

Comparison of the Addition of Siberian Ginseng (*Acanthopanax senticosus*) Versus Fluoxetine to Lithium for the Treatment of Bipolar Disorder in Adolescents: A Randomized, Double-Blind Trial

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ABSTRACT

Background: Bipolar disorder (BD) is a common, recurrent, and often life-long major psychiatric condition characterized by manic, depressive, and mixed episodes. Without treatment, there is substantial risk for morbidity and mortality, making BD a considerable public health problem.

Objective: The purpose of this study was to compare the relative effectiveness and tolerability of *Acanthopanax senticosus* (*A senticosus*)—an herb that is derived from eleutherosides and polysaccharides found in the plant's root—versus fluoxetine added to lithium in the treatment of BD in adolescents.

Methods: This was a double-blind, 6-week study. The patients were randomized into 2 treatment groups—*A senticosus* plus lithium (*A senticosus* group) and fluoxetine plus lithium (fluoxetine group). The patients underwent a baseline assessment using the 17-Item Hamilton Depression Rating Scale (HAMD-17) and the Young Mania Rating Scale (YMRS) during the screening period. Patients were scheduled for clinical visits at the end of weeks 1, 2, 4, and 6. At the end of the 6-week treatment period, each patient's condition was rated as follows: *response* (indicating an improvement of $\geq 50\%$ in the HAMD-17 score from baseline); *remission* (a HAMD-17 score of ≤ 7); and *switching to mania* (a YMRS score > 16 , and meeting the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition, Text Revision] for a manic episode). At each visit (with the exception of the enrollment visit), the patients were queried as to whether they experienced any health problems since the previous visit, a Treatment Emergent Symptom Scale assessment was completed, and the serum lithium concentration was analyzed. The patients were instructed to report adverse events (AEs) at any time during the study. AEs were also observed by the investigator(s) at clinical visits.

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Results: Seventy-nine Chinese adolescents were initially enrolled into the study. However, 76 adolescents were assessed for inclusion (45 females, 31 males; mean [SD] age, 15.4 [30.0] years; age range, 12–17 years) in the study. All included patients completed the study.

After 6 weeks of treatment, the response rate between the *A. senticosus* and the fluoxetine groups was similar (67.6% vs 71.8%, respectively). The remission rate between both groups was also similar (51.4% vs 48.7%). Analyzed by a general line model, the HAM-D-17 scores revealed there was a significant time effect ($F = 183.06$; $P < 0.01$), but not a significant group effect ($F = 0.99$) or group-by-duration of treatment interaction ($F = 0.779$). Three patients in the fluoxetine group experienced switching to mania compared with no patient in the *A. senticosus* group. AEs reported by patients in the *A. senticosus* group were as follows: nausea, 2 (5.4%); rash, 1 (2.7%); and diarrhea, 1 (2.7%). AEs reported by patients in the fluoxetine group were as follows: nausea, 4 (10.3%); anxiety, 3 (7.7%); insomnia, 3 (7.7%); constipation, 1 (2.6%); and tinnitus, 1 (2.6%).

Conclusion: Our study found no significant difference in these adolescents with BD treated with lithium plus adjunctive *A. senticosus* or fluoxetine. All treatments were generally well tolerated. (*Curr Ther Res Clin Exp.* 2007;68:280–290) Copyright © 2007 Excerpta Medica, Inc.

Key words: *Acanthopanax senticosus*, bipolar disorder, adolescent, fluoxetine.

INTRODUCTION

Bipolar disorder (BD) is a common (prevalence of 1.0%–6%),¹ recurrent, and often lifelong serious psychiatric condition characterized by manic, depressive, and mixed episodes that affect the mood. Without treatment, there is substantial risk for morbidity and mortality, making BD a considerable public health problem.² BD was once thought to rarely occur among children and adolescents. However, ~20% of all bipolar patients experience their first episode during adolescence, with the peak onset occurring between 15 and 19 years of age.³

Adolescents with BD generally experience mixed episodes of continuous and rapid cycling of mood states, including depression, irritability, and, less commonly, euphoria.^{4,5} Although there have been multiple studies, albeit mostly open-label studies,^{6–8} published on the treatment of manic symptoms in children and adolescents, the efficacy of agents to treat bipolar depression in this population has not been adequately studied.

