



Chronology of International Drug Regulatory Agency Warnings about Psychotropic Drugs

The following is a sample of psychotropic drug warnings that drug regulatory agencies around the world have issued. These show an ever-increasing awareness of the dangers and misuse of these drugs.

Antianxiety drugs (anxiolytics, benzodiazepines)

October–November 1991: The British Government banned the sedative-hypnotic Halcion because of dangerous side effects.

March 2007: The US Food and Drug Administration (FDA) warned that sedative-hypnotics could cause the dangerous side effect of “sleep-driving”—driving while not fully awake and having no memory of doing so. In February 2008, it also warned Halcion could cause swelling beneath the skin of the tongue, the voice box, as well as breathing difficulty, throat closing, or nausea and vomiting that suggest a severe whole-body allergic reaction.

Antidepressants

February 2000: The Australian Therapeutic Goods Administration (TGA) reported that antidepressants, especially the SSRIs Prozac, Zoloft, Paxil and Celexa, could cause nightmares.

June 2003: UK’s Medicines and Healthcare Products Regulatory Agency (MHRA) recommended that Seroxat (Paxil, Paroxetine) not be used to treat depression in people less than 18 years old because of the increased risk of self-harm and suicidal behavior.

August 2003: The TGA reported that the use of SSRIs during or after pregnancy may result in adverse reactions to newborn babies due to withdrawal effects, including agitation, jitteriness, poor feeding, sleepiness, lethargy and stomach problems.

October 2003: The TGA reported that the antidepressants Remeron, Avanza and Mirtazon could cause convulsions, blood clots, anxiety, agitation, blood disorders, nightmares and hallucinations.

March 2004: The FDA warned that SSRIs could cause “Anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia [severe restlessness that can lead to mania/psychosis], hypomania [abnormal excitement, mild mania] and mania [psychosis characterized by exalted feelings, delusions of grandeur].”

June 2004: Health Canada issued stronger warnings on newer antidepressants that people of all ages were at greater risk of behavioral or emotional changes including self-harm or harm to others.

August 2004: Health Canada issued a warning that newborns were at risk of complications if their mother took antidepressants during pregnancy. Reported symptoms included feeding and/or breathing difficulties, seizures, muscle rigidity, jitteriness and constant crying that required prolonged hospitalization, breathing support and tube feeding.

September 2004: The UK MHRA issued guidelines that children should not be given most SSRI antidepressants because of increased risk of suicide and hostility.

October 2004: The FDA ordered pharmaceutical companies add a “black box” warning that SSRI antidepressants could cause suicidal thoughts and actions in children and teenagers. New Zealand’s Medsafe and, later, Japan issued similar warnings. In May 2007, the FDA increased the age of risk to 24.

June 2005: The FDA warned about a potential increased risk of suicidal behavior in adults taking SSRI antidepressants.

August 2005: The TGA reported that SSRI antidepressants could cause “new onset of suicidality” in adults and also agitation, nervousness and anxiety, with similar symptoms occurring during withdrawal.

August 2005: The European Medicines Agency (EMA) issued its strongest warning against prescribing SSRIs to children because of the suicide risks, aggression, hostility and oppositional behavior and anger.

September 2005: The FDA warned that pregnant women taking antidepressants during their first trimester had given birth to infants with major heart defects or malformations. In March 2006, Health Canada issued a similar warning.

September 2005: The FDA directed Eli Lilly and Company to revise its Strattera labeling to include a “boxed warning” about the increased risk of suicidal thinking in children and adolescents. (Strattera is a newer antidepressant.)

October 2005: The FDA required Eli Lilly and Company to add a warning of liver damage to the packaging of its antidepressant Cymbalta.

November 2005: The FDA updated labeling for the antidepressant Effexor XR (extended release) that it could cause homicidal ideation [ideas].

July 2006: The FDA warned of the risk of a fatal lung condition in newborns whose mothers took SSRIs during pregnancy.

May 8, 2007: Germany's Federal Institute for Drugs and Medical Devices (IDMD) warned that Paroxetine (Paxil) increased the risk of cardiac malformation in newborns when the mother took the drug during pregnancy.

February 2008: The FDA warned that Emsam (antidepressant patch) could result in clinical worsening and suicide risk.

April–September 2008: The FDA added a warning to the safety label of Luvox, Celexa and Lexapro and for Selective Norepinephrine Reuptake Inhibitors (SNRIs) about increased risk of bleeding especially when taken with drugs that prevent blood clots such as aspirin. Australia issued a similar warning in October.

December 2008: The FDA ordered SSRI and SNRI antidepressant safety labeling to carry a risk warning of neuroleptic malignant syndrome.

