

## Retrospective Study

## Wuling capsule combined with sertraline in the therapy of anxiety and depression with insomnia in adolescents

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The treatment of adolescent patients with anxiety, depression and insomnia is challenging, and there is no ideal treatment method.

**AIM**

To evaluate the clinical efficacy of Wuling capsule combined with sertraline in the treatment of adolescent anxiety, depression and insomnia.

**METHODS**

Eighty adolescent patients with anxiety, depression with insomnia who were admitted to our hospital from April 1, 2022 to March 30, 2024. And the subjects were randomly classified into the control group ( $n = 40$ ) and the observational group ( $n = 40$ ). The control group was treated with a combination of sertraline and placebo. The observation group was treated with Wuling capsule in addition to sertraline. The two groups were cured continuously for 8 weeks. Insomnia severity index (ISI), Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD) were used to evaluate the clinical symptoms before treatment and at 2, 4, 6 and 8 weeks after treatment. The Treatment Emergent Symptom Scale (TESS) was used to evaluate adverse reactions during treatment.

**RESULTS**

There was no obvious difference in HAMD, HAMA and ISI scores between the two groups before treatment ( $P > 0.05$ ). After treatment, the HAMD, HAMA and ISI scores of patients in both groups decreased compared with before treatment, and HAMD, HAMA and ISI scores of patients in the observation group were

remarkably lower than those in the control group at each time point after treatment ( $P < 0.05$ ). Compared with the control group, the TESS score of the study group were sharply lower ( $t = 18.239$ ,  $P < 0.001$ ).

## CONCLUSION

Wuling capsule can further alleviate the insomnia symptoms of adolescents with anxiety and depression, and the efficacy and safety are high. It is recommended to promote the application.

**Key Words:** Adolescent; Depression; Anxiety; Insomnia symptom; Sertraline; Wuling capsules

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**Core Tip:** This study discusses the clinical effect of Wuling capsule combined with Sertraline in the treatment of anxiety and depression with insomnia symptoms, and emphasizes that Wuling capsule can further alleviate the insomnia symptoms of anxiety and depression in adolescents, with high efficacy and safety. Therefore, this study proposed a combination treatment method, which can effectively improve the depression state and sleep quality of patients, and is conducive to improving the treatment compliance of patients, and it is recommended to be popularized.

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## INTRODUCTION

Depressive disorder refers to a group of mood disorder syndromes mainly manifested by low mood, anhedonia, reduced interest with decreased initiative, slow thinking and other symptoms of psychomotor retardation[1]. Depressive episodes are mainly manifested by depressed mood, which can be triggered by obvious causes, and can develop from depressed mood to grief, or even depressive rigidity. In severe cases, delusions, hallucinations, mania and other psychotic symptoms can occur[2]. Depressive disorder has a tendency to recur, although each episode can be controlled by medication. But after repeated episodes, it is easy to become chronic or leave the corresponding symptoms. The incidence of adolescent depression has been rising in recent years, and some data suggested that the prevalence of depression in adolescence (12 to 18 years old) was increasing year by year, which was mainly related to the heavy burden of homework, learning pressure and inadequate sleep duration for physical function recovery[3,4]. And most of the patients have a tendency to relapse, and some of them can last until adulthood, which has a serious adverse effect on their growth and development and social functioning to bring serious mental pressure and economic burden to the family and society. Therefore, there is an urgent need to carry out research on adolescent depression to better understand the occurrence and development of depression in various age groups and provide a basis for clinical diagnosis and therapy [5]. Insomnia is a characteristic phenomenon of depressive disorders, which may increase the risk of depressive episodes, and 60% to 80% of patients with depressive disorders are accompanied by sleep disorders. Therefore, insomnia and depression are highly co-existing[6]. It is clinically proven that strengthening the co-morbidity therapy of depression and insomnia is of great significance for clinical prevention and therapy[7]. Generalized anxiety disorder is a neurosis characterized by subjective anxiety. It is expressed as a fearfulness that is not based on concrete evidence and lacks objective goals and concrete concepts, and is accompanied by behavioral disorders such as vegetative nervous system dysfunction and motor restlessness[8]. Anxiety secondary to other psychiatric disorders (such as hallucinations, delusions, depression and phobias) or other physical illnesses (such as coronary heart disease, hypertension and hyperthyroidism) can be collectively referred to as anxiety syndromes. In recent years, with the increase of life pressure, its incidence has gradually increased, which has brought serious impact on the life quality and physical and mental health of patients[9]. A survey of sleep problems associated with mental disorders found that sleep problems are significantly correlated with anxiety disorders[10]. The previous study found that many social anxiety disorder patients also meet the diagnostic criteria for insomnia, in which early waking is insomnia and anxiety levels associated with the highest degree of manifestation[11]. At the same time, insomnia can appear as the most prominent prodrome of anxiety disorders, which can increase the risk of anxiety disorders by more than several times. Therefore, there is a clear practical need and important clinical significance to actively treat anxiety insomnia and to conduct clinical research on anxiety insomnia[12,13]. The modern medicine believes that the pathological factors of the disease are closely related to the abnormal rise of neurotransmitters, especially 5-hydroxytryptamine is the most closely related to the onset of anxiety and depression, and the rest such as norepinephrine, dopamine and  $\gamma$ -aminobutyric acid can also affect the onset of anxiety and depression. At present, the clinical therapy of anxiety and depression disorders with insomnia symptoms is mainly based on drug, including benzodiazepines, tricyclic anti-anxiety drugs, selective serotonin reuptake inhibitors, serotonin and norepinephrine dual reuptake inhibitors and other drugs. However, the drug therapy has different degrees of side effects in the application process, which directly affects the therapeutic effect[14,15]. Sertraline is commonly used in the therapy of adolescent

