

The Haloperidol Story

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Haloperidol was synthesized on the 11th of February 1958 at the Janssen Laboratories, in Belgium. Soon after its synthesis and animal studies, which suggested to Paul Janssen and his colleagues that this butyrophenone drug would be of great interest as its action was similar but much more powerful than that of chlorpromazine, haloperidol was administered to humans at the Liege hospital. The subsequent clinical studies confirmed that this new drug was particularly active against delusions and hallucinations. The introduction of haloperidol in the United States of America was difficult for clinical and legal reasons. For many years, haloperidol had been widely used in western countries, until the introduction of "new antipsychotics."

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INTRODUCTION

Haloperidol was synthesized in 1958 by the Belgian laboratories Janssen and its clinical properties were discovered during the same year in Liège. It is certainly the most popular neuroleptic after chlorpromazine, and it has been probably the most used before the introduction of the "new antipsychotics." Its discovery was due to a different rationale than the one that had led to the synthesis of chlorpromazine by Rhône-Poulenc laboratories in 1950. Haloperidol opens a new chemical family, butyrophenones, but, from a clinical point of view, it belongs to the neuroleptic class as was defined in 1955 by Jean Delay and Pierre Deniker (see Table 1).

Janssen Laboratories

In 1935, Constant Janssen founded a pharmaceutical laboratory, which in 1953 manufactured a large variety of classical products mainly sold in Belgium. Paul Janssen, Constant's son, had understood that the paternal firm needed new products under licence to develop. Hence, he created a research center.

When haloperidol was synthesized in 1958, the Paul Janssen group comprised about 50 scientists. Palfium (dextromoramide), a powerful opioid analgesic, established the public reputation of Paul Janssen, and gave rise to a great number of international scientific contacts. As Paul Janssen told one of us

(BG), they used to synthesize as many molecules as possible, which were then screened by methods as simple as possible. Paul Janssen recognized that initially the process was unorganized, without any hierarchical structure. Most of his collaborators were autodidact and mainly non-academic, because the salaries were too low to hire classical scientists. Still a bachelor as many of his collaborators, Doctor Janssen was working from 6 a.m. until midnight every day of the week. Meetings were forbidden. He led his collaborators as a conductor, each of them playing a different instrument.

Synthesis of Haloperidol

Paul Janssen wanted to develop more powerful analgesics than dextromoramide. To do so, he decided to synthesize phenylpiperidine by-products rather than by-products related to dextromoramide. The idea of synthesizing by-products of meperidine (pethidine) rather than by-products of methadone proved to be very fertile (1–3).

Meperidine had been synthesized by O. Eisleb in 1939. Although it is less powerful than morphine and methadone, it is very simple and allows a large number of chemical variations. Paul Janssen had the idea of the synthesis of haloperidol after a conversation with a friend, Arnold Beckett, in London. Arnold Beckett, a chemist who was interested in the metabolism of meperidine, had concluded, albeit erroneously, that meperidine in itself was not active but needed a demethylation in order to become so. Although the transformation of meperidine into normeperidine is a simple process, it requires a considerable amount of energy. Paul Janssen then estimated that

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if Arnold Beckett's idea was right, a Mannich base of meperidine would be much more active. The synthesis of such a product is achieved very easily by using meperidine, acetophenone and formalin, and takes 30 minutes. The Mannich base of meperidine, known as propiophenone, was synthesized under the code name R 951. Numerous analogues followed, but these compounds resembled products synthesized by Merck and Lilly. As a result, it would have been difficult for Janssen laboratories to patent these products under its name. However, the Mannich base of meperidine injected in mice was 100 or even 200 times more active than meperidine. Such results seemed to confirm Beckett's hypothesis. To avoid the risk of Merck or Lilly issuing interdict proceedings, the chemists of Paul Janssen extended the lateral chain of this Mannich base, which led to the synthesis of the first butyrophenone, the R 1187.

The R 1625 or haloperidol was the forty-fifth butyrophenone synthesized by Janssen laboratories (Figure 1). This product had few similarities with meperidine and proved to be significantly less powerful than opioids but, curiously, whereas opioids excited mice, butyrophenones, in particular haloperidol, excited mice for around a quarter of an hour, then generated a cataleptic state and a sedation close to that provoked by chlorpromazine.

