

Subtle changes in thyroid indices during a placebo-controlled study of an extract of *Withania somnifera* in persons with bipolar disorder

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ABSTRACT

Laboratory indices of thyroid function (TSH, Free T4, and T3) were measured in a randomized clinical trial in which *Ashwagandha* (ASW) was used to improve cognitive function in patients with bipolar disorder. This was done in light of a case-report of ASW-associated thyrotoxicosis, and data from mice administered ASW that showed significant increases in thyroxine levels. Ten (of the original 60) patients showed abnormal results in one of the thyroid measures either at the beginning or end of the 8-week study. One ASW-treated patient had subclinical hypothyroidism (TSH - 5.7 mIU/L) at baseline that normalized, and all three ASW treated patients experienced T4 increases from baseline (7%, 12%, and 24%). Six of 7 placebo-assigned patients showed decreases in T4 from baseline (4% to 23%), and one patient's TSH moved from the normal to subclinical hypothyroid range (6.96 mIU/L). As thyroid indices were done for safety, and not the primary goal of the original study, only 16.7% had abnormal thyroid indices, and as there was no sub-stratification for treatment assignment by thyroid status, unequal numbers of subjects received ASW ($n = 3$) or placebo ($n = 7$). In spite of these limitations, the subtle laboratory changes noted in thyroid indices in an 8-week study suggest that ASW may increase thyroxine levels, and therefore vigilance regarding hyperthyroidism may be warranted. Nonetheless, the thyroid enhancing properties of ASW may also represent a clinical opportunity for the treatment of subclinical hypothyroidism, and these results suggest the need for further study of the effects of ASW on thyroid indices, especially in those with bipolar and unipolar mood disorders.

Key words: Ashwagandha, bipolar disorder, depression, thyroid functions, subclinical hypothyroidism

INTRODUCTION

Dysfunction of the Hypothalamic-Pituitary-Thyroid neuroendocrine axis has been implicated in the pathogenesis of major depressive and bipolar disorders.^[1,2] Moreover, symptoms such as fatigue, tiredness, mental slowing,

concentration and memory impairments, weight gain and depression are common to both overt hypothyroidism and to unipolar depressive and bipolar disorders. Taking this into account, and as the relationship between lithium and hypothyroidism is well known,^[3] thyroid status is often assessed and monitored in mood disorders. Furthermore, there is some support for adjunctive treatment with thyroxine in treatment-resistant depression and in rapid-cycling bipolar disorder.^[1,2]

Extracts of the medicinal herb, *Withania somnifera* (called *Ashwagandha* in Sanskrit, ASW) have been used for centuries in Ayurvedic medical practice in India as an "adaptogen", i.e. to diminish and alleviate mental and physical stress. Modern data point to its immunomodulation, brain antioxidant, neuroprotective, anti-inflammatory, and memory-enhancing properties.^[4] We tested a standardized ASW extract (Sensoril[®]) for its pro-cognitive properties in patients with bipolar disorder.^[5] However, in view of a case-report of thyrotoxicosis associated with ASW,^[6] and animal data suggesting that ASW induces increases in thyroid hormones,^[7,8] we monitored serum levels of thyroid stimulating hormone (TSH), tri-iodothyronine (T3), and

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free thyroxine (T4) as safety parameters. The assessment of these thyroid indices in the bipolar study forms the basis of this report.^[5]

