This Week's Citation Classic®

Janssen P A J, Niemegeers C J E, Schellekens K H L & Lenaerts F M. Is it possible to predict the clinical effects of neuroleptic drugs (major tranquilizers) from animal data? Part IV: an improved experimental design for measuring the inhibitory effects of neuroleptic drugs on amphetamine- or apomorphine-induced "chewing" and "agitation" in rats. *Arzneim.-Forsch.—Drug Res.* 17:841-5, 1967.
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Sixty-four neuroleptic drugs available in 1967 were systematically studied and compared for their effects on amphetamine- and apomorphine-induced agitation and stereotypy in rats. The study, which also includes protection from norepinephrine-induced lethality, is used as a basis for the classification of neuroleptic drugs. [The *SCI*® indicates that this paper has been cited in more than 190 publications.]

A More Precise Classification of Neuroleptics

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This paper is the fourth of a series published in *Arzneimittel-Forschung*, in which the relationship between animal data and clinical antipsychotic activity was explored and established on the basis of effects obtained with a large number of neuroleptic drugs. The first paper of the series[1] was a *Citation Classic* in 1986. Because of the chronicity and heterogenicity of schizophrenia, acute behavioral alterations in animals have rarely been considered representative for the human disease. Amphetamine is known to increase the release of dopamine, and amphetamine-induced behavior appears to be an appropriate experimental model, since amphetamine-induced psychosis in man is, in many respects, indistinguishable from paranoid schizophrenia.[2] Apomorphine is a postsynaptic dopamine receptor stimulant, and antagonism of apomorphine-induced effects has been directly related to the mechanism of action of neuroleptic drugs. It is still widely accepted that dopamine D_2 receptor blocking activity is a very important component in the antipsychotic activity of neuroleptics.[3,4] All known neuroleptics are dopamine receptor blockers.[5]

The separate study of agitation and stereotypy in both the amphetamine and apomorphine tests allowed a more precise classification of neuroleptics with respect to their sedative effects. Neuroleptics with a potent sedative component were found to inhibit agitation more readily than stereotypy. In the same study, the α_1 adrenergic blocking activity was evaluated in the norepinephrine test. Alpha$_1$ blockade is responsible in man for the autonomic side effects of neuroleptics.

The interest in this paper is undoubtedly due to the fact that it represents another attempt, different from parts 1, 2, and 3, to separate, on the basis of animal studies, the antipsychotic activity from the sedative and autonomic side effects in a large number of neuroleptics. The results indicate important experimental differences among neuroleptics, which are too often considered clinically "equivalent." Evaluation of these differences remains essential in the clinical selection of neuroleptics for individually adapted antipsychotic treatment.

1. **Janssen P A J, Niemegeers C J E & Schellekens K H L.** Is it possible to predict the clinical effects of neuroleptic drugs (major tranquillizers) from animal data? Part I. "Neuroleptic activity spectra" for rats. *Arzneim.-Forsch.—Drug Res.* 15:104-17, 1963. (Cited 470 times.) [See also: **Janssen P A J.** Citation Classic. *Current Contents/Life Sciences* 29(42):17, 20 October 1986.]
2. **Beamish P & Kiloh L G.** Psychoses due to amphetamine consumption. *J. Ment. Sci.* 106:337-43, 1960.
3. **Creese I, Burt D R & Snyder S M.** Dopamine receptor binding predicts clinical and pharmacological properties of antischizophrenic drugs. *Science* 192:481-3, 1976. (Cited 715 times.)
4. **Niemegeers C J E & Leysen J E.** The pharmacological and biochemical basis of neuroleptic treatment in schizophrenia. *Pharmaceut. Weekbl.—Sci. Ed.* 4:71-8, 1982.
5. **Niemegeers C J E & Janssen P A J.** A systematic study of the pharmacological activities of dopamine antagonist. *Life Sci.* 24:2201-16, 1979. (Cited 165 times.)

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