Data on the treatment of BD in adults may be informative. However, there is a paucity of data in children, and it is prudent not to extrapolate. For example, tricyclic antidepressants are effective in the treatment of depression in adults but not in children.⁹ In a retrospective chart review,¹⁰ 42 children with BD who were selectively administered selective serotonin reuptake inhibitors (SSRIs), were 7 times more likely to show improvement in depressive symptoms than children with BD who were not administered any medication. However, children administered SSRIs were also 3 times more likely to experi-

ence a subsequent manic episode, a finding not reported when a mood stabilizer was administered.¹⁰

Based on anecdotal evidence, including retrospective chart reviews, SSRIs are thought to increase the risk of manic switching in pediatric BD,^{11,12} although not all studies confirm this conclusion.¹³ A high risk of suicidal thinking and behavior is another adverse event (AE) associated with antidepressant treatment in adolescents with depression. Suicidal behavior has been reported in 4% of adolescents treated with SSRIs compared with 2% in placebo groups.¹⁴ In September 2004, the US Food and Drug Administration required manufacturers to add black box warnings to the product labels of all antidepressants, advising physicians to balance the benefits against the risk of suicide when prescribing antidepressants to depressed adolescent patients.¹⁵

Acanthopanax senticosus (*A senticosus*) is a plant that has been widely used in China to increase performance and quality of life and to decrease infections (eg, respiratory tract infections, colds, and flu). The book, *Ben Cao Gang Mu* (*An Outline of Herbs*), written by Li Shi Zhen in 1596, describes the clinical utility of the *A senticosus* root, which includes promoting vigor, vitality, and longevity.¹⁶ The *A senticosus* root contains eleutherosides A (daucosterol), B (syningin), C, D, and E, which are thought to be its active ingredients.¹⁷ Together the eleutherosides constitute ~0.6% to 0.9% of the net weight of the root.¹⁸ In China, the State Food and Drug Administration (SFDA) approved the ethanol extract of the root of the *A senticosus* plant as the crude drug for an *A senticosus* capsule. The quality control standards for the extract require that the respective weights of eleutheroside B and E equal ~0.31% and 0.51% of the extract, when analyzed using high-performance liquid chromatography.¹⁹

Several recent laboratory studies²⁰ have revealed that the *A senticosus* root is effective in regulating the endocrine system, particularly, the hypothalamic-pituitary-adrenal axis, which is associated with mood, and therefore, might be important in the treatment of mood disorders. Approved by China's SFDA, product labeling for *A senticosus* lists the various uses of the drug. Three capsules TID can be used for insomnia, weakness, lack of appetite, and muscle soreness, all of which are associated with depression. Several clinical studies^{21,22} in adults suggested that *A senticosus* may be helpful in treating depression. For example, a study by Weng et al²¹ found that there were no statistically significant treatment differences between the *A senticosus* capsule and imipramine in adults with moderate depression. In addition, a study by Cai et al²² found that after taking *A senticosus* injection QD for 3 weeks, Zung Depression Rating Scale scores decreased significantly (56.2 [7.75] vs 33.2 [7.23]; $P < 0.05$).

