

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 EC₅₀ 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

higher healthcare resource utilization. There remains a need for new treatment options for patients with persistent, prominent, or predominant negative symptoms which specifically improve this historically hard-to-treat and assess symptom domain.

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Anticholinergics Should Not Be Used to Treat Tardive Dyskinesia: Insights From an Expert Panel of Psychiatry and Neurology Healthcare Professionals

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Abstract

Introduction. Tardive dyskinesia (TD) is a persistent and often disabling hyperkinetic movement disorder associated with prolonged exposure to dopamine receptor blocking agents (e.g., antipsychotics, antiemetics). The use of anticholinergics for the treatment of movement disorders including TD is a common practice, despite a lack of supportive evidence and the potential to worsen TD. Moreover, there are now FDA-approved medications specifically indicated for TD. Two virtual meetings were held with movement disorder experts from neurology and psychiatry to better understand the real-world use of anticholinergics for TD.

Methods. In November 2020, a panel of eight experts was convened to gather insights on the challenges of differentiating TD from other drug-induced movement disorders (DIMDs) and to discuss appropriate treatments for TD and other DIMDs. A follow-up meeting was held in June 2021 to consolidate these insights. Key recommendations based on the panel discussions are presented.

Results. The panel emphasized that while anticholinergics can help with managing some DIMDs, current evidence indicates that they are not effective in TD and may even worsen symptoms. Therefore, FDA-approved vesicular monoamine transporter 2 (VMAT2) inhibitors like valbenazine were recommended by the panel as first-line TD therapies. The panel noted that TD is often grouped under the term “extrapyramidal symptoms,” which leads to difficulty in differentiating TD from other DIMDs and the inappropriate treatment of TD with anticholinergics. The panel agreed that prophylaxis with anticholinergics is only appropriate in patients at high risk of acute dystonia. However, chronic anticholinergic use should be avoided whenever possible due to potentially serious adverse effects (e.g., cognitive difficulties) and anticholinergic burden, particularly in older patients. The potential for abuse, addiction, and diversion should also be considered when prescribing anticholinergics. Abrupt anticholinergic discontinuation can result in cholinergic rebound, which is

characterized by sleep disturbances, gastrointestinal problems, urinary urgency, and manifestations of DIMDs. Thus, when used appropriately (e.g., for acute dystonia), anticholinergics should be prescribed at minimally effective doses and slowly tapered for successful discontinuation.

Conclusions. These findings align with the current TD treatment guidelines, including the lack of evidence for anticholinergic use and recommended first-line treatment with approved VMAT2 inhibitors. Conclusions from this panel highlight educational needs across HCPs on the phenomenology of DIMDs, the inappropriate use of anticholinergics for TD, TD risks and assessment, and treatment strategies for TD.

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Interventions to Reduce the Role Strain of Informal Adult Caregivers of Individuals With Neurocognitive and Mental Disorders

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Abstract

Background. The value of the unpaid labor performed by caregivers is estimated to be at least \$306 billion annually, nearly double the combined costs of home health care (\$43 billion) and nursing home care (\$115 billion). However, studies show caregivers are at risk of developing high levels of physical, emotional, and mental strain, which can negatively impact their role, quality of life, and increase medical costs.

Purpose. The project aims to determine if giving informal caregivers non-pharmacological interventions such as self-guided bibliotherapy, stress reduction interventions, and improving health literacy will reduce the role strain of informal adult caregivers and improve their quality of life.

Method. This project employed a mix-method design focusing on the role strain and quality of life of relatives and friends assisting individuals with neurocognitive or mental health disorders. The subjects engaged in weekly self-guided activities for 8 weeks, and responded to survey questions regarding demographics, depression, anxiety, and stress levels. Personal health information (PHI) was not obtained. The subjects were required to answer qualifying questions. A \$5 Amazon gift card was given to participants who completed the project.

Results. Seven people enrolled in the project, but only four participated. All participants were female. Two were African Americans, one Caucasian, and one Hispanic. All four participants completed the pre-test, demographic surveys, and intervention. However, only two completed the post-test survey. One participant completed the pre-test and post-test on the same day at the end of the project.