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RESEARCH ARTICLE

Effects of a standardized extract of Withania somnifera (Ashwagandha) on depression and anxiety symptoms in persons with schizophrenia participating in a randomized, placebo-controlled clinical trial

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BACKGROUND: Extracts of Withania somnifera (WSE), or Ashwagandha, has traditionally been used as an adaptogen in Ayurvedic medicine, and evidence suggests that it may have efficacy in the treatment of psychiatric disorders, including schizophrenia. This secondary analysis reviewed change in depression and anxiety symptoms in a study using WSE as an adjunctive treatment in patients with schizophrenia experiencing an exacerbation of positive symptoms.

METHODS: We enrolled patients with schizophrenia in a 12-week, randomized, placebo-controlled, double-blind study. Active treatment was with 1,000 mg of standardized WSE. This analysis reviewed outcomes for 66 patients with depression and anxiety symptoms by examining the single-item depression and anxiety-depression cluster subscores extracted from the Positive and Negative Syndrome Scale.

RESULTS: Medium effect sizes of 0.683 (95% confidence interval [CI], 0.16 to 1.21) and 0.686 (95% CI, 0.16 to 1.21) favoring WSE over placebo were observed for depression single-item and anxiety-depression cluster scores, respectively. Adverse events were mild and transient.

CONCLUSIONS: Our findings suggest that WSE may hold promise in the treatment of depression and anxiety symptoms in schizophrenia. While the mechanism of its clinical efficacy requires more exploration, the data suggest that WSE may treat a broad spectrum of symptoms in exacerbated schizophrenia.

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INTRODUCTION

Depression and anxiety symptoms are common in schizophrenia. Most patients with schizophrenia have had an episode of depression, with up to 80% of patients experiencing depression during the early course of illness.[1] While depression can occur during the chronic stages of schizophrenia, it may be most prevalent in acute exacerbations, and the incidence of depression in this stage is estimated to range from 22% to 80%.[2] Anxiety, too, is common in schizophrenia, and nearly 40% of patients have a comorbid anxiety spectrum disorder.[3] Anxiety can also accompany depressive symptoms in schizophrenia and is common in acute episodes of psychosis.

While antipsychotics alone may relieve depression and anxiety in acute and post-psychotic depressive episodes, especially when combined with psychosocial interventions, antidepressant initiation is often recommended if symptoms persist,[2,4] although evidence to support this practice is mixed.[5-8] Limited evidence suggests that treatment of anxiety disorders comorbid with schizophrenia with selective serotonin reuptake inhibitors (SSRIs) can be effective[9]; less is known about effective treatment of anxiety emerging in acute psychosis. Treatment avenues for depression and anxiety symptoms in schizophrenia deserve further investigation. Individuals with schizophrenia and depressive symptoms have poor outcomes in multiple domains, including high utilization of mental health services as well as increased rates of substance use and forensic involvement.[1,10] Depression is a known precursor to suicide in patients with schizophrenia,[11] and rates of completed suicide in schizophrenia hover around 7%.[12]

Withania somnifera is a medicinal plant whose extracts have been long used in Ayurvedic medicine, and recent clinical trials suggest that extracts of this plant could be useful in the treatment of mental illness, especially for patients with anxiety or depression.[13-15] We conducted a randomized, double-blind, placebo-controlled trial of a standardized extract of Withania somnifera (WSE) in patients with schizophrenia who had experienced a recent exacerbation in psychotic symptoms. Withania somnifera extract was well tolerated and resulted in significant improvements for negative and general symptoms.[16] This report represents an analysis of secondary outcomes of this parent study, exploring our hypothesis that benefits in general psychopathology (symptoms other than positive and negative symptoms of schizophrenia) scores, as measured by the Positive and Negative Syndrome Scale (PANSS),[17] with WSE are reflected by improvements in depression and anxiety symptoms.

