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

Paul A.J. Janssen
Janssen Research Foundation
Turnhoutseweg 30
B-2340 Beerse
Belgium

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 series1 was a Citation Classic in 1986. Because of the chronicity and heterogeneity 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 D2 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 α1 adrenergic blocking activity was evaluated in the norepinephrine test. Alpha1 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.