CC/NUMBER 42
OCTOBER 20, 1986

This Week's Citation Classic®

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.* 15:104-17, 1965.
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Forty neuroleptics available in 1965 were systematically studied, using 12 different test models in rats to evaluate behavioral effects, interactions with different amines, and normal body functions. The marked qualitative differences between the 40 compounds were the basis for their empirical classification. [The *SCI*® indicates that this paper has been cited in over 410 publications, making it the most-cited paper published in this journal.]

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August 25, 1986

When starting the Janssen Research Laboratories in 1953, it was obvious that the exploration of relatively simple pethidine-like molecules with narcotic activity was far from complete. In addition, the clinical discovery of chlorpromazine had just added a new dimension to centrally acting drugs. At least two major classes of therapeutic agents appeared to offer interesting fields for structure-activity studies. Pharmacologically, we soon learned to distinguish between morphine-like analgesics and chlorpromazine-like neuroleptics. Chemically, new piperidine and morpholine derivatives were synthesized and some were found to be potent morphinomimetics.

In 1957 molecules with a longer alkyl chain implanted on the piperidine nitrogen produced a blend of morphine-like and chlorpromazine-like effects. It took a few months more to get specific piperidine derivatives (the butyrophenones) with potent chlorpromazine-like activity but devoid of morphine-like effects. Haloperidol (R 1625) was selected and studied in great detail. Soon, the predicted potent neuroleptic activity of haloperidol was confirmed in psychiatry.

The early pharmacological studies with haloperidol and analogues indicated that qualitative differences between neuroleptics could be extremely well documented in rats by behavioral tests and interaction studies with amines such as amphetamine, norepinephrine, and tryptamine. It appeared, therefore, worthwhile to study all available neuroleptics in rats in order to reach a pharmacological rather than a chemical classification. This work was published as the first paper of a series of four in *Arzneimittel-Forschung*. It was the start of an extensive pharmacological and biochemical research effort to better define essential and accessory interactions of neuroleptics with different neurotransmitters.[1,2] The discovery of haloperidol itself has generated to date over 8,755 papers containing original pharmacological, biochemical, toxicological, and clinical observations on the first butyrophenone neuroleptic. Two compounds described in the *Arzneimittel-Forschung* paper, haloperidol and spiperone (spiroperidol), became the ligands for the discovery of dopamine-D_2[3,4] and serotonin-S_2 receptors.[5]

This paper could thus have been cited for several reasons. (1) It provided pharmacologists for the first time with an extensive basis to study new neuroleptics in rats. (2) After the clinical discovery of chlorpromazine, the studies in rats showed that new neuroleptics with various activity spectra could also be selected on the basis of laboratory investigations. (3) It gives a rather complete pharmacological activity profile of haloperidol, the archetype of the butyrophenones, and of chlorpromazine, the archetype of the phenothiazines and related compounds. (4) The data obtained in different standard tests, particularly that concerning apomorphine, amphetamine, conditioned reactions, tryptamine, norepinephrine, and epinephrine, provided a body of information for subsequent correlations with clinical activity,[6] and with *in vitro* receptor-binding studies to dopamine-D_2, serotonin-S_2, and α_1-adrenergic receptors.[7]

1. Niemegeers C J E & Janssen P A J. A systematic study of the pharmacological activities of dopamine antagonists. *Life Sci.* 24:2201-16, 1979.
2. Leysen J E & Niemegeers C J E. Neuroleptics. (Lajtha A, ed.) *Handbook of neurochemistry. Volume 9. Alternations of metabolites in the nervous system.* New York: Plenum, 1985. p. 331-61.
3. Seeman P, Chau-Wong M, Tedesco J & Wong K. Brain receptors for antipsychotic drugs and dopamine: direct binding assays. *Proc. Nat. Acad. Sci. US* 72:4376-80, 1975. (Cited 375 times.)
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