METHODS

We conducted secondary outcomes analyses of a 12-week, double-blind, randomized, placebo-controlled trial of a standardized WSE (Sensoril), used as an adjunctive treatment to antipsychotics, in 66 participants with recent exacerbations in positive symptoms of established schizophrenia spectrum disorders,[16] focusing on the potential antidepressant and anxiolytic effects of WSE.

Briefly, female or male outpatients age 18 to 75, of any race, with a DSM IV-TR diagnosis of schizophrenia or schizoaffective disorder were recruited and provided written informed consent. Symptom exacerbation had to extend ≥2 weeks but ≤1 year. Participants were enrolled only if their PANSS total score was ≥60, with a score ≥5 on any 1 item or ≥4 on any 2 items of the positive symptom cluster or unusual thought content. Inclusion criteria also specified that participants had to be receiving a stable dose of antipsychotic agents for ≥4 weeks. Exclusion criteria included pregnancy or breastfeeding, illicit drug use (marijuana and alcohol use were allowed on a case-by-case basis), unstable medical disorders, and known allergy to WSE.

The study comprised a 1- to 2-week screening period, and a 12-week treatment period for each patient; it was registered at ClinicalTrials.gov (Identifier: NCT01793935) and approved by the Institutional Review Board of the University of Pittsburgh. Participants were randomized to WSE or placebo. The WSE capsules were standardized and each contained 250 mg of the extract. The placebo capsules had the same fill weight as the WSE but only included inactive ingredients; the placebo capsules were exposed to cloth pouches containing WSE powder to make them smell like the WSE capsules.

The active group received 250 mg of WSE by mouth twice a day for a total dose of 500 mg/d for the first week. This was titrated to 500 mg twice daily (1,000 mg/d) at Week 2 and then maintained for the duration of the study. Medication dosage could be lowered based on patient tolerability. Pill counts and medication reconciliation were completed at each of the study's 6 visits to monitor for adherence. Any ongoing psychotropic medications

TABLE
PANSS depression and anxiety symptoms scores, baseline to end of treatment

	WSE		Placebo		
Measure	**Baseline n = 33**	**End of treatment n = 28**	**Baseline n = 33**	**End of treatment n = 31**	**Statistics**
Depression single-item,[a] mean ± SD	2.85 ± 0.94	2.25 ± 0.89	2.79 ± 0.93	2.71 ± 1.16	$t = 2.62$ df = 57 $P = .011$
Depression anxiety cluster,[b] mean ± SD	11.30 ± 2.82	8.89 ± 2.15	11.33 ± 2.59	9.97 ± 2.92	$t = 2.62$ df = 57 $P = .011$

[a]Score from the depression single-item of the PANSS.
[b]Score from the depression-anxiety cluster of the PANSS, which includes somatic concern, anxiety, guilt feelings, and depression.

PANSS: Positive and Negative Syndrome Scale; SD: standard deviation; WSE: standardized Withania somnifera extract (Sensoril).

(eg, antidepressants, anti-anxiety and hypnotic agents) were continued.

Primary outcomes were assessed using the PANSS total, positive, negative, and general symptoms scores. These assessments were conducted at each study visit. For the secondary outcomes, the PANSS single-item depression score was isolated to determine outcomes for depressed mood, as was the PANSS anxious/depression cluster, which encompasses PANSS items of somatic concern, anxiety, guilt feelings, and depression, similar to work done by previous research groups studying depression and anxiety symptoms in patients with psychoses.[18]

