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The anti-depression effect of Xylaria nigripes in patients with epilepsy: A multicenter randomized double-blind study

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ABSTRACT

Purpose: The comorbidity of depression in patients with epilepsy is common and treatment is still controversial. This pilot study was aimed at evaluating the efficacy and safety of Xylaria nigripes for treating depressive symptoms in patients with epilepsy during 12 weeks of treatment.
Methods: A multicenter, double-blind, placebo-controlled, randomized superiority study was performed. A total of 104 patients with epilepsy who fulfilled the study criteria were randomized 1:1 to receive Xylaria nigripes (the Wu Ling group) or placebo (the placebo group) treatment in the 12-week period of study. The participants were visited on weeks 0, 2, 4, 8, and 12 of the treatment course.
Results: Eighty-one patients finished all of the visits. The primary efficacy endpoint in this study was the total effective rate for depression, which was significantly greater in the Wu Ling group (51.3%, $n = 39$) than in the placebo group (35.7%, $n = 42$, 0.51–0.36 = 0.15, 95% CI −0.06 to 0.37, $U = 2.83$, $P = 0.002$) after 12 weeks of treatment. No differences in seizure frequency or changes in severity were found between the Wu Ling and the placebo groups. In addition, the quality of life and seizure worry subscale scores in patients with epilepsy were also improved more notably in the Wu Ling group than in the placebo group ($P < 0.05$). Most of the adverse effects (AEs) in this study were mild and had no differences between the Wu Ling and the placebo groups.
Conclusion: Xylaria nigripes could alleviate depressive symptoms within 12 weeks treatment and was well tolerated in patients with epilepsy.

1. Introduction

Depression is the most frequently occurring psychiatric comorbidity in patients with epilepsy, with an average prevalence of 20–30% [1,2]. Depression has significant negative impacts on quality of life in patients with epilepsy [3], and is associated with a poor response to pharmacological and surgical treatments of epileptic disorders [4,5].

However, depressive symptoms in epilepsy have not been fully recognized by neurologists. The treatment for comorbid depression in patients with epilepsy is also challenging. Some reports of pharmaceutical and psychotherapeutic approaches for depressive symptoms in patients with epilepsy are open-labeled [6–9]. The safety of selective serotonin reuptake inhibitor (SSRI) antidepressants in patients with epilepsy is still controversial. Although some

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investigations showed that SSRIs had little effects on seizure frequency [10,11], others indicated that SSRIs could exacerbate seizures by lowering the seizure threshold or by interacting with antiepileptic drugs (AEDs) [12,13], especially when taken in overdose [14,15]. There have been no guidelines, expert consensus or recommendations for the treatment of comorbidity of depression in patients with epilepsy until now. Randomized clinical trials and new therapies are urgently needed.

Xylaria nigripes (also referred to as Wu Ling Shen) is a traditional Chinese medicine which belongs to the Xylariaceae family of fungi. It grows several feet underground in the fungus combs of the Odontotermes termite species during the spring and summer seasons, and contains many bioactive molecules such as glycosides, steroids and amino acids [16,17]. Studies demonstrated Xylaria nigripes had antidepressant and sleep-regulating effects, and was used to treat depression and insomnia in clinical practice [18,19]. In a multicenter randomized double-blind parallel study, Xylaria nigripes (under the brand name 'Wu Ling Capsule') had a similar effect to Deanxit to alleviate depressive, anxiety and insomia symptoms in patients with depression [20]. In animal studies, Xylaria nigripes was found to prolong the latency of convulsive seizure and delay the kindling process in penty1enetetrazol induced rat epilepsy models [21]. The pharmacological mechanisms of Xylaria nigripes appeared to be complicated. As indicated by Ma et al. [22], Xylaria nigripes promoted the activity of glutamate decarboxylase and the combination of γ-aminobutyric acid (GABA) with GABA receptors. It also had anti-oxidative and anti-inflammatory effects [23–25]. In this study, therefore, we used Xylaria nigripes as an anti-depressive therapy in patients with comorbidity of epilepsy and depression to evaluate its effects on depression and safety for seizures.

The primary objective of this study was to evaluate the efficacy of Xylaria nigripes on depressive symptoms in patients with epilepsy during 12 weeks of treatment. The secondary objectives included two aspects: (1) assessing the influences of Xylaria nigripes on seizure frequency, seizure severity, sleep quality and quality of life for patients with epilepsy; (2) evaluating the safety of Xylaria nigripes in patients with epilepsy.