depressive disorders, which can effectively improve depression and anxiety[16]. However, in the patient's sleep disorder symptoms of improvement, the therapeutic effect of the drug is slightly worse than other drugs. It is generally necessary to combine sedation and hypnosis drugs. Although it can achieve certain efficacy, the concern about the adverse effects of the drug can affect the patient's adherence to treatment[17]. Traditional Chinese medicine has been gradually adopted clinically in recent years for its remarkable efficacy and few adverse reactions. Wuling capsule is a kind of biotechnology refined pure traditional Chinese medicine preparation, which has obvious effects on insomnia and depressive disorder. In order to further analyze the effectiveness and safety of sertraline combined with Wuling capsule in the therapy of mild to moderate anxiety and depression patients with insomnia symptoms[18]. A control study was conducted on 80 adolescent patients with anxiety, depression with insomnia who were admitted to our hospital from April 1, 2022 to March 30, 2024. The results were as follows.

## MATERIALS AND METHODS

### General information about patients

Eighty adolescent patients with anxiety, depression with insomnia who were admitted to our hospital from April 1, 2022 to March 30, 2024. And the subjects were randomly classified into the control group ( $n = 40$ ) and the observational group ( $n = 40$ ) according to random number table method. According to the sample size calculation formula:  $n = (U\alpha + U\beta) 2 P (1 - P) / (P1 - P0) 2$  and 5% loss of follow-up rate of "optimal clinical trial", at least 39 samples should be included in each group in this study. In control group, patients ranged in age from 12 to 18 years, with an average age of  $15.31 \pm 2.08$  years. There were 18 males and 22 females. The average course of disease was  $3.44 \pm 0.15$  months, ranging from 1 to 5 months. In observation group, patients aged 12 to 18 years and mean aged  $15.29 \pm 2.06$  years. There were 17 males and 23 females. The average course of disease was  $3.46 \pm 0.13$  months, ranging from 1 to 6 months. There was no statistically significant difference between the two groups ( $P > 0.05$ ), so the study could be conducted.

### Inclusion and exclusion criteria

**Inclusion criteria:** (1) Patients with definite clinical diagnosis of anxiety or depression disorder; (2) Patients with insomnia severity index (ISI) score  $\geq 8$ , accompanied by insomnia symptoms; (3) Adolescents aged 12-18 years old; (4) Patients with normal laboratory indicators; (5) Patients with Hamilton Depression Scale (HAMD) score  $\geq 20$  or Hamilton Anxiety Scale (HAMA) score  $\geq 14$ ; and (6) Patients and guardians were informed of this study and participated voluntarily.