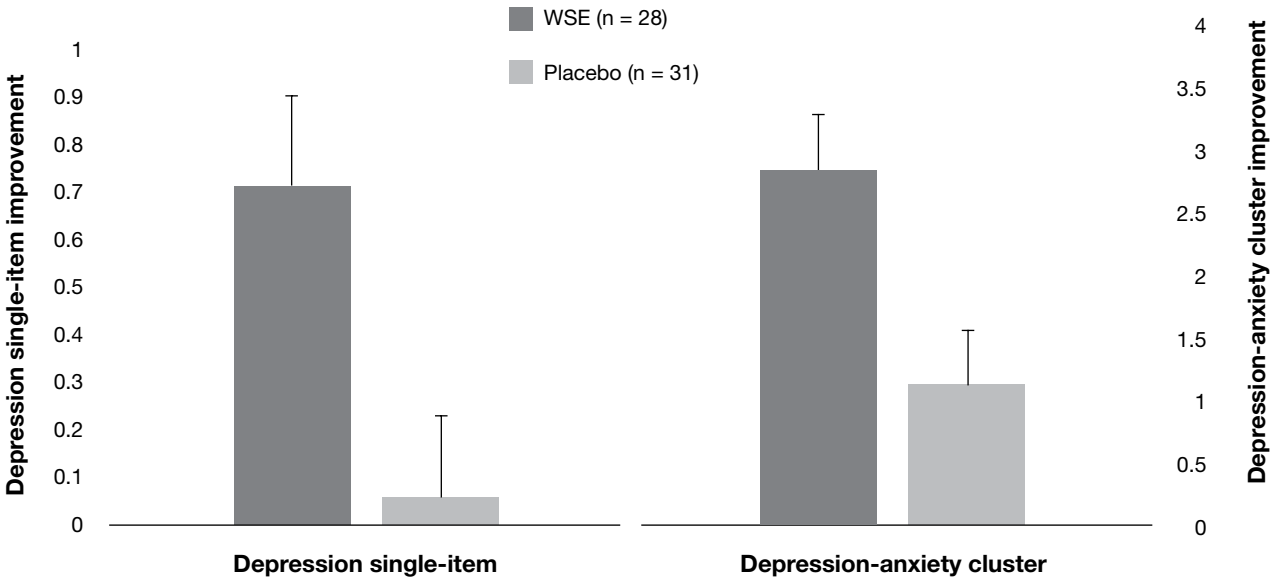
Homogeneity of treatment groups at baseline for demographic and illness variables, and for antipsychotic and other psychotropic medications, was established by examining the efficiency of randomization.[16] Independent *t*-tests were used to examine differences in the mean change scores from baseline to end of treatment, for depression single-item score, and the anxiety-depression scores between WSE and placebo groups. Significance levels were estimated using an alpha set at .05. The size of the treatment effect was computed using Cohen's *d* using the difference in means from baseline to endpoint, between WSE and placebo, divided by the pooled standard deviation.

RESULTS

None of the illness, demographic, or medication characteristics differed significantly between the WSE and placebo groups.[16] The mean duration of symptoms exacerbation was 16 weeks at the time of trial inclusion. Patients were, on average, in their 40s, had ≥7 lifetime hospitalizations over at least 20 years of illness, and had a DSM-IV-TR diagnosis of schizophrenia (61%). The remainder (39%) had a DSM-IV-TR diagnosis of schizoaffective disorder. Most patients were prescribed 1 atypical antipsychotic agent; daily olanzapine equivalents were similar between groups.[19] Other psychiatric medications, including antidepressants, mood stabilizers, anxiolytics, hypnotic/sedatives and anticholinergic agents, were evenly distributed between treatment groups. There were no significant changes in these medications during the study period between groups.[16] Two participants randomized to WSE had SSRIs decreased or stopped; no antidepressant changes were noted in the placebo group. One placebo participant had their anti-anxiety medication stopped, while another had their medication increased, but no such changes were made in the WSE group.

There were no significant differences at baseline between the 2 treatment groups for either the depression single-item score or for the anxiety-depression cluster score. At the end of WSE treatment, the mean improvement score for the depression single-item was significantly better at 0.71 ± 0.97 than for placebo, 0.06 ± 0.93. Mean change anxiety-depression cluster scores for patients who received WSE were also significantly higher (2.86 ± 2.56) than were mean change scores for patients who received placebo (1.19 ± 2.32) (**TABLE** and **FIGURE 1**). Medium treatment effect sizes of 0.683 (95% confidence interval [CI], 0.16 to 1.21) and 0.686 (95% CI, 0.16 to 1.21) favoring WSE over placebo were observed for depression single-item and anxiety-depression cluster scores, respectively.