2. Methods

2.1. Study design

This study (temporarily referred to as WL-2010) was a multicenter, double-blind, randomized, placebo-controlled, superiority clinical trial. The patients in this study were randomized 1:1 to receive Xylaria nigripes (the Wu Ling group) or a placebo (the Placebo group) for 12 weeks.

For the primary endpoint, the total effective rate for depressive symptoms in patients with epilepsy was compared between the Wu Ling and the Placebo groups at the end of 12 weeks' treatment. The sample size was determined to be about 100 cases for each group by the statistical calculation formula, using at least 10% difference of the total effective rate for depression between the Wu Ling and the Placebo groups. Randomization was performed centrally by the Clinical Research Organization (CRO). The random numbers were generated using the PROC PLAN process of the SAS 9.2 software. Randomization lists were assigned to every study center. Investigators and participants were all blinded to the assignment. The Wu Ling Capsule and the placebo could not be differentiated from appearance.

All of the measurement scales in this study, including the Hamilton Depression Rating Scale (HAMD), the National Hospital Seizure Severity Scale (NHS3), the Pittsburgh Sleep Quality Index (PSQI), and the Quality of Life in Epilepsy Inventory (QOLIE-31) were evaluated in each center by one or two neurological doctors who had been trained in advance and whose evaluations were found to be in good agreement.

The protocol of the trial was approved by the local independent ethics committees of all the participating hospitals. All the patients recruited had to agree with and sign a written informed consent prior to entering the study. This study had been registered at the ClinicalTrial.gov system of the U.S. National Institutes of Health and the Identifier was NCT01125241.

2.2. Patients

The patients were recruited from the epileptic clinics of nine hospitals located in Shanghai, Hangzhou, Guangzhou and Beijing. Patients were enrolled if they consented to participate in the study and met the following inclusion criteria: (1) older than or equal to 18 years of age (no gender limitation); (2) a diagnosis of epilepsy based on clinical data and EEG recording, and having had regular treatment with AEDs for at least 6 months, without recent adjustments to medication, in order to avoid the confounding effects of AEDs adjustment; (3) at least 24 h from the last seizure before accepting psychological evaluation to avoid the effect of postictal state; (4) having a HAMD score of greater than or equal to 17; (5) not taking any antidepressants or antipsychotics in the previous 2 weeks.

The exclusion criteria included the following: (1) having a history of psychiatric symptoms other than depression; (2) having a history of suicidal thoughts or suicidal behaviors; (3) having severe cognitive impairment, chronic organic failures or malignant tumors; (4) liver function tests indicating alanine aminotransferase (ALT) or aspartate aminotransferase (AST) higher than 1.5 times the normal reference value, or a white blood count of less than 2500/μl, or a neutrophils count of less than 1000/μl; (5) being pregnant or lactating.

The patients were fully informed of the benefits and risks of entering this study. They had the right to drop out the study at any time if they felt no improvement of depression or experienced exacerbation of seizures. They would be recommended to visit a psychiatrist if they had suicidal thoughts or had very severe depressive symptoms. If they improved markedly and wanted to continue taking the medicine, they would receive another extra free supply of the Wu Ling Capsule for 3 months after ending the study. This extra period of taking the Wu Ling Capsule was also monitored.

2.3. Study endpoints

The efficacy of Xylaria nigripes on depression in patients with epilepsy was evaluated by the HAMD reductive rate. As firstly recommended by Snaith et al. [26], the HAMD scale has become a common tool to assess severity of depressive symptoms and the efficacy of treatment [27]. The HAMD reductive rate is calculated as: (score before treatment − score after treatment)/score before treatment × 100%. There are four levels of efficacy based on the HAMD reductive rate: ≥75% means clinical recovery, 50–74% means significantly improved, 25–49% means slightly improved, and <25% means ineffectiveness. The total effective rate for depression is calculated as: (clinical recovery rate + significantly improved rate)/*n*. The primary efficacy endpoint was to evaluate the total effective rate for depression in patients with epilepsy. The secondary efficacy endpoints included changes in seizure frequency, seizure severity (the NHS3 score), sleep quality (the PSQI score) and quality of life (the QOLIE score). Adverse events (AEs), laboratory data and vital signs were analyzed as safety variables.

2.4. Study procedures

The Wu Ling Capsule and the placebo were both produced by Zhejiang Jolly Pharmaceutical Limited Corporation (Hangzhou,