March 10, 2009: Germany's IDMD added notification to SSRI packaging of increased risk of suicidal behavior in adults under 25 years old.

May 2009: Japan's Ministry of Health, Labor and Welfare (MHLW) revised the label warnings on SSRI antidepressants stating, "There are cases where we cannot rule out a causal relationship [of hostility, anxiety, and sudden acts of violence] with the medication."

August 2009: The TGA warned that Cymbalta could cause serotonin syndrome (excessive serotonin), the symptoms of which include restlessness, hallucinations, loss of coordination, fast heartbeat, rapid changes in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting and diarrhea.

Antipsychotics

August 2000: The FDA added a "black box" warning to the packaging of the antipsychotic drug Mellaril about the potential risk of fatal cardiovascular effects.

February 2002: The FDA added a "black box" warning to the package insert for Clozaril, about potential risk of myocarditis (inflammation of the heart muscle).

September 2003: The FDA requested the six atypical (newer) antipsychotic drug makers to caution about the potential risk of diabetes and blood sugar abnormalities.

June 2004: The TGA reported that atypical antipsychotics could increase the risk of diabetes.

April 2005: The FDA warned that the antipsychotics Zyprexa, Abilify, Risperdal and Seroquel use by elderly patients with dementia could place them at increased risk of death. In June 2008, it increased this warning to its strongest “black box” level.

April 2007: The TGA warned that atypical antipsychotics could cause life-threatening neuroleptic malignant syndrome, manifested by muscle rigidity, fever, delirium, unstable blood pressure and coma.

May 2007: The FDA approved safety label changes for the injectable form of Haldol to warn it could cause heart abnormalities and “sudden and unexpected death.”

August 2007: The TGA reported that all atypical antipsychotics could cause involuntary movements and muscle rigidity. More than 1,200 people who reported this condition had not recovered.

January 2008: The FDA added information to the safety labeling of Seroquel to warn of elevated cholesterol and serious heart conditions.

December 2008: South Africa’s Medicines Control Council warned that atypical antipsychotics placed elderly patients with dementia at increased risk of strokes, stroke-like events and death. The UK’s MHRA and the Irish Medicines Board issued similar warnings in March and April 2009 respectively.

April 2009: Health Canada warned that atypical antipsychotics could cause a potentially life-threatening condition called agranulocytosis, a reduction of a type of white blood cell leading to serious ailments.

June 2009: The MHRA warned that antipsychotic use may be associated with an increased risk of a potentially deadly blood-clotting condition.

Stimulants

August 2004: The FDA ordered the packaging for Adderall to include a warning about sudden cardiovascular deaths, especially in children with underlying heart disease.

June 2005: The FDA announced labeling changes on methylphenidate-based (Ritalin) products to warn they may cause “psychiatric events such as visual hallucinations, suicidal ideation [ideas], psychotic behavior, as well as aggression or violent behavior.”

February 2006: Health Canada added tougher warnings for Ritalin and similar stimulants cautioning those with a family history of heart problems or who engaged in strenuous physical activity that the drugs could increase blood pressure and pulse. In May it added

this could result in “cardiac arrests, strokes or sudden deaths.” And in September also warned the drugs could increase agitation and hallucinations.

October 18, 2006: The TGA ordered manufacturers of Ritalin and dexamphetamine to add stronger warnings because of complaints that Ritalin caused headaches, nausea, anorexia, drowsiness and depression.

February 21, 2007: The FDA warned that stimulants were associated with serious psychiatric and cardiovascular problems, including stroke, heart attack and sudden death.

October 17, 2007: Japan’s MHLW panel removed Ritalin from its list of approved medicines to treat depression because of its abuse potential.

January 2009: The EMEA said methylphenidate products (Ritalin, Concerta, Equasym, Medikinet and Rubifen) should carry warnings about associated psychiatric (hostility, psychosis, depression and mania), suicide and cardiovascular risks, and that those patients taking the drugs for more than a year should be reevaluated to determine whether treatment should be continued.

February 2009: The TGA required manufacturers to place a “boxed warning” on Concerta and Ritalin packaging, warning that chronic abuse could lead to addiction with abnormal behavior and psychotic episodes.

Mood Stabilizers

August 2000: The FDA ordered the manufacturers of drugs containing valproate (such as Depakote) to put a “black box” warning about potential fatal cases of inflammation of the pancreas.

March 2008: The FDA added a warning for Depakote about potential hypothermia (abnormally low body temperature), suicidal thoughts and altered thyroid function.

April 2009: The TGA reported that valproate was classified among drugs that have caused an increased incidence of birth defects.

April 2009: The FDA ordered eight mood stabilizers prescribed for “bipolar” (also used as antiepileptic seizure drugs) to carry a new warning regarding the risk of suicidal ideation [ideas].