MATERIALS AND METHODS

The parent clinical trial, which has been described previously^[5] was registered at ClinicalTrials.gov (Identifier: NCT00761761). The study protocol obtained ethical approval by the internal review board and written informed consent was obtained from all participants. In brief, sixty subjects with bipolar disorder participated in an 8 week, randomized, double-blind, placebo-controlled trial. The intervention group received 500mg/day of standardized ASW (Sensoril®) extract in addition to their existing medication regimen, which included medications for treatment of bipolar disorder, comorbid psychiatric conditions, and other medical conditions. Thyroid-stimulating Hormone (hTSH) was measured in serum using a third generation, two-site immunoenzymatic (“sandwich”) assay with a reference range of 0.300-5.000 mIU/L in adults. Total T3 was measured in serum using a competitive binding immunoenzymatic assay with a reference range of 0.60 to 1.81 ng/ml. Free thyroxine in serum (T4) was measured using a direct, labeled antibody, and competitive immunoassay. During the tenure of the study, the T4 reference range initially was 0.76 to 2.12 ng/dL, but was changed to 0.80 to 1.80 ng/dL. The T4 values of two patients were impacted by this change in that they had one reference range at entry and a different one at study exit, and so the results of those two subjects were excluded. Subjects were diagnosed with Bipolar I, Bipolar II, or Bipolar Disorder not otherwise specified (*DSM-IV*), and their Young Mania Rating Scale and Montgomery-Asberg Depression Rating Scale scores were ≤ 10 for 4 weeks prior to study entry, with stable doses of their mood-stabilizing medication ≥ 4 weeks. Eligible subjects were randomized using a 1:1 randomization to ASW or placebo, starting at 250 mg/day orally, for 1 week and increasing to 250 mg twice daily beginning the second week until the end of the 8-week study. They were seen at six scheduled visits over a 2-month period. Thyroid indices were measured at baseline and the end of the study. Subjects whose thyroid indices fell outside the reference ranges either at study entry or upon completion of the study were mainly reviewed for this report.

RESULTS

Twelve (20%) of the 60 randomized subjects in the original study^[5] had values outside the reference range of one of the three thyroid indices however, the T4 results of two patients (receiving placebo) were excluded as these values

were confounded by a change in the laboratory reference ranges as noted earlier. Details of demography, diagnoses, and medications of the ten patients are provided in Table 1, and results of their thyroid indices are noted in Table 2. Patients with bipolar disorder comprised a group of adult men and women treated with mood stabilizers (lithium, valproate, and lamotrigine), anti-psychotic agents, and anti-depressant and anxiolytic agents, mostly in combinations. These psychotropic medications had been used for months to years in most subjects, and their mood ratings are reflective of a stable patient cohort at study entry and at exit. Only one of the group of 10 patients had pre-existing hypothyroidism, which was treated with levothyroxine.

Two subjects had TSH measurements in the subclinical hypothyroid range [Table 2]. One subject assigned to placebo received 150 micrograms/day of levothyroxine for hypothyroidism had a normal TSH value at study entry but was in the subclinical hypothyroid range (6.96 mIU/L) at exit. He experienced corresponding decreases in T4 and T3 and was counseled to review these changes with his primary care physician for further actions. Another subject who received ASW had an elevated TSH at baseline (5.7 mIU/L), which normalized upon study completion with a corresponding 23.7% increase in the free T4 level from baseline.

Three patients had elevated T3 values at study entry [Table 2], and two of them normalized upon completion, one having received ASW and the other placebo. A placebo-assigned subject continued to have abnormal T3 results at the beginning and at the end of the study.

Among those with abnormal free T4 values [Table 2], three placebo-assigned subjects had normal T4 values at baseline but moved below the lower reference limit (hypothyroid) at study exit, and a fourth subject who also received placebo had low T4 values at both time-points. One ASW treated patient had a low free T4 value at study entry, which normalized at study exit.

The percentage increases in free T4 levels in the three ASW-treated patients were 7%, 12.1%, and 23.7%. Among the placebo-assigned patients, with one exception, free T4 values decreased over a 2-month period, ranging from 3.9% to 23.3% with corresponding decreases in the T3 levels. Two patients (one placebo and one ASW) received lithium treatment, which in itself has been shown to effect thyroid indices. The ASW-treated patient had an elevated T3 that normalized, and interestingly the T4 levels increased by 12.1%, while TSH remained normal. The placebo-assigned patient had a normal T4 at baseline, but it dipped into the hypothyroid range at study exit; T3 decreased as well, but TSH remained normal.

