

01 - 1. Historical overview

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□ In 1915, Macht and Mora coined the term "psychopharmacology" when studying opioid alkaloids on rat behavior in a circular maze. □ In 1931 Sen & Bose, Indian physicians from Calcutta, reported on the antipsychotic properties of the plant Rauwolfia serpentina. Reserpine was rediscovered by Kline in 1954. □ In 1949, Cade in Australia discovered the use of lithium compounds in mania, initially on the basis of a presumed relationship between urate metabolism and mania. Lithium urate was prescribed to promote the solubility of uric acid. Later he noted that lithium ion itself had calming properties even in healthy controls. □ Between 1950 & 1952 presurgical antihistamine chlorpromazine was shown to have antipsychotic effects independently by Delay and Deniker's team, and Charpentier from Rhône-Poulenc in France. In 1955 Delay coined the term neuroleptic. □ The first true antidepressant was discovered in 1952. Mood lifting properties of Iproniazid, an anti-tuberculosis treatment, led to the discovery of the antidepressant class. But hypertensive reactions precluded the large-scale use of iproniazid. Imipramine, which was manufactured as chlorpromazine derivative, came to market soon after. □ The first benzodiazepine, chlordiazepoxide (Librium) was discovered serendipitously by the Austrian scientist Leo Sternbach in 1954. □ Kuhn (1958) discovered that among the various different psychiatric disturbances 'endogenous' depression responded best to imipramine. In 1961, second TCA amitriptyline was introduced. □ In 1958, Janssen synthesised butyrophenone haloperidol from pethidine. Wide scale use of antipsychotics started from this time. Antipsychotics came to be known as major tranquilizers while barbiturates and benzodiazepines were called minor tranquilizers. Large scale hospital discharges and deinstitutionalization started. □ 1963 Cheese reaction was proposed to be the mechanism for MAOI associated hypertension by Blackwell.

© SPMM Course □ Janssen synthesized an atypical agent risperidone in 1989.

□ Carlsson synthesized purpose made SSRI Zimeldine – but this was withdrawn due to the incidence of hypersensitivity syndrome and demyelinating disease that followed its use. □ In 1970s, Fluoxetine was tested as a noradrenaline reuptake inhibitor but was discarded as it had a poor activity in this regard. Later it was rediscovered as serotonin reuptake inhibitor, reaching the market in 1987. □ Kane et al. 1988 rediscovered clozapine via a multicentre randomized design comparing chlorpromazine vs. clozapine in 'treatment resistant' schizophrenia. 4% showed response to chlorpromazine while 30% showed response to clozapine. □ 1990s 'Prozac era' – widescale antidepressant prescription started □ Reappraisal of suicides associated with

antidepressant treatment – ‘black box warning’ issued for prescribing antidepressants to adolescents and children. □ CATIE study results published in 2005 – reappraisal of the usefulness of atypical and typical antipsychotics. CuTLASS study from UK follows with a demonstration of no apparent economic gain from atypicals.

Revision #1

Created 2026-01-04 20:04:04 UTC by Omar Ayman

Updated 2026-01-04 20:04:04 UTC by Omar Ayman