No AEs were observed when *A senticosus* root 350 g/kg was administered QD intragastrically to mice or when 18.2 g/kg was administered intragastrically to mice for 15 days.²³ To our knowledge, AEs have been rarely reported with *A senticosus* capsule usage. We performed a literature search using the digital library of the Chinese National Knowledge Infrastructure, using Chinese translation for keywords *A senticosus* and *side effects*, *A senticosus* and *adverse event*, and

A senticosus and *adverse drug reaction*, the search returned no results. However, the search revealed that from 1994 to 2002, there were 86 reports of AEs associated with *A senticosus* injections—allergic response, 51 cases; hypertension, 3; hypotension, 1; palpitations, 3; heart failure, 1; angina pectoris, 1; conjunctival hyperemia, 6; asthma, 4; celiodynia, 4; headache, 3; lactation, 2; and others, 7.²⁴

This study compares the relative effectiveness and tolerability of *A senticosus* versus fluoxetine added to lithium in the treatment of BD in adolescents.

PATIENTS AND METHODS

Patients

The study was conducted at the Department of Psychiatry at Renmin Hospital, a division of Wuhan University, Wuhan, China. Adolescent patients enrolled in the study were randomized into 2 groups—1 group treated with *A senticosus* plus lithium (*A senticosus* group) and the other group treated with fluoxetine plus lithium (fluoxetine group). Informed written consent was obtained from the parents or legal guardians of the patients, and written and verbal assent was obtained from the patients. The study protocol was approved by the hospital's ethics committee. The study was conducted in accordance with the principles of the Declaration of Helsinki²⁵ and Good Clinical Practice.²⁶

Males and females aged 12 to 17 years, with a diagnosis of BDI or BDII according to the criteria set forth in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) (DSM-IV-TR)²⁷ were eligible to participate in the study. BDI classification required a history of ≥ 1 manic episode, which is characterized by ≥ 7 days of elevated, irritable, or expansive mood, and 3 concurrent DSM-IV-TR "B" criteria. However, if the mood was irritable and not elevated, 4 DSM-IV-TR "B" criteria had to be met. BDII classification required the occurrence of ≥ 1 major depressive episode accompanied by ≥ 1 hypomanic episode, which is characterized by a distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting ≥ 4 days. Patients were also required to have been currently experiencing a major depressive episode, and to have obtained a score of ≥ 18 on the 17-Item Hamilton Depression Rating Scale (HAMD-17).²⁸ The HAMD-17 score range is 0 to 54, and score indicators are as follows: < 7 = no depression; > 7 but < 17 = moderate depression; and > 24 = severe depression.

Patients were excluded from the study if they had any of the following conditions: mental retardation, panic, psychotic, anxiety, attention-deficit/hyperactivity, or seizure disorder, or any serious physical disease. Patients believed to be at risk for suicide were also excluded.

Patients taking drugs to treat BD (eg, mood stabilizers or antidepressants) had to discontinue those drugs before randomization and undergo a washout period of 5 times the $t_{1/2}$ of the drug. Patients taking fluoxetine were excluded because of the drug's long $t_{1/2}$, which might have possibly confounded the study result. Because of the perceived effects of psychotherapy (lasting effect

on patient's mood), psychotherapy initiated within 1 month prior to the study was prohibited.

Treatments

The drugs used in the study were lithium 250-mg tablets (Hunan Qianjin Xiangjiang Pharmaceutical Corp., Hunan, China), fluoxetine* 20-mg capsules, and *A senticosus* extract 250-mg capsules (Heilongjiang Wusulijiang Pharmaceutical Co., Ltd., Jixi City, China). The *A senticosus* group received *A senticosus* 750 mg TID and lithium BID (noon and evening). The fluoxetine group received fluoxetine 20 mg plus placebo QD (morning) and lithium plus placebo BID (noon and evening). Because the AEs of lithium are related to the serum concentration of the drug, the serum lithium concentration was monitored weekly, and the researchers adjusted the lithium dose to achieve serum lithium concentrations of 0.6 to 1.2 mmol/L.²⁹

Randomization and Blinding Procedures

In the hospital pharmacy, fluoxetine and placebo tablets were packed into capsules identical in appearance to the *A senticosus*. The randomization scheme was maintained in the same location, and the investigators did not have access to it for the duration of the study. However, individual treatment codes, indicating the treatment randomization for each patient, were made available to the investigators. The treatment codes, however, would be disclosed only in case of a medical emergency (eg, when appropriate management of the patient required drug treatment disclosure).

