverse Drug Reactions Bulletin*, Vol 23, No. 6, Dec. 2004, p. 22.

- <sup>24</sup> "European drug regulators revisit SSRIs, warn doctors on antidepressants," Pharma Marketletter, 10 Dec. 2004; Press release, CHMP meeting on Paroxetine and other SSRIs, European Medicines Agency *Press office*, London, 9 Dec. 2004, Doc. Ref. EMEA/192570/2004.
- <sup>25</sup> "EU calls for tougher warnings on antidepressants for kids," News-Medical.Net, 25 Apr. 2005.
- <sup>26</sup> FDA "Statement on Concerta and Methylphenidate for the June 30 Pediatric Advisory Committee," 28 June 2005.
- <sup>27</sup> "Alert for Healthcare Professionals Duloxetine hydrochloride (marketed as Cymbalta). FDA, 30 June 2005.
- <sup>28</sup> "Suicidality in Adults Being Treated with Antidepressant Medications," FDA Public Health Advisory, 30 June 2004.
- <sup>29</sup> FDA "Talk Paper," entitled "FDA Reviews Data for Antidepressant Use in Adults," 1 July 2005.
- <sup>30</sup> "Suicidality with SSRIs: adults and children," The Australian Therapeutic Goods Administration (TGA Adverse Drug Reactions Bulletin, Col 24, No. 4, Aug. 2005, p. 14.
- <sup>31</sup> Commission of the European Communities Commission Decision concerning the placement on the market, under Article 21 of the Directive 2001/83/EC of the European Parliament and of the Council, of the medicinal products for human use which contain (lists of SSRI/SNRI antidepressants)," Brussels 19-VIII-2005, C (2205) 3256.
- <sup>32</sup> "Suicidal Thinking in Children and Adolescents Being Treated with Strattera (Atomoxetine)," FDA Public Health Advisory, 29 Sept. 2005.
- <sup>33</sup> "Updated warnings on the risk of suicidal thoughts with Strattera," UK Medicines and Healthcare Products Regulatory Agency. 20 Sept. 2005.
- <sup>34</sup> FDA's Safety Information and Adverse Event Reporting Program, Effexor XR, Nov. 2005.
- <sup>35</sup> Kate Jaimet, "'I've learned a lesson in the worst way possible': What drove a loving father to kill his son?," *Ottawa Citizen*, 27 Aug. 2006.
- <sup>36</sup> "Revised warning note of anti-depressant drugs: First mention of 'Risk of suicide'," *Chugoku Newspaper*, 9 Feb 2006
- <sup>37</sup> "Paxil's maker, FDSA warn of suicide risk," *Chicago Tribune*, May 13, 2006.
- <sup>38</sup> "Suicide victim was medicated, wife says," *The Journal News* (Westerchester County, New York), 2 May 2006.
- <sup>39</sup> "Danger of increasing attempt of suicide: The Health Ministry calls for attention on Paxil," Shimotsuke Newspaper, 14 June 2006.
- <sup>40</sup> Matthew Franklin, "ADHD drug risk for kids," *The Australian*, 18 Oct. 2006.
- <sup>41</sup> <http://www.tga.gov.au/adr/aadrb/aadr0704.htm>
- <sup>42</sup> "Health Canada advises consumers not to use herbal sleep supplement Sleepes which contains a habit-forming drug," Health Canada Advisory, 23 Feb. 2007.
- <sup>43</sup> <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01624.html>