The R 1625 was synthesized by Bert Hermans on the 11th of February 1958. After a very simple chemical analysis, the

determination of its fusion point, its molecular weight, and its ultraviolet spectrum, the substance was ready to be tested and was labelled by the code name R 1625 on the 15th of February 1958. The animal tests started two days after.

Animal Studies on Haloperidol (4-7)

Two days after the synthesis of R 1625, R. Fredericks was the first to inject the R 1625 in a mouse at the dose of 10mg per kg. After the injection, the recovery reflex on the hotplate was completely inhibited and the reaction time was superior to 30s over three hours. The pupil's diameter did not change.

As part of their research into more relevant, cheaper, and more scientific animal tests, Janssen and his staff designed two simple and harmless tests: in the former, the diameter of the pupil was measured with a measuring microscope and in the latter, the duration of the licking reflex was recorded after the mouse had been exposed to a plate heated with a mixture of 50% acetone and 50% ethylformate, a combination that boils at 55 °C. By using these two simple tests, three pharmacological classes could be differentiated: anticholinergics, narcotic analgesics and neuroleptics.

First Clinical Studies on Haloperidol

Five weeks after its synthesis, R 1625 was given to C. Bloch, a psychiatrist in Brussels. He made an intravenous injection of two milligrams of R 1625 to a few patients suffering from delirium tremens. In a letter to Dr. J. Collard, the assistant of Pr. Divry in Liège, Mullie, in charge of clinical trials at Janssen's, wrote on the 4th of April 1958 that "the study of Dr Bloch shows that there are neither sedative effects after an intravenous injection of 2mg of R 1625 nor adverse reactions, leaving aside a slightly and temporary blood pressure decrease." Bloch had then to study the tolerance of the product, but not to assess clinical effects. Moreover, his name does not appear in any publication.

In less than 15 days, on the 16th of April 1958, Collard sent a letter to Mullie: "Yesterday I made the first clinical test with R 1625 under the supervision of Pr Divry. The patient was a young woman of 25 years old with a good physical condition who presented an emotional crisis (hypermotricity). A slow injection of 1ml was immediately followed by a slight sedation and three minutes later by drowsiness. Three hours later, the sedative reaction was still present, but to a lesser extent. Her blood pressure decreased from 120/70 to 95/70 mmHg while her heartbeat went from 25X4 (excitation) to 19x4 (sedation)." This letter is, thus, the first account of the effects of the psychiatric use of R 1625. According to other sources, and as has been confirmed by Doctor P. Janssen, the initiative of this first application of haloperidol was taken by A. Pinchard, resident in the department of Pr. Divry.

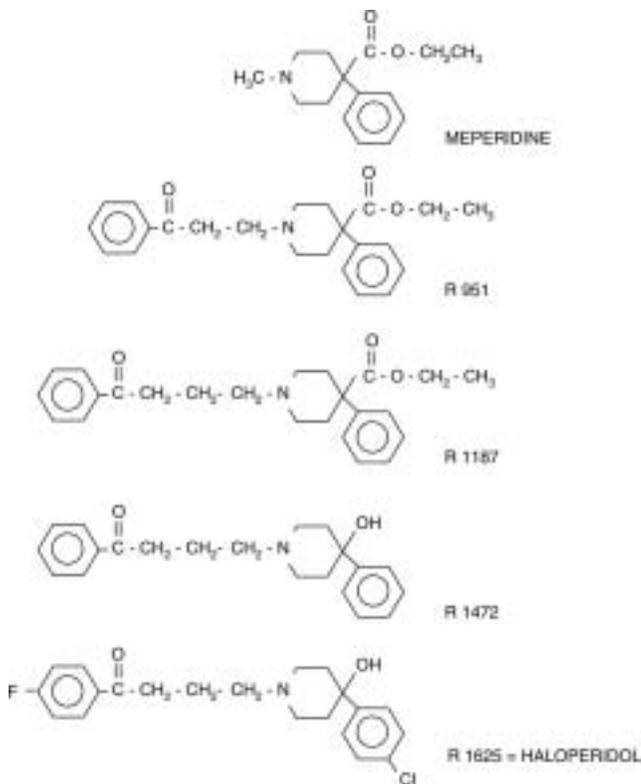


Figure 1 Design of haloperidol.

