Back to the Future of Psychopharmacology

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Iclepertin

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Schizophrenia affects millions worldwide, and for many, cognitive symptoms remain a persistent and debilitating challenge. A new drug, iclepertin, may soon change that. Iclepertin is an experimental treatment and glycine transporter 1 inhibitor designed to address the brain mechanisms underlying cognitive impairment associated with schizophrenia (CIAS).

Cognitive symptoms in schizophrenia are often present even before the onset of the illness and remain pronounced even after successful treatment with antipsychotics. These symptoms include impairments in working memory and executive functions, difficulties in expressing thoughts, reduced information processing speed and diminished attention [1]. CIAS are frequent and contribute to functional dysfunction in everyday life. They significantly reduce patients' quality of life, lead to poorer functional outcomes, while the severity of these impairments is considered the best predictor of long-term functional outcomes [2]. When it comes to antipsychotics and unmet needs, it is well-known that antipsychotics primarily address positive symptoms, such as delusions and auditory hallucinations, however, they are not effective in treating negative and cognitive symptoms. Currently, there are no approved pharmacotherapies specifically targeting CIAS.

To understand how glycine transporter inhibitors work, it is essential to have a basic understanding of glutamatergic neurotransmission. Glutamatergic synapses are responsible for excitatory neurotransmission in the cortex. Glutamate is the primary excitatory neurotransmitter, facilitating signal transmission from the presynaptic to the postsynaptic neuron, while glycine supports glutamatergic neurotransmission and functions in two main roles. The first one is as an inhibitory neurotransmitter in glycinergic neurons (in the brainstem) and the second one, which is more important for this context is, as a co-agonist for N - methyl D - aspartate (NMDA) receptors in glutamatergic neurotransmission (in the telencephalon and diencephalon) [3]. Glutamate is released presynaptically and first binds to α – amino – 3 – hydroxyl – 5 – methyl – 4 - isoxazolepropionic acid (AMPA) receptors. This binding opens channels that allow sodium ions to enter the postsynaptic neuron, leading to depolarization of the postsynaptic membrane. NMDA receptors are activated after magnesium dissociates from the receptor and both glutamate and glycine bind to it. This activation opens channels that permit the influx of calcium ions. The calcium signal in the postsynaptic neuron triggers intracellular pathways that enhance synaptic plasticity, a process crucial for learning and memory [4].

NMDA receptors provide excitatory stimulation to inhibitory GABAergic interneurons, which are essential for reciprocal signalling between excitatory glutamatergic neurons. This process supports the generation of coordinated neural oscillations and the overall synchronization of the neural network, both of which are crucial for cognitive function and sensory processing. In patients with schizophrenia, prolonged hypofunction of NMDA receptors, particularly in the prefrontal cortex, leads to impaired synaptic plasticity and reduced cognitive functioning. The mechanisms of NMDA receptor hypofunction in CIAS are linked to a reduced excitatory

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influence on NMDA receptors located on GABAergic inhibitory interneurons in cortical brain regions. This leads to reduced functional inhibition of excitatory pyramidal neurons by interneurons, a phenomenon known as the disinhibition of pyramidal cells. It causes an imbalance between excitation and inhibition, disrupting function in the prefrontal cortex [5].

It is well known that patients with schizophrenia exhibit measurable sensory disturbances and disruptions in neural networks, which can be assessed using neurophysiological parameters measured by electroencephalography (EEG). Deficits in cortical networks, including disruptions in gamma oscillations, are associated with cognitive processes such as working memory and executive functions. Unlike healthy individuals, patients with schizophrenia fail to increase the power of gamma oscillations in the dorsolateral prefrontal cortex during tasks that require working memory. The role of NMDA receptor hypofunction in CIAS is also supported by the effects of the NMDA receptor non-competitive antagonist ketamine. When administered to healthy individuals, ketamine induced psychotic symptoms, including cognitive impairments. Patients with autoimmune NMDA receptor encephalitis may experience psychotic symptoms, memory problems, and catatonic symptoms. Considering the evidence of NMDA receptor hypofunction in CIAS, it can be hypothesized that increasing synaptic glycine levels through GlyT1 inhibition could help normalize NMDA receptor hypofunction. This would lead to the subsequent optimization of glutamatergic neurotransmission and synaptic plasticity [6-8].

