

PSYCHOPHARMACOLOGY **UPDATE**



Janssen-Cilag – 50 years of innovation

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For more than 50 years, Janssen-Cilag has pioneered new treatments for mental illness that have revolutionised schizophrenia management and transformed the lives of thousands of patients. The company's history dates back to 1953, with the founding of Janssen Pharmaceutica by the Belgian chemist, Paul Janssen, who is widely recognised as one of the most creative and innovative scientists of the 20th century. As Janssen Pharmaceutica grew, it joined the Johnson & Johnson group and, in 1995, merged with the Swiss pharmaceutical company, Cilag. Today, Janssen-Cilag is one of the world's largest research-based drug discovery companies, operating in more than 40 countries and employing over 27 000 people globally.

Through the development of novel pharmaceuticals, Janssen-Cilag aims to improve quality of life for people with medical needs across the world. The company has a strong customer focus and identifies its primary responsibility as being towards the patients and medical professionals who use its products. Janssen-Cilag markets prescription medications across a range of therapy areas, including neurology, anaemia and HIV, but the company has a particularly distinguished heritage in the field of psychiatry. Under the leadership of Dr Janssen, researchers made a series of advances that not only radically changed schizophrenia management, but also helped to alter the public perception of mental illness. Through its continued commitment to the identification of novel chemical entities and innovative design of new delivery systems, Janssen-Cilag remains at the forefront of psychiatry research today.

1950s: Haloperidol

In the years following the Second World War, management options for schizophrenia were very limited. Lobotomy, insulin shock treatment and electroconvulsive therapy were all commonplace and patients frequently faced long-term (or even life-long) institutionalisation.

Determined to understand schizophrenia at the molecular level, Dr Janssen adopted a fresh approach that would help usher in the era of 'brain-based pharmacology.' He was struck by the similarities between some schizophrenic symptoms and the effects of amphetamine intoxication in professional cyclists using these drugs for their performance-enhancing properties. This prompted him to look for compounds that would antagonise the action of amphetamines in mice, a search that culminated in the discovery of the novel antipsychotic haloperidol. Amongst its benefits, this agent provided a fast and long-acting effect on positive symptoms and was relatively devoid of anti-adrenergic effects, such as sedation and sexual dysfunction.^{1,2}

The introduction of haloperidol was a major breakthrough. Finally, patients were offered relief from some of their most disturbing symptoms and many previously institutionalised patients could be discharged from hospital. By redefining treatment goals, haloperidol helped to instigate a shift in the way schizophrenia was perceived in both the medical community and the world at large. Research with haloperidol also provided evidence for the role of dopaminergic pathways in psychosis, which remains a central feature of pathophysiological theories of schizophrenia in the present day.

1960s: Haloperidol decanoate

Haloperidol quickly became established as a gold standard for schizophrenia treatment and patients worldwide benefited from this agent. However, poor adherence

was widely acknowledged as a major barrier to realising its full therapeutic potential. Non-adherent patients had high rates of relapse and rehospitalisation, and often cycled between discharge and subsequent readmission.

To address this significant clinical issue, researchers at Janssen Pharmaceutica developed haloperidol decanoate, a long-acting injectable formulation of haloperidol that for many patients could be administered once per month. With the improved adherence offered by this depot formulation, long-term discharge from hospital became a reality for thousands of patients. In many countries, this stimulated a paradigm shift in schizophrenia management that emphasised care in the community and recognised the feasibility of social reintegration.

1970s and 1980s: Continued advances

In the decades that followed, ongoing breakthroughs at Janssen led to the expansion of therapeutic options for patients with schizophrenia. Novel antipsychotics continued to emerge from their research and development programme, including bromperidol, fluspirilene and penfluridol.

Janssen also sought to improve the tolerability of antipsychotic drug regimens. At that time, a major limitation of medications for schizophrenia was their association with a group of movement disorders known as extrapyramidal symptoms (EPS). In response to this issue, Janssen launched dextetimide in 1972, an anticholinergic agent that effectively controlled EPS in patients receiving neuroleptics.

