

A timeline for neuroleptics

Excerpted from:

"The case against antipsychotic drugs: a 50-year record of doing more harm than good," by Robert Whitaker, author of *Mad In America: Bad Medicine, Bad Science and the Enduring Mistreatment of the Mentally Ill*.

Published in the journal *Medical Hypotheses* (2004)

62, 5–13

Preclinical

1883 Phenothiazines developed as synthetic dyes.

1934 USDA develops phenothiazines as insecticide.

1949 Phenothiazines shown to hinder rope-climbing abilities in rats.

1950 Rhone Poulenc synthesizes chlorpromazine, a phenothiazine, for use as an anesthetic.

Clinical history/standard neuroleptics

1954 Chlorpromazine, marketed in the US as Thorazine, found to induce symptoms of Parkinson's disease.

1955 Chlorpromazine said to induce symptoms similar to encephalitis lethargica.

1959 First reports of permanent motor dysfunction linked to neuroleptics, later named tardive dyskinesia.

1960 French physicians describe a potentially fatal toxic reaction to neuroleptics, later named neuroleptic malignant syndrome.

1962 California Mental Hygiene Department determines that chlorpromazine and other neuroleptics prolong hospitalization.

1963 Six-week NIMH collaborative study concludes that neuroleptics are safe and effective "antischizophrenic" drugs.

1964 Neuroleptics found to impair learning in animals and humans.

1965 One-year followup of NIMH collaborative study finds drug-treated patients more likely than placebo patients to be rehospitalized.

1968 In a drug withdrawal study, the NIMH finds that relapse rates rise in direct relation to dosage. The higher the dosage that patients are on before withdrawal, the higher the relapse rate.

1972 Tardive dyskinesia is said to resemble Huntington's disease, or "postencephalitic brain damage".

1974 Boston researchers report that relapse rates were lower in pre-neuroleptic era, and that drug-treated patients are more likely to be socially dependent.

1977 A NIMH study that randomizes schizophrenia patients into drug and non-drug arms reports that only 35% of the non-medicated patients relapsed within a year after discharge, compared to 45% of those treated with medication.

1978 **California investigator Maurice Rappaport reports markedly superior three-year outcomes for patients treated without neuroleptics. Only 27% of the drug-free patients relapsed in the three years following discharge, compared to 62% of the medicated patients.**

1978 **Canadian researchers describe drug-induced changes in the brain that make a patient more vulnerable to relapse, which they dub "neuroleptic induced supersensitive psychosis".**

1978 **Neuroleptics found to cause 10% cellular loss in brains of rats.**

1979 **Prevalence of tardive dyskinesia in drug-treated patients is reported to range from 24% to 56%.**

1979 **Tardive dyskinesia found to be associated with cognitive impairment.**

1979 Loren Mosher, chief of schizophrenia studies at the NIMH, reports superior one-year and two-year outcomes for Soteria patients treated without neuroleptics.

1980 NIMH researchers find an increase in "blunted effect" and "emotional withdrawal" in drug-treated patients who don't relapse, and that neuroleptics do not improve "social and role performance" in non-relapsers.

1982 Anticholinergic medications used to treat Parkinsonian symptoms induced by neuroleptics reported to cause cognitive impairment.

1985 Drug-induced akathisia is linked to suicide.

1985 Case reports link drug-induced akathisia to violent homicides.

1987 **Tardive dyskinesia is linked to worsening of negative symptoms, gait difficulties, speech impairment, psychosocial deterioration, and memory deficits. They conclude it may be both a "motor and dementing disorder".**

1992 **World Health Organization reports that schizophrenia outcomes are much superior in poor countries, where only 16% of patients are kept continuously on neuroleptics. The WHO concludes that living in a developed nation is a "strong predictor" that a patient will never fully recover.**

1992 **Researchers acknowledge that neuroleptics cause a recognizable pathology, which they name neuroleptic induced deficit syndrome. In addition to Parkinson's, akathisia, blunted emotions and tardive dyskinesia, patients treated with neuroleptics suffer from an increased incidence of blindness, fatal blood clots, arrhythmia, heat stroke, swollen breasts, leaking breasts, impotence, obesity, sexual dysfunction, blood disorders, skin rashes, seizures, and early death.**

1994 **Neuroleptics found to cause a swelling of the caudate region in the brain.**

1994 Harvard investigators report that schizophrenia outcomes in the US appear to have worsened over past 20 years, and are now no better than in the first decades of 20th century.

1995 "Real world" relapse rates for schizophrenia patients treated with neuroleptics said to be above 80% in the two years following hospital discharge, which is much higher than in pre-neuroleptic era.