Table 1: Demographics, illness, medications and mood ratings in an Ashwagandha trial

ID/Ashwagandha/ placebo	Age (years), sex, race	Diagnosis BPI, II, NOS	Thyroid associated diagnosis	Psychotropic medicines Daily dose	MADRS Total		YMRS Total	
					Screening	Exit	Screening	Exit
5/ASW	54, M, C	Bipolar I	None	Lithium 900 mg	2	1	3	1
28/ASW	63, M, C	Bipolar I	None	Quetiapine 500 mg	10	9	6	1
35/ASW	45, M, C	Bipolar I	None	Clonazepam 3 mg Valproate 2000 mg Aripiprazole 25 mg Benztropine 1 mg	8	2	1	2
12/placebo	27, M, A	Bipolar I	None	Aripiprazole 30 mg Mirtazapine 30 mg	10	5	4	4
13/placebo	22, F, C	Bipolar I	None	Lamotrigine 300 mg Ziprasidone 80 mg	1	1	7	2
29/placebo	62, M, C	Bipolar II	Hypothyroidism levothyroxine 150 micrograms/day	Lamotrigine 225 mg Escitalopram 20 mg	10	7	8	9
36/placebo	33, F, C	Bipolar NOS	None	Clonazepam prn Desvenlafaxine 100 mg Lamotrigine 200 mg Trazodone 100 mg Bupropion 100 mg	7	14	5	2
38/placebo	51, F, C	Bipolar II	None	Aripiprazole 15 mg Lamotrigine 150 mg Citalopram 30 mg	3	7	1	0
48/placebo	42, F, C	Bipolar II	None	Bupropion 400 mg Lithium 600 mg Lamotrigine 400 mg	10	6	7	6
52/placebo	37, F, C	Bipolar I	None	Bupropion 200 mg Lamotrigine 200 mg	1	0	2	0

ASW=Ashwagandha (Sensoril®), a standardized extract of withania somnifera. M=Male, F=Female, C=Caucasian, A=African-American. DSM IV TR Diagnosis: Bipolar I, II or NOS disorder. MADRS=Montgomery-Asberg Depression Rating Scale Total Score, YMRS=Young Mania Rating Scale Total Score. Total scores ≤8 on the YMRS and MADRS - mania and depression scales are generally seen as minimal to no symptoms, scores in the 8 to 15 range as sub-syndromal symptoms, and scores >16 as symptomatic, but of mild severity

Table 2: Thyroid indices in a clinical trial using Ashwagandha

ID	Ashwagandha/ Placebo	TSH (mIU/L) at screening	TSH (mIU/L) at exit	T ₃ (ng/mL) at screening	T ₃ (ng/mL) at exit	T ₄ (ng/dL) at screening	T ₄ (ng/dL) at exit	Percentage ↑ or ↓ in T ₄
5	ASW	2.648	1.4638	1.93 (A)	1.44	1.32	1.48	↑ 12.1
28	ASW	1.720	1.454	0.77	0.60	0.71 (A)	0.76	↑ 7.04
35	ASW	5.7 (A)	1.626	0.91	0.81	0.97	1.20	↑ 23.7
12	Placebo	2.895	1.116	1.09	0.9	0.98	0.7(A)	↓ 28.6
13	Placebo	0.939	0.921	2.06 (A)	1.86 (A)	1.08	0.93	↓ 13.9
36	Placebo	1.716	1.139	2.66 (A)	0.80	0.90	1.04	↑ 15.6
29	Placebo	3.219	6.963 (A)	0.95	0.80	1.10	1.01	↓ 8.2
38	Placebo	1.037	0.974	1.12	0.96	1.03	0.79 (A)	↓ 23.3
48	Placebo	2.999	1.996	1.43	0.98	0.86	0.78 (A)	↓ 6.9
52	Placebo	1.488	1.006	0.76	0.65	0.77(A)	0.74(A)	↓ 3.9

A=Abnormal value highlighted, ASW=Ashwagandha, TSH=Thyroid Stimulating Hormone (Normal Range: 0.3 to 5 mIU/L), T₃=Triiodothyronine (Normal Range: 0.6-1.81 ng/mL), T₄=Free Thyroxine (The reference range for Free T₄ was 0.76 to 2.12 ng/dL initially, later in the study it was changed to 0.8-1.80 ng/dL)

For the rest of the 60 patients whose thyroid indices were reported in the normal range, the three thyroid measures were analysed for baseline to end-point differences between the two treatment groups using the non-parametric Wilcoxon Rank Sum Test. Few patients were impacted by a change in the laboratory reference range for the T₄ test during the study period, and some had missing values for all three indices either at the beginning or at the end of the study, therefore the total number of

patients varied slightly for each test. However, none of the results were statistically significantly different for any of the thyroid measures reported as normal between the treatment groups. However, and interestingly, over a 2-month period, ASW treated patients (*n* = 18) showed numerically higher values of free T₄ (mean increase from baseline: 0.13 ± 0.24 ng/dl) compared to those receiving placebo, *n* = 19, (mean increase: 0.02 ± 0.18 ng/ml) even though this difference was not statistically significant.