Previously studied glycine transporter inhibitors, such as sarcosine and bitopertin, unfortunately, did not reach phase III clinical trials. Iclepertin (BI 425809) is a new, potent, and selective GlyT1 inhibitor currently being developed by Boehringer Ingelheim for the treatment of CIAS. Target engagement, specifically the inhibition of GlyT1 in the brain, was assessed by measuring the increase in glycine levels in the cerebrospinal fluid of rodents, depending on the dose. The effects of this inhibition were evaluated in rodents in terms of sensory processing, cortical network function, and cognitive performance, including working memory and social recognition. The NMDA receptor antagonist MK - 801 was used to induce deficits in the cortical network, which were then measured by EEG to determine the effects of iclepertin on sensory processing and cortical network function. The results showed that iclepertin reduced MK - 801-induced deficits in, for example, N1 amplitude, as well as in 40 Hz ASSR-evoked gamma power. The increase in basal gamma power caused by MK-801 was significantly attenuated. These findings confirm the effects of GlyT1 inhibition by iclepertin on cortical network function, such as the brain's ability to synchronize

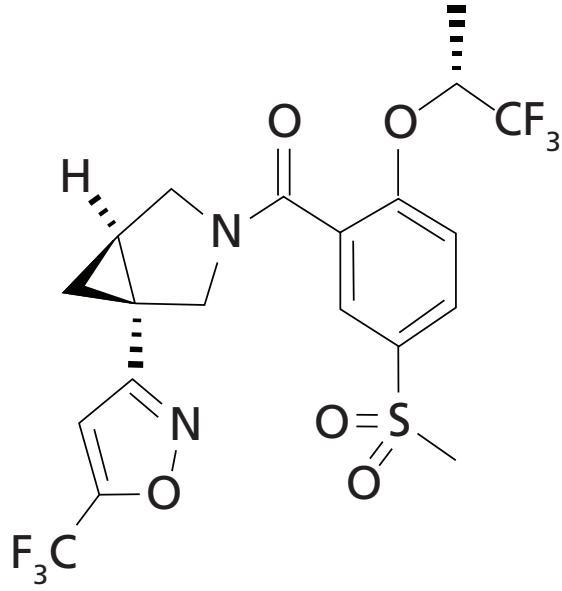

Figure 1. Chemical structure of iclepertin

neuronal oscillations with repetitive auditory stimuli. The pro-cognitive efficacy of iclepertin has been demonstrated, namely, it has been shown that iclepertin attenuates MK - 801-induced deficits in working memory in the spontaneous alternation task in mice. Additionally, it improves episodic memory function in rats, as assessed using the social recognition test with a 24-hour forgetting paradigm [9].

The results of Phase I clinical trials showed that iclepertin is safe and well-tolerated in healthy volunteers at multiple doses up to 75 mg once and twice daily (i.e., 150 mg daily). The efficacy and safety of iclepertin for treating cognitive impairments in patients with schizophrenia were evaluated in a Phase II randomized, double-blind, placebo-controlled trial with parallel groups. The study was conducted at 81 centers across 11 countries and included 509 adult male and female patients diagnosed with schizophrenia. Patients were randomly assigned (1:1:1:1:2) into groups receiving doses of 2 mg, 5 mg, 10 mg, and 25 mg, or a placebo. They received treatment once daily for 12 weeks alongside their stable antipsychotic therapy. Data from the Phase II trial in patients with CIAS showed significant cognitive improvements compared to placebo at the 10 mg and 25 mg doses of iclepertin, as measured by the MATRICS Consensus Cognitive Battery (MCCB) and the Schizophrenia Cognition Rating Scale (SCoRS). No additional benefit was observed with the 25 mg dose compared to the 10 mg dose [10,11]. Currently, three multinational Phase III trials are underway, further investigating the efficacy and safety of iclepertin in improving cognition and daily

functioning. The goal is to recruit 586 patients, aged 18 to 50 years, who have been treated with 1-2 antipsychotics (≥ 12 weeks on the current medication; ≥ 35 days on the current dose before treatment) and who exhibit functional impairments in daily activities. Patients will be randomized in a 1:1 ratio to receive either 10 mg oral iclepertin once daily (n = 293) or a placebo (n = 293) for a duration of 26 weeks. The trials include: CONNEX 1, CONNEX 2, and CONNEX 3, with an additional open-label study, CONNEX - X, aimed at expanding safety data [12].

The completion of aforementioned trials is expected in the first quarter of 2025. Assuming Phase III trials are successful, iclepertin could become the first approved pharmacotherapy to be taken once daily, effectively improving cognition with the potential to address the urgent, unmet clinical need for schizophrenia patients who live with the burden of CIAS on a daily basis.

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