The 1980s was the first decade of true community care. As the hospital became displaced from the core of management, psychiatric services aimed to support patients as they live integrated in the community. During this period, a number of patient advocacy groups were founded, which strived to empower patients and their carers to become more actively involved in management decisions. In this new climate, research at Janssen focussed on developing the next generation of antipsychotics that could support patients living in the community, by delivering improvements in both positive and negative symptoms and offering an improved side-effect profile.

1990s: Risperidone

The influence of serotonin on schizophrenia has been recognised since the discovery of LSD and the psychotic symptoms associated with it. Key research conducted at Janssen demonstrated that the potent serotonin antagonist, ritanserin, when combined with conventional neuroleptics, improved negative symptoms and reduced the incidence of EPS. Equipped with this knowledge, researchers focussed on developing a single agent that could inhibit both dopaminergic and serotonergic neurotransmission.

The fruit of this strategy was the discovery of risperidone, an atypical antipsychotic that antagonises dopamine and serotonin receptors. With efficacy against both positive and negative symptoms and a low incidence of EPS at approved doses, risperidone was another major advance in schizophrenia management.³⁻⁶

The introduction of risperidone in 1993 brought benefits to patients, as highlighted by the famous quote from Dr Janssen: "physicians thanked me for haloperidol, but patients thanked me for risperidone." More than a decade and a half after its launch, risperidone has now been approved in more than 100 countries and is one of the most widely prescribed atypical antipsychotics in the world.

2000s: Long-acting injectable risperidone and paliperidone extended-release

As the new millennium got under way, the World Health Organization's 2001 World Health Report identified effective management of mental illness as a global priority.⁷

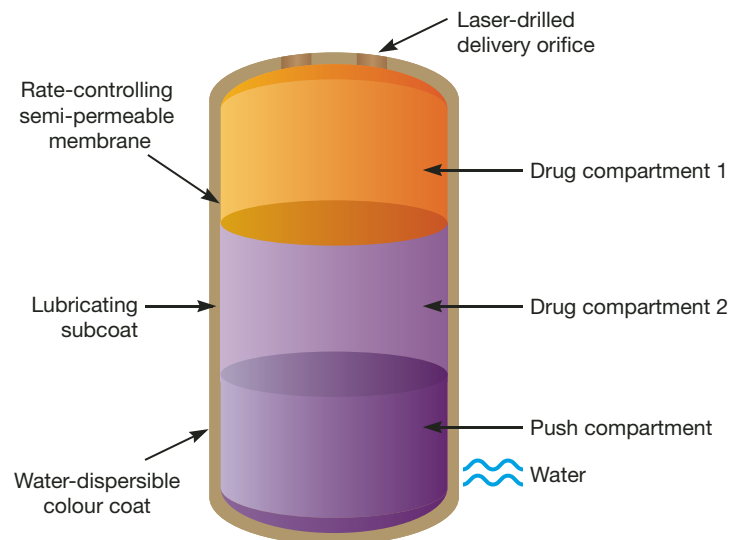
With patients worldwide benefiting from risperidone, Janssen-Cilag focussed on supporting patient adherence by developing a long-acting injectable form of this agent. In this aqueous formulation, unmodified risperidone is encapsulated within microspheres composed of a biodegradable glycolic acid-lactate copolymer. Once injected into the muscle, the copolymer is gradually hydrolysed, providing a slow and steady release of the drug.

As the first injectable formulation of an atypical antipsychotic, long-acting injectable risperidone raised the expectations for schizophrenia treatment still further, by offering effective symptom control, preventing relapse and rehospitalisation, and providing high levels of patient satisfaction.⁸⁻¹¹ Long-term remission (and relapse prevention) became an increasingly achievable goal.

A drive to increase choice for physicians and patients led Janssen-Cilag to develop paliperidone extended-release, a novel antipsychotic that combines high efficacy and a favourable safety profile with a reduced risk of hepatic drug-drug interactions.^{12,13} The extended-release formulation employs an advanced osmotic-controlled release oral delivery system (OROS®).¹⁴

Each capsule has a trilayer structure, with two drug compartments and an osmotically active 'push' layer enveloped by a semi-permeable membrane (see Figure 1). As the capsule travels through the gastrointestinal tract, water crosses the membrane at a controlled rate, causing the hydrophilic polymers in the core to swell and gradually push the drug through two laser-drilled orifices in the top of the capsule. This delivery mechanism ensures steady plasma levels of the therapeutic agent over a 24-hour period following a single dose (therefore avoiding peak and trough effects) and permits once-daily dosing.¹⁴

The availability of long-acting injectable risperidone and paliperidone extended-release increased choice for physicians and allowed the route and frequency of atypical antipsychotic administration to be tailored to the individual patient.