**Exclusion criteria:** (1) Patients with serious tendency of suicide and self-injury; (2) Patients with severe symptoms (ISI score  $\geq 22$ ), HAMA score  $\geq 29$ , HAMD score  $\geq 35$ ; (3) Patients with bipolar affective disorder; (4) Patients with allergic reactions to the drugs used in this study; (5) Those with serious physical and organic diseases such as kidney, lung, brain and heart; (6) Those with immune function diseases; (7) Those with mental illness; and (8) Patients who could not cooperate with the study and lost to follow-up.

### Methods

The control group was treated with a combination of sertraline (Manufacturer: Zhejiang Huahai Pharmaceutical Co., LTD; Specification: 50 mg) and placebo. Sertraline application method: Oral, 25-50 mg per day as the starting dose, and the dose was adjusted appropriately according to the patient's condition after 2 weeks of treatment, the maximum dose is 100 mg per day. The observation group was treated with Wuling capsule (Manufacturer: Zhejiang Zoli Pharmaceutical Co., LTD.; Specification: 0.33 g per capsule) in addition to sertraline. The capsules were taken orally, 1-3 capsules each time, 3 times a day. The two groups were cured continuously for 8 weeks.

### Observation index

Clinical effect: ISI and HAMD scores were used as the basis to judge the treatment effect. Judging criteria: ISI score  $\leq 7$  points, HAMD score  $\leq 8$  points are judged to be cured; ISI score and HAMD score reduced by 50% or more are considered effective; The reduction of ISI score and HAMD score  $< 50\%$  are considered as ineffective, effective rate + cure rate = total effective rate.

ISI, HAMA and HAMD were used to evaluate the clinical symptoms before treatment and at 2, 4, 6 and 8 weeks after treatment.

The Treatment Emergent Symptom Scale (TESS) was used to evaluate adverse reactions during treatment.

### Statistical analysis

SPSS 27.0 analysis software was applied. The measurement data expressed by mean  $\pm$  SD, and *t*-test was adopted. The count data were statistically described by percentages, and the comparison of rates between groups was performed using the  $\chi^2$  test.  $P < 0.05$  indicating that the difference was statistically significant.

## RESULTS

### Comparison of improvement of clinical symptoms

Table 1, 2 and 3 suggested that there was no obvious difference in HAMD, HAMA and ISI scores between the two groups before treatment ( $P > 0.05$ ). After treatment, the HAMD, HAMA and ISI scores of patients in both groups decreased compared with before treatment, and HAMD, HAMA and ISI scores of patients in the observation group were remarkably lower than those in the control group at each time point after treatment ( $P < 0.05$ ). The results indicated that Wuling capsule combined with Sertraline could effectively improve the depressive symptoms, anxiety degree and insomnia of adolescent patients with anxiety, depression and insomnia.

### Comparison of treatment effect

Table 4 indicated that compared with the control group, the total effective rate of the observation group was apparently higher ( $P < 0.05$ ). The results indicated that Wuling capsule combined with sertraline could effectively improve the depressive symptoms, anxiety degree and insomnia of adolescent patients with anxiety, depression and insomnia.

### Comparison of TESS scores

The TESS scores of the observation group and the control group were  $2.15 \pm 0.43$  and  $5.85 \pm 1.21$ , respectively. Compared with the control group, the TESS score of the study group were sharply lower ( $t = 18.239$ ,  $P < 0.001$ ). The results indicated that Wuling capsule combined with sertraline could effectively reduce the occurrence of adverse reactions in adolescent patients with anxiety, depression and insomnia.

