Drug Regulatory Agency Warnings on Psychiatric Drugs and Violence

There have been 22 drug regulatory agency warnings from five countries and the European Union, on psychiatric drugs causing violence, hostility, aggression, psychosis, mania and homicidal ideation. These are as follows:

1. **United States, November 2005:** The FDA's Safety Information and Adverse Event Reporting Program reported "**homicidal ideation**" as an adverse event of **Effexor** ER (extended release).[1]

2. **United States, March 22, 2004**: The FDA issued a Public Health Advisory on **antidepressants** stating: "**Anxiety**, **agitation**, panic attacks, insomnia, **irritability**, **hostility**, impulsivity, **akathisia [severe restlessness]**, **hypomania [abnormal excitement, mild mania]** and **mania** [psychosis characterized by exalted feelings, delusions of grandeur and overproduction of ideas], have been reported in adult and pediatric patients being treated with antidepressants."[2]

3. **United States, October 1995**: The U.S. Drug Enforcement Administration (DEA) said **Ritalin** use could lead to addiction and that "**psychotic episodes**, **violent behavior** and **bizarre mannerisms** had been reported" with its abuse.[3]

4. **United States, June 28, 2005:** The FDA announced labeling changes for **Concerta** and other methylphenidate (**Ritalin**) products (stimulants) to include, "psychiatric events such as visual hallucinations, suicidal ideation**, psychotic behavior**, as well as **aggression** or **violent behavior**."[4]

5. **Canada, February 2006**: Health Canada approved a new warning label for **Paxil** that stated: "A small number of patients taking drugs of this type may feel worse instead of better. For example, they 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**.[5]

6. **Canada, June 03, 2004**: Health Canada issued an advisory to the public that stated people taking **antidepressants** at any age are at greater risk of behavioral or emotional changes including **self-harm** or **harm to others**. The advisory said, "A small number of patients taking drugs of this type may feel worse instead of better…. For example, they may experience unusual feelings of **agitation**, **hostility** or **anxiety**, or have **impulsive or disturbing thoughts that could involve self-harm or harm to others**."[6]

7. **Japan, May 2009:** The Japanese Ministry of Health, Labor and Welfare revised the label on newer antidepressants to warn that, "There are cases where we cannot rule out a causal relationship [of **hostility**, **anxiety**, and **sudden acts of violence**] with the medication."[7]

8. **European Union, August 19, 2005:** The Commission of the European Communities issued the strongest warning against child **antidepressant** use as recommended by Europe's Committee for Medicinal Products for Human Use (CHMP) stating that the drugs were shown to cause suicidal behavior including suicide attempts and suicidal ideation, as well as **aggression and hostility (predominantly aggression, oppositional behavior and anger)** and/or related behavior.[8]

9. **Australia, February 2009:** The Australian Therapeutic Goods Administration placed a boxed warning (the strongest warning) onto the ADHD psychostimulant drug methylphenidate (**Concerta and Ritalin**) for drug dependence. It warns that chronic abuse of methylphenidate can lead to a marked tolerance and psychological dependence with varying degrees of **abnormal behavior** and **frank psychotic episodes** can also occur.[9]

10. **Australia, December 2004:** The Australian Therapeutic Goods Administration published an Adverse Drug Reactions Bulletin recommending that any use of SSRI **antidepressants** in children and adolescents should be carefully monitored for the emergence of suicidal ideation and that there was an increase in adverse psychiatric events of suicide, **self-harm**, **aggression** and **violence**.[10]

11. **United States, July 01, 2009**: The FDA required the manufacturers of the smoking cessation aids varenicline (Chantix) and bupropion (Zyban, aka the antidepressant **Wellbutrin**) to add new Boxed Warnings and develop patient Medication Guides highlighting the risk of serious neuropsychiatric symptoms in patients using these products. These symptoms include changes in behavior, **hostility**, **agitation**, depressed mood, suicidal thoughts and behavior, and attempted suicide.[11]

12. **United Kingdom, March 2009:** Medicines and Healthcare products Regulatory Agency (UK) published in their Drug Safety Update newsletter new information about Atomoxetine (Strattera, a non-stimulant ADHD drug). They warned that Atomoxetine is associated with **treatment-emergent psychotic or manic symptoms** in children without a history of such disorders.[12]

13. **Australia, December 2008:** The Australian Adverse Drug Reactions Bulletin advised that the psychostimulant **Modafinil** has been reported to cause serious adverse skin and psychiatric reactions including **anxiety, hallucination, aggression**, and **mania**.[13]

14. **European Union, November 20, 2008:** Eli Lilly added to the label for **Strattera** in Europe warnings that the drug causes "hallucinations, delusional thinking, **mania** or **agitation** in children and adolescents without a prior history of psychotic illness or mania…"[14]

15. **United States, September 2007:** The Vice President of Medical Services at the drug company Cephalon sent out a letter to health care professionals informing them of new warnings for the company's psychostimulant **Provigil**. The letter stated that there are now "Warnings regarding serious rash, including Stevens Johnson Syndrome [a life-threatening

condition affecting the skin] and hypersensitivity reactions, and psychiatric symptoms (including **anxiety**, **mania**, hallucinations, and suicidal ideation)."[15]