Looking to the future

The pace of development at Janssen-Cilag continues and new innovations on the horizon are set to further advance schizophrenia care. It is hoped that the licence for the risperidone long-acting injection will soon be extended in Europe to include deltoid administration. The deltoid formulation will give patients who find gluteal injection embarrassing the choice of having their injection in the arm. Both formulations are given every two weeks. Janssen-Cilag is also developing paliperidone palmitate, a long-acting injectable formulation of paliperidone that can be administered just once per month.

The last half-decade has seen the process of drug development evolve from a traditional functional pharmacological approach to embrace target-driven discovery strategies. Today, research at Janssen-Cilag remains at the cutting edge, with the use of genomics, electrophysiology, imaging techniques and biomarkers to boost the power of functional pharmacology and drive forward drug development.

Current thinking in psychiatry is also progressing, with many clinicians advocating a move from a purely categorical approach to mental illness to a dimensional system that explores the course of disease and recognises inter-patient variability in symptom patterns and severity. In line with this dimensional-functional thinking, Janssen-Cilag is researching personalised treatments for schizophrenia that will target both established and novel systems, with the aims of improving symptoms and modifying the underlying disease. The basis of this treatment will be an innovative fast D₂ receptor platform for the relief of positive symptoms, which can be combined with personalised 'plug-in' treatments to address individual symptomatology through specified targets. For example, dopamine D₃ receptor antagonists might be employed to reduce negative symptoms, or the 5-HT₆ receptor could be targeted in the hope of improving cognition.

The last 50 years of innovation in psychiatry owe a great deal to the inspiration and insight of Dr Paul Janssen, whose vision lives on in the pioneering research of the Janssen-Cilag team. Breakthrough drugs such as haloperidol, haloperidol decanoate, risperidone, long-acting injectable risperidone and paliperidone extended-release have all helped redefine treatment expectations and realise the revolution in schizophrenia care. Psychiatric services are no longer focussed on patient containment but on supporting patients in the community, and with these advances have come changes in the way mental illness is perceived in the world at large. Above all, these agents have paved the way toward the ultimate goal of complete social reintegration for people with schizophrenia.

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Summary of product characteristics can be found at:

Invega® (paliperidone prolonged release tablets):

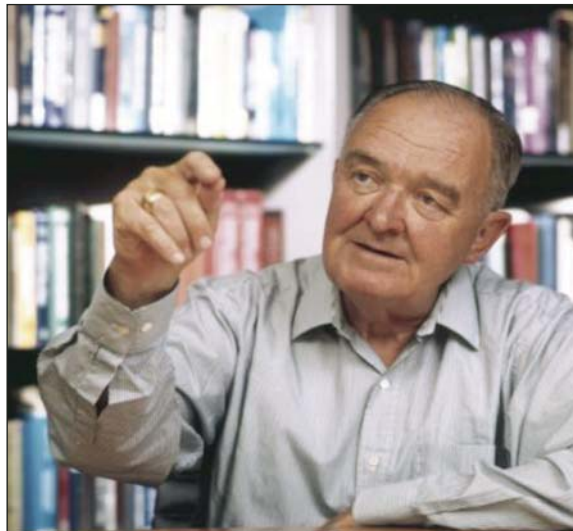
<http://www.emea.europa.eu/humandocs/PDFs/EPAR/invega/H-746-PI-en.pdf>

Risperdal® (risperidone):

http://www.emea.europa.eu/pdfs/human/referral/Risperdal/risperdal_annexI_IV_en.pdf

Risperdal® Consta® powder and solvent for prolonged-release suspension for intramuscular injection:

http://www.emea.europa.eu/pdfs/human/referral/risperdal-consta/risperdal_consta_annexI_III_en.pdf



Dr Paul Janssen (1926–2003)

The artwork on the cover is called Geostat and is by Ian Morris, a talented artist who experiences schizophrenia

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