## DISCUSSION

With the development of many aspects of society, the pressure brought by work, life and study is increasing, and the incidence of anxiety and depressive insomnia is growing[19]. Relevant studies have shown that insomnia occurs in 90% of adolescents with depressive disorders. It often as the first symptom, and residual insomnia after acute therapy is also a major component of persistent depressive episodes[20]. Anxious insomnia can seriously affect people's life quality, but also lead to a series of physical and mental illnesses, such as the circulatory system (common hypertension, tachycardia), the digestive system (common peptic ulcer and anorexia nervosa), the endocrine system (common diabetes mellitus, obesity), and the urinary system (common menstrual disorders, impotence and premature ejaculation)[21]. At present, the effective therapy of adolescent anxiety and depression disorders with insomnia symptoms has gradually gained clinical attention, and the research on them has gradually deepened and diversified.

Currently, adolescents with depressive disorders are mainly cured with medications, and the preferred drugs are selective serotonin reuptake inhibitors[22]. Sertraline, as a selective and potent serotonin reuptake inhibitor, is supported by sufficient evidence-based medical evidence in the therapy of adolescent depression at home and abroad, which can effectively improve anxiety and depression. However, the drug has obvious affinity for benzodiazepine receptors and  $\gamma$ -amino-butyric acid receptors, so it cannot effectively improve insomnia symptoms[23,24]. The combination of sedative-hypnotic drugs (such as benzodiazepine agonists, non-benzodiazepine agonists, melatonin agonists, antidepressants with hypnotic effect, antihistamines) is commonly used to improve sleep, which not only increases the risk of suicide and the experience of depression, but also has more adverse effects and poor patient compliance. To some extent, it restricts the clinical application of the drug[25].

According to Chinese medicine, insomnia is related to the liver, heart, spleen, stomach and kidney. The heart, as the commander of the blood and the seat of consciousness, controls emotional activities. The emotional disorders and restlessness of the heart and mind are the main causes of insomnia. The Chinese medicine believes that the disorder between the internal organs and the heart is also the cause of insomnia[26,27]. The common causes include deficiency of kidney yin, weakness of the spleen and stomach and insufficiency of blood in the heart. The pathogenesis of depression and anxiety mainly involves liver qi stagnation, and it is also related to the imbalance between the internal organs of the heart, spleen and kidneys. The core of Chinese medicine is to improve the patient's sleep condition by adjusting the function of qi and blood in the body's internal organs. The clinical treatments are often used to nourish the heart and tranquilize the mind, and nourish the kidney and yin. The Chinese medicine treats insomnia mainly with Chinese herbs, acupuncture and other non-pharmacological therapies. For thousands of years, Chinese medicine has played an important role in the healthcare of insomnia patients in China[28,29]. The main ingredient of Wuling Capsules is fermented powder of Wuling Mushroom, containing adenosine, adenine, uridine, guanosine, polysaccharides, mannitol, ergosterol and 19 kinds of amino acids, such as aspartic acid, glutamic acid and lysine. It belongs to the kidney meridian, and has the effect of nourishing the kidney[30,31]. It has the function of nourishing kidney yin and lowering heart fire, especially suitable for insomnia caused by heart fire and kidney water insufficiency. At the same time, it has the effect of nourishing the heart and tranquilizing the mind, which can greatly alleviate the symptoms of anxiety caused by the loss of the heart and the mind[32].

For adolescents with mild-to-moderate depressive disorder and anxiety with insomnia, the concept of prevention is better than cure is adopted to reduce the possibility of recurrence of the disease. Our study found that the therapeutic effect of sertraline combined with Wuling capsule was better. Compared with the control group, the total effective rate of the observation group was apparently higher, and the HAMD score, HAMA score, ISI, and TESS score were significantly lower at 2, 4, 6, and 8 weeks after the treatment ( $P < 0.05$ ), which indicated that the effectiveness and safety of sertraline combined with Wuling capsule is higher, and it effectively improved the clinical symptoms of patients. The effective

**Table 1 Comparison of Hamilton Depression Scale between the two groups**

HAMD score	Control group (n = 40)	Observation group (n = 40)	t value	P value
Before treatment	24.23 ± 2.02	24.40 ± 1.52	0.438	0.662
2 weeks after treatment	18.58 ± 2.39	16.78 ± 2.69	3.158	0.002
4 weeks after treatment	15.67 ± 4.02	12.85 ± 3.71	3.268	0.002
6 weeks after treatment	12.60 ± 2.38	9.05 ± 2.09	7.086	< 0.001
8 weeks after treatment	8.63 ± 1.05	6.65 ± 1.19	7.861	< 0.001

HAMD: Hamilton Depression Scale.