DISCUSSION

Since the parent study was not designed to primarily examine thyroid function in bipolar patients treated with ASW,^[5] the sample size is small and unequally divided between patients who received placebo ($n = 7$) or ASW ($n = 3$). Furthermore, the thyroid tests were not repeated for confirmation. Nevertheless, as noted earlier, a case report of ASW-associated thyrotoxicosis,^[6] as well as animal studies^[7,8] showing increases in T4 levels in mice treated with ASW, prompted us to assess thyroid measures as a safety goal in the study. Increases in free T4 in the three ASW-treated bipolar patients are consistent with the data in mice administered ASW, which also experienced significant increases in T4.^[7,8] Moreover, TSH levels in the subclinical hypothyroid range (5.7 mIU/L) normalized in one ASW-treated patient, whereas the other two ASW-treated subjects had normal TSH levels throughout. T4 levels decreased by nearly 4% to 29% during an 8-week period among six of seven subjects assigned to placebo, and one subject who received placebo had a normal TSH level at entry but moved into the subclinical hypothyroid range (6.96 mIU/L) at study exit. This result occurred in spite of ongoing levothyroxine treatment. T3 levels decreased in all subjects regardless of treatment assignment (within the normal range with one exception). Interestingly; in one set of animal experiments, ASW had no statistically significant impact on the enzyme iodothyronine 5'-mono-deiodinase, which is primarily responsible for the extra-thyroidal conversion of T4 to T3.^[7] The authors opined that ASW's actions are mainly driven by stimulation of the thyroid gland to release T4,^[7] though the precise mechanism(s) remains unknown.

Typically, overt hypothyroidism (clinical symptoms along with TSH levels >10 mIU/L) is treated with levothyroxine in the general population,^[9,10] and also in patients with mood disorders. However, as in the general population, the use of levothyroxine in those mood disorder patients in the subclinical hypothyroid range (i.e. TSH levels from 4.5 to ≤ 10 mIU/L and lacking thyroid antibodies and/or other risk factors) remains somewhat unclear and is not without risk or controversy.^[9-11] Studies have suggested the use of adjunctive thyroxine in treatment-resistant depression or supra physiological doses of thyroxine in rapid cycling bipolar disorder^[1,2] but such treatments have not gained wide acceptance.

What can we learn from this preliminary dataset? Possibly, these changes in thyroid measures occurred randomly, or were caused by an interaction of ASW with the existing medication, or were an independent

effect of ASW on the thyroid gland/receptor. These explanations require further investigation. Interestingly, however, all three ASW-treated patients showed a rise in free T4 (although small changes) similar to the results in animal experiments^[7,8] but replicative studies are required to confirm these early data. At best, this early report is suggestive of the T4 elevating actions of ASW. Future prospective studies that are hypothesis driven with an adequate sample size to demonstrate a thyroid promoting effect for ASW are required. Moreover, confirmatory and repeat laboratory testing of thyroid indices in future work will provide greater confidence of the results obtained in this study. Therefore, even though a single case of thyrotoxicosis associated with ASW has been reported in the literature, vigilance may be well advised when ASW is utilized in clinical practice. This highlights the importance of thyroid function testing before starting ASW among Ayurvedic or other healthcare practitioners and emphasizes that repeat testing may be required if there is clinical suspicion of hyperthyroidism during ASW treatment. The current report of ASW elevating T4, along with its anti-inflammatory, neuroprotective, anti-oxidant, and anti-depressant properties,^[4] suggest that ASW can be considered for treatment of sub-clinical hypothyroidism in mood disorders. Prospective controlled studies among patients with laboratory confirmed subclinical hypothyroidism (i.e. TSH and free T4 along with thyroid antibodies), and other risk factors may provide answers to whether ASW extracts are more specifically beneficial in persons with unipolar or bipolar disorders with treatment resistant depression or rapid cycling.

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