As the results were good, the Belgian psychiatrists decided to continue testing the drug. The first publication on R1625 was issued in *Acta Neurologica et Psychiatrica Belgica*, and entitled "R1625: a new symptomatic treatment of psychomotor agitation." The authors are P. Divy, J. Bobon and J. Collard (8). In the conclusion of this study on 18 agitated patients, the authors declare that haloperidol reveals itself a "powerful sedative of agitation." They add that being more sedative than hypnotics, this product presents a big advantage since "sedation without sleep does not affect the taking of food and allows a psychotherapeutic contact subsequent to the injection." They write at the end: "the excellence of the sedative action of R 1625 upon psychomotor agitation is such that this drug has become of common usage in our hospital department. From this single perspective alone, the R 1625 is of interest. We are expecting on an extension of its field of application." They do not mention neurological effects.

In their second publication (9), the psychiatrists of Liège complete their initial observations and provide a different analysis of the product. The article is entitled: "Study and clinical experimentation of R 1625 or haloperidol, a new neuroleptic and neurodysleptic." In their introduction, the authors write without hesitation:

the brilliant effects obtained intravenously in the symptomatic treatment of agitation have led us to continue the experiment by oral administration, as a long-term or symptomatic treatment of neuropsychiatric diseases. The first results published here are enough to show, as we had guessed during episodic injections, that R 1625 is not a basic sedative but a genuine neuroleptic. These neuroleptic effects even exceed the common frame. They are the most powerful that we know. The R 1625 easily produces a parkinsonism. This parkinsonism is known with chlorpromazine and reserpine. But here, parkinsonism is the norm, not the incident.

The year 1959 is notable for the conference of Beerse, which occurred in September. Janssen laboratories gathered there a fair number of authors having tried haloperidol. This international congress was held only one year and a half after the synthesis of the drug. In their inaugural report, Divry, Bobon and Collard declared: "We consider its hallucinolytic action to be greater than that of any other neuroleptic (10)." Fifteen reports were published in 1960 in *Acta Neurologica and Psychiatrica Belgica*. They were due to Divry, Bobon, Collard (Belgium), Delay, Pichot, Lempérière, Ellissalde (France), Boissier, Pany, Mouille, Forest (France), Chantrain, Meurice, Pairoux (Belgium), De Haene (Belgium), von Eiff and Jesdinsky (Germany), Gerle (Sweden), Humbeeck (Belgium), Kristjansen (Denemark), Loret (Belgium), Meurice (Belgium), Oles (Germany), Paquay, Arnould, Burton (Belgium), Scarlato and Rovetta (Italy), Seabra-Dinis and Moreira Da Silva (Portugal), Waelkens (Belgium). Following the Beerse congress, the reputation of the drug increased considerably.

French Clinical Studies on Haloperidol

At the international conference of Beerse, P. Pichot (11) presented the first French series signed by J. Delay, P. Pichot,

T. Lempérière and B. Elissalde. The communication of the French school, the most notorious at that time, most notably for its initial work on chlorpromazine and the conceptual frame of neuroleptics due to J. Delay and P. Deniker, involves 40 cases, all female ones.

The use of psychiatric appreciation scale of Wittenborn makes the originality of the French work. Until then, the French school was very reluctant to use this kind of scale and to use statistics more widely. Pierre Pichot had translated the scale of Wittenborn and got involved, initially about haloperidol, but later more generally in psychiatry, in spreading those instruments that are now fully part of the clinical battery. One can actually set the origin of this trend of French contemporary psychiatry to this initial study on haloperidol.

In their findings, Delay and his staff underline the interest of haloperidol: the action of haloperidol is mostly spectacular not only in the manias and the agitation states where a complete sedation is obtained in one or a few hours, but also in some chronic delusions that seemed resistant to treatments. The detailed report of the cases underlines the effect of haloperidol upon hallucinations and delusions.