FIGURE 1
Mean change scores in PANSS depression single-item and depression-anxiety cluster scores



PANSS: Positive and Negative Syndrome Scale; WSE: standardized Withania somnifera extract (Sensoril).

Withania somnifera extract was generally well-tolerated. Adverse effects, including somnolence, loose stool/diarrhea, and epigastric discomfort/stomach pain, were more commonly reported in the WSE group. However, there were no statistically significant differences between WSE and placebo for adverse events.[16]

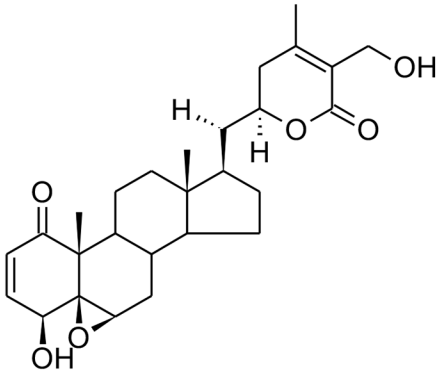
DISCUSSION

Our findings suggest that depression and anxiety symptoms in exacerbated schizophrenia may be significantly improved by adjunctive treatment with WSE. Evidence from previously reported clinical trials suggests that WSE has anti-anxiety properties in participants who are stressed,[15] participants reporting anxiety,[14] and in those with diagnosed anxiety disorders.[13] Withania somnifera extract has also shown to have antidepressant effects.[20] The effects of WSE in schizophrenia have not widely been explored; to the best of our knowledge, this study represents the only report of WSE being of benefit for mood and anxiety symptoms in schizophrenia.

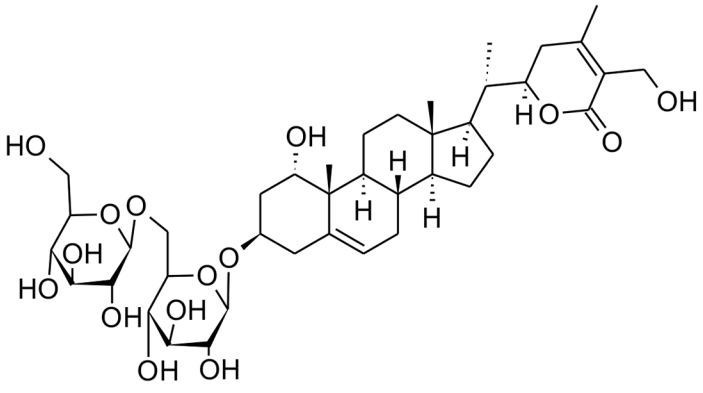
Immune and inflammatory pathways likely play a role in some depressive illnesses,[21] anxiety disorders,[22] and schizophrenia.[23] In schizophrenia and depression, antioxidants and anti-inflammatory agents have been investigated as adjunctive treatments.[24-26] Modern animal and human studies have confirmed WSE exhibits potent anti-inflammatory, immunomodulating, and antioxidant properties,[27-30] making it a candidate for the treatment of these major mental disorders. As noted in the primary study,[16] patients treated with WSE experienced a lowering of 2 inflammatory markers that were measured, high sensitivity C-reactive protein and S100 calcium binding protein B, relative to participants who were treated with placebo, but the data were significantly skewed and there were outliers in both groups. The differences in both markers from study entrance to completion were not statistically significant between treatments. While further exploration of WSE's mechanistic actions is needed, it is possible that restoration of disturbed immune-inflammatory homeostasis and poor antioxidant defenses by WSE helps remedy dysfunctional neural circuits and alterations in neurotransmitters associated with depression and anxiety symptoms in schizophrenia. As such, WSE may