**Table 2 Comparison of Hamilton Anxiety Scale between the two groups**

HAMA score	Control group (n = 40)	Observation group (n = 40)	t value	P value
Before treatment	22.87 ± 2.43	23.12 ± 2.59	0.445	0.658
2 weeks after treatment	18.07 ± 3.12	15.53 ± 3.71	3.326	0.001
4 weeks after treatment	14.78 ± 3.72	12.03 ± 4.28	3.067	0.003
6 weeks after treatment	11.63 ± 2.52	8.35 ± 2.38	5.976	< 0.001
8 weeks after treatment	8.75 ± 1.26	5.68 ± 1.31	10.723	< 0.001

HAMA: Hamilton Anxiety Scale.

**Table 3 Comparison of Insomnia severity index between the two groups**

ISI score	Control group (n = 40)	Observation group (n = 40)	t value	P value
Before treatment	17.85 ± 2.74	17.78 ± 2.76	0.122	0.903
2 weeks after treatment	15.63 ± 3.65	12.63 ± 4.01	3.499	< 0.001
4 weeks after treatment	13.75 ± 2.42	10.83 ± 3.15	4.658	< 0.001
6 weeks after treatment	11.90 ± 2.31	7.58 ± 2.15	8.679	< 0.001
8 weeks after treatment	8.73 ± 1.11	5.63 ± 1.00	13.101	< 0.001

ISI: Insomnia severity index.

**Table 4 Comparison of treatment effect between the two groups, n (%)**

Index	Control group (n = 40)	Observation group (n = 40)	χ <sup>2</sup>	P value
Cure	15 (37.50)	27 (67.50)		
Effective	14 (35.00)	11 (27.50)		
Ineffective	11 (27.50)	2 (5.00)		
Total effective rate	29 (72.50)	38 (95.00)	7.440	0.006

therapeutic effect can be seen from the pharmacological mechanism that Wuling capsule is a supplement to the pharmacological mechanism of sertraline. Wuling Capsule is a pure Chinese medicine preparation with a single ingredient, which is diuretic and tonic to the heart and mind, and it has medicinal value for insomnia, vomiting of blood and post-partum blood loss. It can nourish the heart, tranquillize the mind and tonify the kidneys and the brain.

The drug has obvious effect of calming the center, it can effectively regulate the nerve function, improve the effect of memory disorders[33,34]. The brain-healthy and brain-protecting effect is better. Wuling Capsules can promote neuropeptide Y and 5-hydroxytryptamine content, reduce the content of substance P, so as to balance the monoamine neurotransmitters, in order to effectively improve the patient's insomnia symptoms. The drug is safe and has no adverse effects[35]. Our results indicated that both Wuling capsule and sertraline have anti-anxiety, anti-depression and sedative



hypnotic effects. After combined administration, patients' anxiety, depression and insomnia symptoms are remarkably improved, suggesting that Wuling capsule can regulate natural sleep rhythm by regulating central neurotransmitter and neurophysiological balance, and at the same time enhance the function of viscera. The clinical symptoms of insomnia patients with anxiety and depression have been improved.

## CONCLUSION

Sertraline combined with Wuling capsule has ideal effect on adolescent patients with anxiety, depression and insomnia symptoms, which can effectively improve the depressive state and sleep quality of patients, and is conducive to improving the treatment compliance of patients.

## FOOTNOTES

**Author contributions:** Duo LL and Rao GF contribute equally to this study as co-corresponding authors. Duo LL designs research; Duo LL conducts case collection; Rao GF guide the research.

**Institutional review board statement:** The study was reviewed and approved by the Taizhou Hospital of Integrated Chinese and Western Medicine Institutional Review Board.

**Informed consent statement:** All the participants or their legal guardians signed the informed consent form.

**Conflict-of-interest statement:** The authors deny any conflict of interest.

**Data sharing statement:** No additional data are available. This study followed ethics review board regulations to ensure privacy rights and data confidentiality of all participants.

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