In their conclusion, they add: "haloperidol raises some serious issues from a theoretical and practical point of view:

1. the relationship between therapeutic effects and neurological syndromes,
2. as a consequence of the previous point, the matter of dosage: we think desirable to maintain to a moderate level the neurological effects, which their intensity can lead to stopping the treatment, they can mask the results appreciation, and the therapeutic effect is not parallel to them."

The idea that extrapyramidal syndromes and acute dyskinesia have to be considered more like secondary effects rather than therapeutic ones is revealed, which goes against some of the ideas argued previously, for instance in the second publication of the Belgian psychiatrists.

The second French communication was presented at the "Société médico-psychologique" on the 21st of December 1959 (12). The conclusions are identical to the ones that were taken from the initial set of 40 patients.

The third French publication dates from July 1960 in the *Presse Médicale* (13). Its conclusions are even more drastic than that of the previous publication: "as far as paranoid states are concerned, haloperidol proved to be more efficient than the other neuroleptics. One should also notice the very powerful effect of haloperidol upon hallucinations that disappear so quickly that some long-time hallucinated patients are rather troubled by their lack and asked why they can no more experience them."

Haloperidol in the United States

Denber, Rajotte, and Kauffman (14) published a clinical note entitled "Problems in evaluation of R 1625" in the *American Journal of Psychiatry* in 1959. It states that the troubles of behavior sometimes got worse under haloperidol. The authors

Table 1 Main Events of the Haloperidol Story

Date	Event
1935	Setting up of Janssen Laboratories by Constant Janssen
1954	Constant's son, Paul, takes the first patent of Janssen Laboratories
1958, February 11	Synthesis of R1625 (haloperidol) by Bert Hermans in Beerse
1958, February	First animal studies of haloperidol at Janssen Laboratories
1958, March	Tolerance study by Bloch, in Brussels
1958, April	First clinical study in Liege (Department of P. Divry)
1958, October	First publication on R1625 by Divry P, Bobon J, Collard J
1959, September	International conference of Beerse
1959, October	First American publication by Denber HC, Rajotte P, Kauffman D
1969	Patent approval in the United States of America

even wonder whether the product with which they were provided was the same as the one used by authors reporting positive results. According to Paul Janssen, most of the patients of Denber's department suffered from hebephrenia. His collaborator, Mrs. Zimmermann, injected more and more concentrated haloperidol doses, which explains the worsening results that were at times noted. Besides, according to Paul Janssen, the American psychiatrists were rather reluctant to use chemotherapies, as they were influenced by Freudian theories. For them, admitting that a simple molecule could modify the human psyche was hard to accept.

Moreover, Janssen experienced serious difficulties in obtaining the patent in the U.S. Arnold Beckett, mentioned above — it was he, who, studying the metabolism of meperidine, had driven Janssen to the synthesis of by-products that led to haloperidol — received confidential information from Paul Janssen, and as an adviser to SmithKline & French's, he provided information on the work of Paul Janssen to that competitor which in turn attempted to synthesize molecules similar to haloperidol.

When the firm McNeil, Johnson & Johnson group subsidiary, attempted to register the patent for haloperidol and close products, it had to face the drastic rules of the American administration inherited from the thalidomide drama. From 1962 onwards, expanded security tests and clinical experiments were made compulsory by the Kefauver amendments to the Food, Drug and Cosmetic Act. Furthermore, an interdict was served by the patent office on the firm McNeil, since one of their submitted compounds was similar to a product presented by SK&F. Nevertheless after Janssen sued successfully SK&F, the patent was obtained in 1969 with a duration of 17 years until 1986. From 1969, haloperidol was widely used in the United States as a major tranquilizer.

CONCLUSION

Very rapidly after its synthesis in 1958, haloperidol was considered a major progress in the treatment of agitation and

psychosis. It is a very powerful drug, whose properties against delusions and hallucinations had been noticed by the first Belgian and French clinical investigators. For many years, haloperidol had been widely used in western Europe and the U.S., even if in this last country, its beginnings were not as easy as in Europe, for clinical and legal reasons.

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