1995 "Quality of life" in drug-treated patients reported to be "very poor".

1998 MRI studies show that neuroleptics cause hypertrophy of the caudate, putamen and thalamus, with the increase "associated with greater severity of both negative and positive symptoms".

1998 Neuroleptic use is found to be associated with atrophy of cerebral cortex.

1998 **Harvard researchers conclude that "oxidative stress" may be the process by which neuroleptics cause neuronal damage in the brain.**

1998 **Treatment with two or more neuroleptics is found to increase risk of early death.**

2000 **Neuroleptics linked to fatal blood clots.**

2003 **Atypicals linked to an increased risk of obesity, hyperglycemia, diabetes, and pancreatitis.**

References :

- [1] Cole J, Klerman G, Goldberg S. The National Institute of Mental Health Psychopharmacology Service Center Collaborative Study Group. Phenothiazine treatment in acute schizophrenia. *Arch Gen Psychiatry* 1964;10:246–61.
- [2] Gilbert P, Harris M, McAdams L, Jeste D. Neuroleptic withdrawal in schizophrenic patients. *Arch Gen Psychiatry* 1995;52:173–88.
- [3] Shorter E. *A history of psychiatry*. New York: Wiley; 1997. p. 255.
- [4] Hegarty J, Baldessarini R, Tohen M, Waternaux C. One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Am J Psychiatry* 1994;151:1409–16.
- [5] Holden C. Deconstructing schizophrenia. *Science* 2003; 299:333–5.
- [6] Weiden P, Aquila R, Standard J. Atypical antipsychotic drugs and long-term outcome in schizophrenia. *J Clin Psychiatry* 1996;57(Suppl 11):53–60.
- [7] Harvey P. Cognitive impairment in schizophrenia: its characteristics and implications. *Psychiatr Ann* 1999;29: 657–60.
- [8] Stip E. Happy birthday neuroleptics! 50 years later: la folie du doute. *Eur Psychiatry* 2002;17(3):115–9.
- [9] Brill H, Patton R. Analysis of population reduction in New York State mental hospitals during the first four years of large scale therapy with psychotropic drugs. *Am J Psychiatry* 1959;116:495–508.
- [10] Brill H, Patton R. Clinical-statistical analysis of population changes in New York State mental hospitals since introduction of psychotropic drugs. *Am J Psychiatry* 1962;119:20–35.
- [11] Council of State Governments. *The mental health programs of the forty-eight states*. Chicago: The Council; 1950. p 4–13.
- [12] Rusk H. States map a new attack to combat mental illness. *New York Times* 1954;21:4–13.
- [13] Epstein L, Morgan R, Reynolds L. An approach to the effect of ataraxic drugs on hospital release rates. *Am J Psychiatry* 1962;119:36–47.
- [14] Scull A. *Decarceration: community treatment and the deviant, a radical view*. New Brunswick, NJ: Rutgers University Press; 1984.
- [15] Schooler N, Goldberg S, Boothe H, Cole J. One year after discharge:community adjustment of schizophrenic patients. *Am J Psychiatry* 1967;123:986–95.
- [16] Prien R, Levine J, Switalski R. Discontinuation of chemotherapy for chronic schizophrenics. *Hosp Community Psychiatry* 1971;22:20–3.
- [17] Gardos G, Cole J. Maintenance antipsychotic therapy: is the cure worse than the disease? *Am J Psychiatry* 1977;133: 32–6.
- [18] Bockoven J, Solomon H. Comparison of two five-year follow-up studies: 1947–1952 and 1967–1972. *Am J Psychiatry* 1975;132:796–801.
- [19] May P, Tuma A, Dixon W. Schizophrenia: a follow-up study of the results of five forms of treatment. *Arch Gen Psychiatry* 1981;38:776–84.
- [20] Carpenter W, McGlashan T, Strauss J. The treatment of acute schizophrenia without drugs: an

investigation of some current assumptions. *Am J Psychiatry* 1977;134: 14–20.

[21] Rappaport M, Hopkins H, Hall K, Belleza T, Silverman J. Are there schizophrenics for whom drugs may be unnecessary or contraindicated. *Int Pharmacopsychiatry* 1978; 13:100–11.

[22] Mathews S, Roper M, Mosher L, Menn A. A non-neuroleptic treatment for schizophrenia: analysis of the two-year postdischarge risk of relapse. *Schizophr Bull* 1979;5:322–32.

[23] Bola J, Mosher L. Treatment of acute psychosis without neuroleptics: two-year outcomes from the Soteria Project. *J Nerv Ment Dis* 2003;191:219–29.