The patients underwent physical examination, electrocardiography, hematologic (hematocrit, leucocyte count, blood platelet count, hemoglobin, leukocyte differential count, volume packed cells, and mean platelet volume) and urine (glucose, bilirubin, ketone body, specific gravity, pH, urobilinogen, nitrite, protein, occult blood, leucoprotease, pathocast, red blood cell, white blood cell, and epithelial cell) testing, blood chemistry screening (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total protein, albumin, globulin, direct bilirubin, total bilirubin, urea, creatinine, uric acid, glucose, total cholesterol, and triglyceride), and HAMD-17, and Young Mania Rating Scale (YMRS)³⁰ assessments during the screening period.

After screening, patients were randomized using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina). The *A senticosus* and the fluoxetine treatment packs were randomly numbered from 1 to 80. After patients successfully completed screening, they received a number according to the time they entered the trial (eg, patient 1 received drug 1, patient 2 received drug 2). Patients were also assigned to a clinical investigator (X.W., S.W., or J.T.) and scheduled to see the same clinical investigator after weeks 1, 2, 4, and 6 for consultation and assessment using the HAMD-17, the YMRS, and the Treatment

*Trademark: Prozac (Eli Lilly and Company, Indianapolis, Indiana).

Emergent Symptom Scale (TESS), a scale routinely used to evaluate symptoms during psychiatric clinical trials. A final assessment was completed at the end of the 6-week treatment period. Assessment ratings were as follows: *response* (indicating an improvement of $\geq 50\%$ in the HAMD-17 score from baseline); *remission* (a HAMD-17 score of ≤ 7); and *switching to mania* (a YMRS score > 16 , and meeting the diagnostic criteria for a manic episode).

At each clinical visit, patients were questioned as to whether they had experienced any health-related issues since the previous visit, a TESS assessment was administered, and serum lithium concentration was monitored. The patients were instructed to report AEs at any time during the study. At the final visit, physical examination, electrocardiography, hematologic and urine testing, and blood chemistry screening were repeated.

At each clinical visit, the investigator performed a drug count to determine compliance. If the ratio was $< 75\%$, the patient was considered noncompliant.

Statistical Analysis

We used intent-to-treat analysis, which included all patients randomized to treatment, even those without a postbaseline assessment, in which case, the last observation was carried forward to impute for any missing data. HAMD-17 scores were analyzed using the general linear model (GLM). Response and remission rates were compared using the χ^2 test. All statistical analyses were 2-tailed and a $P < 0.05$ was considered statistically significant. All data analyses were attained using SPSS for Windows version 11.5 (SPSS Inc., Chicago, Illinois). A power analysis was not performed.

RESULTS

Seventy-nine patients were initially enrolled into the study, and 3 of these patients were excluded for the following reasons: 1 reported fluoxetine usage within 2 weeks of the study, 1 had abnormal hepatic function, and 1 withdrew informed consent. Therefore, 76 patients (45 females, 31 males; mean age [SD] 15.4 [30.0] years; age range, 12–17 years) were randomized to the *A senticosus* group ($n = 37$) or the fluoxetine group ($n = 39$). There were no significant differences between the groups in any baseline demographic or clinical characteristic (**Table**).

After 6 weeks of treatment, there was no significant difference in the response rate of the *A senticosus* group compared with the fluoxetine group (67.6% [25/37] vs 71.8% [28/39], respectively). The remission rates were also similar for the 2 groups (51.4% [19/37] vs 48.7% [19/39]). The GLM analysis of the HAMD-17 scores indicated a significant time effect ($F = 183.06$; $P < 0.01$) but no significant group effect ($F = 0.99$) or group-by-duration of treatment interaction ($F = 0.779$) (**Figure**).