16. **United States, February 21, 2007:** The FDA directed **ADHD drug** manufacturers to distribute "patient friendly" guides to consumers warning about serious psychiatric and cardiovascular problems, including stroke, heart attack, sudden death and psychotic reactions caused by ADHD drugs. The psychiatric adverse events included hearing voices, becoming suspicious for no reason, or **becoming manic**, even in patients who did not have previous psychiatric problems.[16]

17. **United States, August 21, 2006:** The FDA said that **ADHD drug** manufacturers have to strengthen their warning labels to warn that the drugs can cause suppression of growth, **psychosis**, bipolar illness, **aggression**, and 'serious' cardiovascular side effects, including misuse possibly leading to sudden death from heart attacks and strokes.[17]

18. **European Union, April 25, 2005:** The European Medicines Agency's scientific committee, the Committee for Medicinal Products for Human Use, concluded that **Prozac-type antidepressants** were associated with increased suicide-related behavior and **hostility** in young people. It recommended the inclusion of strong warnings across the whole of the European Union to doctors and parents about these risks and that the drugs should not be used in children and adolescents in off label situations.[18]

19. **United Kingdom, September 21, 2004:** The British Healthcare Products Regulatory Authority issued guidelines that children should not be given most SSRI antidepressants because of clinical trial data showing an increase rate of harmful outcomes, including **hostility**.[19]

20. **European Union, April 22, 2004**: The European Agency for the Evaluation of Medicinal Products issued a press release stating that, according to clinical trials, **Paroxetine** (**Paxil** in the U.S.) could cause suicidal behavior and **hostility** in children. It recommended that Paroxetine not be used in children and recommended that young adults be observed carefully for signs and symptoms of suicidal behavior or **hostility**.[20]

21. **Canada, August 22, 2003:** Wyeth Pharmaceuticals, the makers of the antidepressant **Effexor**, issued a warning to U.S. and Canadian doctors that use of this drug could cause **hostility**, suicidal ideation and **self-harm** in patients under the age of 18.[21]

22. **United States, May 2007:** The FDA published a warning on the psychostimulant **Desoxyn** stating that the drug could cause sudden death with pre-existing structural cardiac abnormalities or other serious heart problems, psychiatric adverse events including **aggression** and the **emergence of new psychotic or manic symptoms**, long-term suppression of growth, seizures, visual disturbance, as well as serious cardiovascular adverse event.[22]

[1] "Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) — November 2005," FDA MedWatch, November 2005.
[2] "WORSENING DEPRESSION AND SUICIDALITY IN PATIENTS BEING TREATED WITH ANTIDEPRESSANT MEDICATIONS," FDA Public Health Advisory, 22 Mar. 2004.
[3] "Methylphenidate," U.S. Drug Enforcement Administration (DEA), October 1995.
[4] "Statement on Concerta and Methylphenidate for the June 30 PAC", Food and Drug Administration (FDA), June 2005.
[5] 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.
[6] Jirina Vlk, "Health Canada advises Canadians of stronger warnings for SSRIs and other newer anti-depressants," Health Canada, 2004-31, June 3, 2004.
[7] "Japan Revises SSRI Warnings–Hostility, Violence," Medical News Today, May 28, 2009.
[8] 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, Brussels 19-VIII-2005, C (2205) 3256.
[9] "Boxed Warning, Contraindications and strengthened Precautions for Methylphenidate," Janssen-Cilag, February 2009.
[10] "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.
[11] "Information for Healthcare Professionals: Varenicline (marketed as Chantix) and Bupropion (marketed as Zyban, Wellbutrin, and generics)," FDA, July 1, 2009.
[12] Medicines and Healthcare products Regulatory Agency, Drug Safety Update newsletter, Vol. 2, March 8, 2009.
[13] Adverse Drug Reactions Advisory Committee, Australian Adverse Drug Reactions Bulletin, Vol. 27, No. 6, December 2008.
[14] "Official warnings issued: The ADHD drug Strattera CAUSES psychosis, hallucinations, mania and agitation" TransWorldNews, November 20, 2008.
[15] Jeffrey M. Dayno, M.D., "Dear Healthcare Professional," Cephalon, September 2007.
[16] "FDA Directs ADHD Drug Manufacturers to Notify Patients about Cardiovascular Adverse Events and Psychiatric Adverse Events," FDA News, February 21, 2007.
[17] "UPDATE 2-US FDA calls for new warnings on ADHD drugs", Reuters, August 21, 2006.
[18] "EU calls for tougher warnings on antidepressants for kids" News-Medical.net April 25, 2005.
[19] "Antidepressant aggression concern," BBC News, 21 Sept. 2004.
[20] "European Agency for the Evaluation of Medicinal Products: Committee for Proprietary Medicinal Products 20-22 April 2004″ EMEA, The European Agency for the Evaluation of Medicinal Products, Press Release April 2004.
[21] Wyeth Pharmaceuticals, "Dear Health Care Professional…" Health Canada, Health Products and Food Branch, August 22, 2003.
[22] Food and Drug Administration (FDA), "Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER)", FDA MedWatch, May 2007.