U.S. National Library of Medicine
National Center for Biotechnology Information

**NLM Citation:** LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Antipsychotic Agents. [Updated 2017 Jul 20].
**Bookshelf URL:** https://www.ncbi.nlm.nih.gov/books/

# Antipsychotic Agents

Updated: July 20, 2017.

## OVERVIEW

Psychotic disorders include schizophrenia, the manic phase of manic-depressive illness (bipolar illness), acute psychosis and other conditions marked by acute, severe agitation. The antipsychotic medications are invaluable adjuncts to the treatment of psychosis and bipolar illness and have revolutionized management of these conditions.

The antipsychotic agents in clinical use include the phenothiazines and structurally similar compounds such as thioxanthenes, benazepines, butyrophenones, diphenylbutylpiperidines and miscellaneous similar heterocyclic compounds. The antipsychotic medications are usually classified into conventional and atypical agents, based upon relative risks for extrapyramidal side effects that are greater with the older, conventional agents. They are also referred to as first and second generation antipscyhotic agents.

The initial antipsychotic medications introduced into clinical practice were the phenothiazines, but they have been largely replaced in recent years by the atypical agents. Phenothiazines in current use (with initial brand names and date of first approval) include chlorpromazine (Thorazine: 1957, the initial prototype antipsychotic agent), fluphenazine (Prolixin: 1972), perphenazine (Trilafon: 1957), prochlorperazine (Compazine: 1956, used mostly as therapy of nausea rather than psychosis), thioridazine (Mellaril: 1978), and trifluoperazine (Stelazine: 1959). Miscellaneous conventional antipsychotic medications include haloperidol (Haldol: 1967), loxapine (Loxitane: 1976), molindone (Moban: 1974) and pimozide (Orap: 1984, used largely for Tourette syndrome). Lithium is also frequently discussed in the context of antipsychotic therapies, although its major use is for stabilization of bipolar illness.

The atypical antipsychotic agents are more recently introduced drugs that generally have greater potency and fewer extrapyramidal side effects. Currently, these are the most commonly used antipsychotic agents. They include aripiprazole (Abilify: 2002), asenapine (Saphris: 2007), brexpiprazole (Rexulti: 2015), cariprazine (Vraylar: 2016), clozapine (Clozaril: 1975-79, 1989), iloperidone (Fanapt: 2010), lurasidone (Latuda: 2010), olanzapine (Zyprexa: 1996), paliperidone (Invega: 2006), pimavanserin (Nuplazid: 2016), quetiapine (Seroquel: 1997), risperidone (Risperdal: 1993) and ziprasidone (Geodon: 2001). Some of these agents are also used to treat bipolar illness and major depression.

The phenothiazines are well established causes of drug induced liver disease and typically cause a cholestatic injury arising within 1 to 4 weeks of starting treatment. Indeed, during the 1960s and early 1970s, chlorpromazine was one of the most common causes of drug induced liver disease ("Thorazine jaundice"). The other phenothiazines were found to cause a similar cholestatic hepatitis, although much less frequently than chlorpromazine. The other conventional antipsychotic medications have been linked to liver injury only rarely, if at all, and do not exhibit a characteristic signature pattern of injury. Many but not all of the atypical

antipsychotic medications have been linked to serum enzyme elevations during therapy, but clinically apparent liver injury with jaundice from these agents is very rare.

- First Generation
  - Phenothiazines
    - Chlorpromazine, Fluphenazine, Perphenazine, Prochlorperazine, Thioridazine, Trifluoperazine
  - Other
    - Haloperidol, Lithium, Loxapine, Molindone, Pimozide
- Second Generation (Atypicals)
  - Aripiprazole, Asenapine, Brexpiprazole, Cariprazine, Clozapine, Iloperidone, Lurasidone, Olanzapine, Paliperidone, Pimavanserin, Quetiapine, Risperidone, Ziprasidone

## ANNOTATED BIBLIOGRAPHY

References updated: 20 July 2017

Zimmerman HJ. Neuroleptic drugs. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 483-91.

*(Expert review of hepatotoxicity of neuroleptic drugs including chlorpromazine and the phenothiazines, haloperidol, sulpiride, loxapine, molindone, pimozide, clozapine and risperidone published in 1999).*

Larry D, Ripault MP. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 443-62.

*(Review of hepatotoxicity of psychiatric agents).*

Meyer JM. Pharmacotherapy of psychosis and mania. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 417-55.

*(Textbook of pharmacology and therapeutics).*

Drugs for psychotic disorders. Med Lett Drugs Ther 2016; 58 (1510): 160-4. PubMed PMID: 27960194.

*(Concise review of drugs for psychiatric disorders mentions side effects of ALT elevations and hepatotoxicity for olanzapine only).*