FIGURE 2

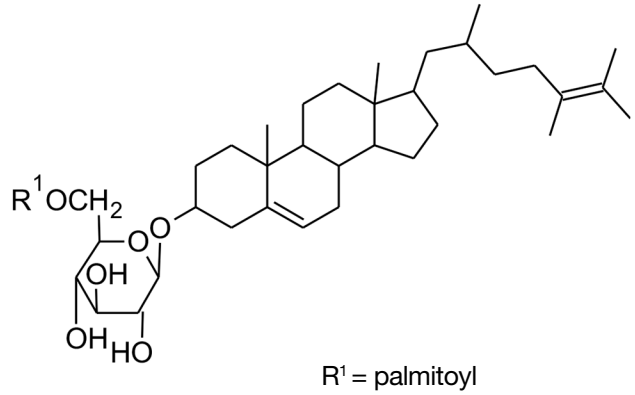
Chemical structures of bioactive constituents present in the standardized Withania somnifera extract (Sensoril) used in the study



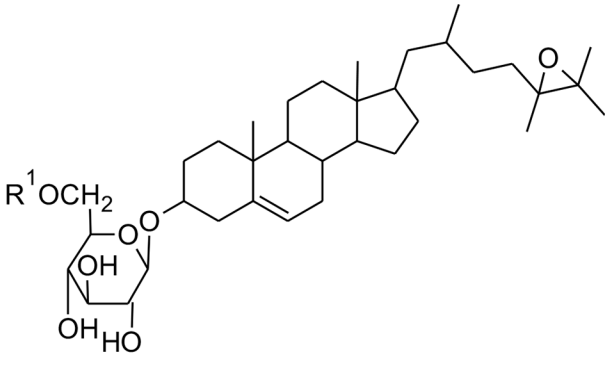
Withaferin A



Withanoside IV



R^1 = palmitoyl
Sitoindoside VII



R^1= palmitoyl
Sitoindoside VIII

represent a clinically well-tolerated treatment option for depression and anxiety in schizophrenia, regardless if these symptoms are related directly to the schizophrenia spectrum illness itself or if they are secondary to a comorbid mood or anxiety disorder.

A few points regarding the standardized WSE used in this study, the patented formulation Sensoril, are pertinent. Sensoril is comprised of a combination of a minimum concentration of the following bioactives: Withanolide glycosides: ≥8% (including withanosides and sitoindosides), carrier oligosaccharides: ≥32%, and Withaferin A: ≤2%.[31] **FIGURE 2** shows the medicinal chemistry structures of some of these compounds. Furthermore, in addition to ensuring batch-to-batch reliability of the product, including appropriate ratios of withanolides to aglycones, the lack of contaminants, toxins, microbes, and toxic heavy metals are important for replication of the clinical results of herbal botanical products.

Limitations

Our study was designed to recruit for individuals with exacerbation of positive symptoms of schizophrenia rather than for symptoms of depression and/or anxiety. We did not use scales specific to elucidating depression in schizophrenia (for example, the Calgary Depression Scale for Schizophrenia[32]). Interestingly, negative symptoms showed improvement under treatment with WSE, beginning at 4 weeks and becoming more sustained and robust at 12 weeks,[16] whereas depression and anxiety symptoms showed significant improvements in comparison with placebo only at the end of the 12-week treatment period. Further replication of our findings through a larger, prospective study focusing on the treatment of anxiety and depression in schizophrenia would be needed to validate our results.

CONCLUSIONS

Our findings suggest that WSE may hold promise in the treatment of depression and anxiety symptoms in schizophrenia. While the mechanism of its clinical efficacy requires more exploration, the data suggest that WSE may treat a broad spectrum of symptoms in exacerbated schizophrenia. ■

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