Preclinical Pharmacology of Solriamfetol: Potential Mechanisms for Wake Promotion

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Abstract

Introduction. Solriamfetol is a wake-promoting agent (WPA) approved for the treatment of excessive daytime sleepiness associated with narcolepsy and obstructive sleep apnea. The wake-promoting mechanism of solriamfetol may result from dopamine and norepinephrine reuptake inhibition. Preclinical pharmacology studies were conducted to further elucidate the molecular targets activated by solriamfetol and compare them to that of known WPAs and traditional stimulants.

Methods. *In vitro* binding and functional studies were conducted in a panel of cell lines or membrane preparations expressing transmembrane receptors and monoamine transporters to measure the activity of solriamfetol, comparator WPAs, and traditional stimulants. Electrophysiology studies were conducted in slice preparations from mouse ventral tegmental area (VTA). Studies to measure locomotor activity and wake-promoting effects were conducted in mice.

Results. *In vitro* functional studies showed agonist activity of solriamfetol at human, mouse, and rat TAAR1 receptors. hTAAR1 EC_{50} values (10–16 μM) were within the clinically observed therapeutic solriamfetol plasma concentration range and overlapped with the observed DAT/NET inhibitory potencies of solriamfetol *in vitro*. TAAR1 agonist activity was unique to solriamfetol; neither the WPA modafinil nor the DAT/NET inhibitor bupropion had TAAR1 agonist activity. Solriamfetol (1–10 μM) dose-dependently inhibited the firing frequency of dopaminergic VTA neurons in mouse brain slices, similar to known TAAR1 agonists; however, these effects were inhibited by a D2 antagonist, suggesting a DAT-mediated effect. Unlike traditional stimulants, solriamfetol did not increase locomotor activity in naive mice, but inhibited the increase in locomotor activity in DAT knockout mice.

Conclusions. Preclinical studies have identified agonist activity at the TAAR1 receptor and, possibly, lower potency agonist activity at 5-HT1A receptors as potential pharmacological targets for solriamfetol, in addition to its activity as a DAT/NET inhibitor. Given the current understanding of TAAR1 agonists as modulators of monoamine transmission with potential wake-promoting effects in multiple preclinical species, agonist activity at the hTAAR1 receptor may represent an additional pharmacological target underlying the wake-promoting effects for solriamfetol, in addition to its DNRI activity.

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Psychiatric Inpatient Healthcare Resource Utilization and Treatment Patterns Among Patients With Predominant Negative Symptoms in Schizophrenia

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Abstract

Introduction. Currently approved treatments for schizophrenia (antipsychotics) have demonstrated effectiveness for treating positive symptoms; however, these agents are largely ineffective in treating other domains. Negative symptoms, including avolition, alogia, blunted affect, and asociality, are difficult to treat, and often persist despite adequate control of positive symptoms. Additionally, some patients experience "predominant" (moderate-to-severe negative symptoms that have greater relative severity than co-occurring positive symptoms) or "prominent" (severity of negative symptoms [moderate-to-severe] without any reference to positive symptoms) negative symptoms. These symptoms are known to have great impact on patient social functioning and quality of life, and are associated with poorer clinical course and outcomes for patients. Here, we examined inpatient healthcare resource utilization in patients with schizophrenia experiencing predominantly negative symptoms (PNS).

Methods. De-identified data were extracted from electronic health records in the NeuroBlu Database across 25 US mental healthcare providers. Positive and negative symptom data were derived from free-text records using natural language processing. PNS was defined as the presence of three or more negative symptoms and three or fewer positive symptoms at first clinical contact following schizophrenia diagnosis. Groups were balanced for baseline demographic and clinical characteristics by minimizing the generalized Mahalanobis distance and compared using chi-square and t-tests. Treatment patterns were visualized using Sankey diagrams.

Results. A total of 4444 patients with schizophrenia were identified and 8% were classified as PNS. A balanced cohort of 720 patients (50% PNS) was generated. Patients with PNS were more likely to be hospitalized in the 12 months following diagnosis (PNS: 76%, non-PNS: 60%, χ^2: 22.5, $p < 0.001$) and were switched to a second-line antipsychotic after a shorter first-line treatment duration. The most frequently prescribed antipsychotics differed between groups (PNS: risperidone, aripiprazole, haloperidol; non-PNS: risperidone, olanzapine, other atypical).

Discussion. This study demonstrates that negative symptoms in schizophrenia may be associated with worse illness course and

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