Attrition rates were similar in the *A senticosus* group and the fluoxetine group (5.4% [2/37] vs 12.8% [5/39]). No patient was withdrawn due to lack of efficacy. The reasons for patient withdrawal after receiving ≥ 1 dose were similar in the

Table. Baseline demographic and clinical characteristics in adolescent patients with bipolar disorder (N = 76).

Characteristics	Lithium + AS (n = 37)	Lithium + Fluoxetine (n = 39)
Age, mean (SD), y	15.4 (1.3)	15.5 (1.2)
Sex, no. (%)		
Female	21 (56.8)	24 (61.5)
Male	16 (43.2)	15 (38.5)
Medical history		
Psychotic episode, no. (%)	37 (100)	39 (100)
Hospitalized for mood-related disturbances, no. (%)	4 (10.8)	7 (17.9)
Attempted suicide, no. (%)	5 (13.5)	6 (15.4)
Age of depression onset, mean (SD), y	14.7 (1.8)	15.6 (1.5)
Age of first mania/hypomania/mixed episode, mean (SD), y	13.2 (2.1)	12.7 (2.1)
No. of depression episodes in past year, mean (SD)	1.0 (0.0)	1.1 (0.3)
No. of mania/hypomania episodes in past year, mean (SD)	0.4 (0.5)	0.6 (0.7)
Psychotropic medication use, no. (%)		
≥1 Prior treatment	26 (70.3)	30 (76.9)
Valproate	6 (16.2)	7 (17.9)
Carbamazepine	2 (5.4)	1 (2.6)
Lithium	13 (35.1)	14 (35.9)
Antidepressants	10 (27.0)	12 (30.8)
Antipsychotics	4 (10.8)	6 (15.4)
Duration of index depression of 1 to 4 weeks, no. (%)	37 (100)	39 (100)
HAMD-17 scale ^{28*} score at screening, mean (SD)	24.8 (6.4)	26.8 (6.5)
YMRS scale ^{30†} score at screening, mean (SD)	3.2 (0.7)	3.4 (0.8)

AS = *Acanthopanax senticosus*; HAMD-17 = 17-Item Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.

*The HAMD-17 score range is 0 to 54, and score indicators are as follows: <7 = no depression; >7 but <17 = moderate depression; and >24 = severe depression.

†The YMRS is primarily used to assess patient's manic symptoms at baseline and over time. The YMRS score range is 0 to 60, and score indicators are as follows: >12 = mania; >3 = depression; and >2 = euthymia. Scores >12 indicate the graded severity of mania.

