**Back to the Future of Psychopharmacology**

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# Evenamide

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In light of the persistent struggles encountered with treatment-resistant schizophrenia (TRS), the pressing urgency remains for the development and implementation of novel therapeutic interventions, an essential requirement in the realm of health care as a notable portion of individuals diagnosed with schizophrenia exhibit minimal positive reactions to antipsychotic medications, even with proper treatment. TRS is characterized by an absence or insufficient alleviation of symptoms despite undergoing treatment with appropriate doses of two different antipsychotics belonging to distinct chemical categories for a considerable duration. Approximately 15 % of patients experience TRS right from the onset of the illness, while roughly one-third of all patients eventually encounter this condition [1].

Increasing evidence indicates irregularities in glutamate neurotransmission within TRS, which is an aspect not addressed by current antipsychotics. This, coupled with unaltered dopaminergic synthesis, sheds light on the inefficacy of the majority of conventional and newer antipsychotics. The absence of targeting glutamate-related abnormalities, despite their relevance, highlights why most typical and atypical antipsychotics fail to yield substantial benefits in TRS cases [2].

Evenamide, a newly developed oral compound, exhibits selective inhibition of voltage-gated sodium channels (VGSCs) while displaying negligible impact on over 130 other central nervous system (CNS) targets. VGSCs serve as fundamental ion channels responsible for neuronal excitability, playing a pivotal role in maintaining the resting potential and facilitating the creation and transmission of action potentials within neurons. The nervous system boasts a minimum of nine distinct sodium channel isoforms discovered thus far. Recent research has unveiled that these channels are not only integral to the normal electrophysiological functions of neurons but also show significant connections with various disorders. This revelation indicates the critical involvement of VGSCs in both normal neuronal function and the pathogenesis of diverse neurological and psychiatric conditions [2,3].

Primary action of evenamide involves the normalization of glutamate release, specifically induced by irregular sodium channel activity (veratridine-stimulated), without altering baseline glutamate levels, achieved through the inhibition of VGSCs. Notably, in animal models of psychosis, combinations of evenamide with various other antipsychotics, including clozapine, demonstrated beneficial outcomes. This suggests potential synergistic mechanisms that could offer advantages to individuals who demonstrate inadequate responses to current antipsychotics, such as clozapine [2,4].

The findings derived from Newron's study 014/015 yield notably positive outcomes. Evenamide exhibited excellent tolerability, eliciting minimal adverse effects, with 85 out of 100 patients continuing the treatment for 30 weeks. Furthermore, the extent of improvement observed among these individuals diagnosed with TRS, who previously showed little to no response to their current antipsychotic, was substantial. This improvement trend demonstrated an increase over time and is likely to hold significant clinical relevance. Should these findings

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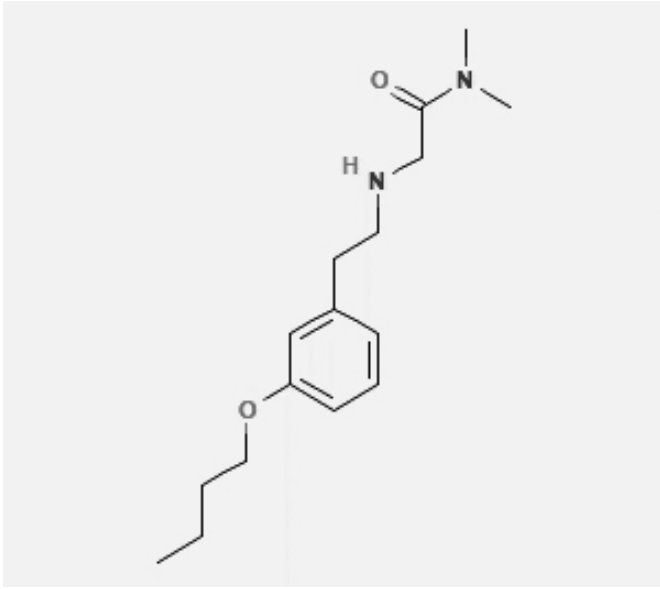


**Figure 1.** Chemical structure of evenamide

be corroborated through a forthcoming randomized and placebo-controlled trial, evenamide could potentially emerge as a medication capable of supplementing existing antipsychotics to ameliorate symptoms in cases of TRS [4,5].

## References


1. Labiotech UG. Newron announces interim results from treatment-resistant schizophrenia trial [Internet]. Berlin (DE): Labiotech UG; 2023 [updated 2023, cited 2024 Jan 6]. Available from: https://www.labiotech.eu/trends-news/newron-interim-results-treatment-resistan-schizophrenia-trial/
2. Newron Pharmaceuticals SpA. Newron announces striking six-month interim results from its exploratory clinical trial evaluating evenamide as add-on therapy for patients with treatment-resistant schizophrenia [Internet]. Bresso (IT): Newron Pharmaceuticals SpA; 2023 [updated 2023; cited 2024 Jan 6]. Available from: https://www.newron.com/news-and-media/regulatory-news/newron-announces-striking-six-month-interim-results-its-exploratory
3. Wang J, Ou SW, Wang YJ. Distribution and function of voltage-gated sodium channels in the nervous system. Channels (Austin). 2017;11:534-554.
4. ClinicalTrials.gov. Study to Determine the safety, tolerability, and efficacy of evenamide in patients with chronic schizophrenia [Internet]. Bethesda (US): National Library of Medicine; 2021 [updated 2021; cited 2024 Jan 6]. Available from: https://clinicaltrials.gov/study/NCT04461119
5. Outsourcing Pharma. Remarkable effect of evenamide, Newron's treatment resistant schizophrenia drug [Internet]. Crawley (GB): William Reed Ltd; 2021 [updated 2021; cited 2024 Jan 6]. Available from: https://www.outsourcing-pharma.com/Article/2023/10/10/Remarkable-effect-of-evenamide-Newron-s-schizophrenia-drug