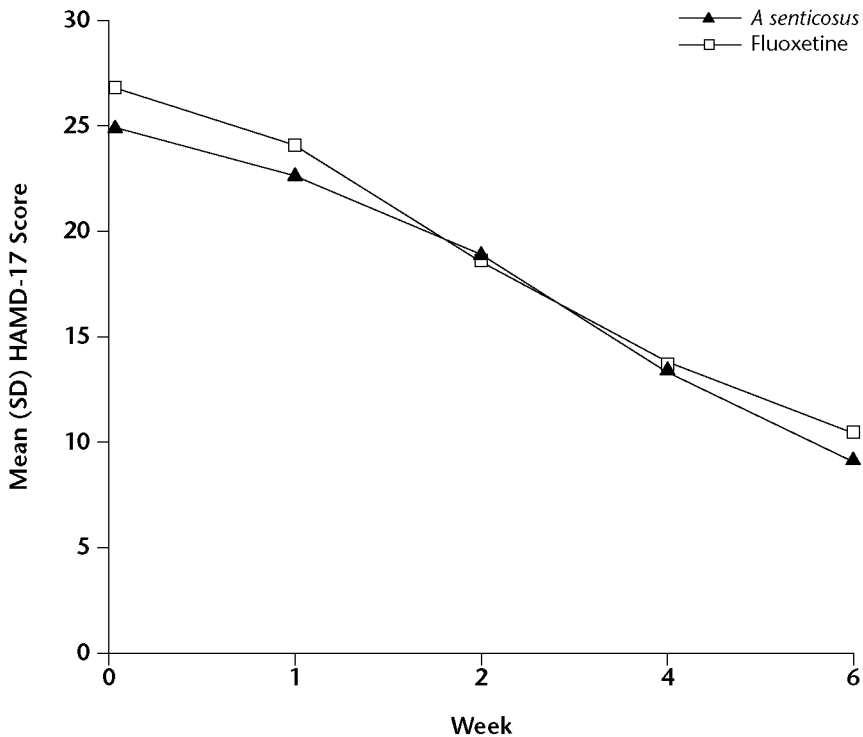


Figure. Mean (SD) 17-Item Hamilton Depression Rating Scale (HAMD-17) scores over 6 weeks of treatment with either *Acanthopanax senticosus* and lithium or fluoxetine and lithium in adolescent patients with bipolar disorder (N = 76). The HAMD-17 score range is 0 to 54, and score indicators are as follows: <7 = no depression; >7 but <17 = moderate depression; and >24 = severe depression.

A senticosus group compared with the fluoxetine group: lost to follow-up, 1 vs 0; noncompliance, 1 vs 1; AE, 0 vs 1; and switching to mania, 0 vs 3, respectively.

Patients in the *A senticosus* group reported the following AEs: nausea, 2 (5.4%); rash, 1 (2.7%); and diarrhea, 1 (2.7%). Patients in the fluoxetine group reported the following AEs: nausea, 4 (10.3%); anxiety, 3 (7.7%); insomnia, 3 (7.7%); constipation, 1 (2.6%); and tinnitus, 1 (2.6%). There were no abnormal laboratory findings throughout the study.

DISCUSSION

To our knowledge, this is the first randomized, double-blind study of lithium plus adjunctive *A senticosus* or fluoxetine in the treatment of BD in adolescents. There were no significant differences in the *A senticosus* group compared with the fluoxetine group in response rate (67.6% vs 71.8%, respectively) or remis-

sion rate (51.4% vs 48.7%). The GLM analysis did not reveal a group effect ($F = 0.99$), suggesting there was no significant difference between the 2 groups.

The attrition rates were not significantly different between the 2 groups. There were no episodes of mania in the *A senticosus* group, while there were 3 reported episodes in the fluoxetine group. While the difference in rate of switching to mania was not statistically significant between groups, it would be valuable to examine this rate in larger studies.

One AE (nausea) occurred in >5% of the patients who were administered *A senticosus*, while 3 AEs (nausea, anxiety, and insomnia) occurred in >5% of the fluoxetine group. This finding suggests that *A senticosus* was well tolerated.

Limitations

The study had no placebo arm. Although the response rate and remission rate of both groups were satisfactory (>50%), it was unclear whether the findings in either group might have been different from the findings with lithium treatment alone. The small sample size and lack of a power analysis were also limitations of this study, indicating that the study might not be generalizable to a larger population. Additionally, at baseline, the average HAMD-17 score was 24.8 in the *A senticosus* group and 26.8 in the fluoxetine group, indicating moderate to severe depression. Therefore, findings of this study might not be generalized to patients with more severe bipolar depression. Finally, the present study was 6 weeks in duration. Prolonged emergence of manic symptoms or depression relapse in either group was not known at the conclusion of the study, which suggests that longitudinal studies might be necessary. In addition, placebo-controlled studies will be required to evaluate whether *A senticosus* is more effective than placebo and to determine the long-term efficacy of *A senticosus* in preventing relapse and manic episodes in bipolar patients.

CONCLUSIONS

The results of this study suggest that lithium plus adjunctive *A senticosus* was not significantly different compared with lithium plus fluoxetine treatment in adolescents with BD. All treatments were generally well tolerated.

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