JoP Journal of Pharmacopuncture

Journal of Pharmacopuncture 2023;26(1):38-43
pISSN: 2093-6966 • eISSN: 2234-6856
https://doi.org/10.3831/KPI.2023.26.1.38

Original Article

Check for updates

Effectiveness of the Shugan Jieyu Capsule against Psychiatric Symptoms in Epilepsy: a protocol for systematic review and meta-analysis

Sejin Kim[1], Yunna Kim[1,2,3]*, Seung-Hun Cho[1,2,3]*

[1]College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea
[2]Research Group of Neuroscience, East-West Medical Research Institute, WHO Collaborating Center, Kyung Hee University, Seoul, Republic of Korea
[3]Department of Clinical Korean Medicine, Graduate School, Kyung Hee University, Seoul, Republic of Korea

Received August 2, 2022
Reviewed August 6, 2022
Accepted February 22, 2023

***Corresponding Author**
Seung-Hun Cho
Kyung Hee University Medical Center, Kyung Hee University, 23 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Republic of Korea
Tel: +82-2-958-9186
E-mail: chosh@khmc.or.kr

Yunna Kim
Kyung Hee University Medical Center, Kyung Hee University, 23 Kyungheedaero, Dongdaemun-gu, Seoul 02447, Republic of Korea
Tel: +82-2-958-9186
E-mail: yunna.anna.kim@khu.ac.kr

Objectives: Psychiatric symptoms in epilepsy are very common, and the most common symptoms are depression, insomnia, and anxiety. These symptoms not only lower the quality of life of epilepsy patients, but also elevate the risk of epileptic seizures. There are no specific criteria for the available antiepileptic drugs to ameliorate these symptoms in patients with epilepsy, and there is a lack of evidence to support the efficacy and safety of existing drugs. The Shugan Jieyu capsule (SJC) is a traditional herbal medicine composed of *Acanthopanax senticosus* and *Hypericum perforatum* and is reported to be effective in relieving psychiatric symptoms. The purpose of this study was to assess the efficacy of SJC as a treatment for psychiatric symptoms in epilepsy patients.

Methods: Electronic databases will be investigated for publications in English, Korean, Japanese, and Chinese. The participants of the study are epilepsy patients with psychiatric symptoms diagnosed using any validated criteria. All types of controls will be compared—placebo, conventional treatments, and no treatment—to groups treated with SJC or modified SJC. We will measure the degree of improvement in psychiatric symptoms and check epileptic symptoms, such as the frequency of seizures. The study selection and data extraction will be performed by two independent reviewers, who will also assess methodological quality using the risk-of-bias tool by Cochrane. We will use Review Manager software (RevMan) to carry out all statistical analyses.

Results: This systematic review and meta-analysis will be performed in accordance with the PRISMA-P statement.

Conclusion: This systematic review is the first study to assess the efficacy and safety of SJC for the treatment of psychiatric symptoms in epilepsy. We expect that this study will provide clinically applicable evidence for patients with epilepsy when selecting drug treatments.

Keywords: epilepsy, shugan jieyu capsule, psychiatric symptoms, systematic review, meta-analysis

INTRODUCTION

Epilepsy is a chronic pathological condition of the brain characterized by recurrent seizures [1]. Patients with epilepsy, particularly treatment-resistant epilepsy, which accounts for one-third to one-half of all cases, have an increased risk for psychological disorders [2]. The prevalence of depression, the most common psychiatric disorder in epilepsy, is between 12% and 37% [3]. Psychiatric symptoms of epilepsy include not only depression, but also fatigue, sleep disturbances, anxiety, and poor quality of life [4].

The relationship between epilepsy and psychiatric symptoms

is bidirectional. Both epilepsy and depression share mechanisms associated with a hyperactive hypothalamic-pituitary-adrenal axis and a deficient serotonin and norepinephrine system [5]. Clinically, epilepsy can influence the onset of depression through exposure to chronic stress [6], while depression elevates the risk of developing epilepsy by two to seven times and is a risk factor for refractory epilepsy [7]. Anxiety and insomnia are common symptoms of epilepsy that affect epilepsy onset [8]. The lifetime prevalence of anxiety was 2.4 times higher in epilepsy patients than in those without epilepsy [9], and the prevalence of insomnia disorder (ICSD-2 or DSM-IV-TR) was shown to range from 36.0% to 74.4% in epilepsy patients [10].

In addition to the prominent prevalence of psychiatric symptoms in epilepsy patients, psychiatric symptoms, such as depression, anxiety, aggression, delusions, drowsiness, and reduced concentration, are the main side effects of antiepileptic drugs (AEDs) [11, 12]. AEDs regulate the sleep-wake cycle by decreasing rapid eye movement (REM), slow-wave sleep (SWS), and sleep latency [13]. Some antidepressants, which can be used to reduce psychiatric symptoms, can increase the risk of epileptic seizures [14] and can cause discomfort, such as nausea, dizziness, and sedation, which can worsen the quality of life in epilepsy patients [15].

Treatment is difficult due to the complex relationship between these multiple symptoms and drugs, and psychiatric symptoms create a vicious cycle in patients with epilepsy, followed by reduced compliance to antiepileptic drugs or triggering seizures [16]. Therefore, we need to effectively treat psychiatric symptoms.

Nevertheless, it is difficult for patients to receive adequate treatment for psychiatric symptoms. This is because there are no established criteria on antidepressants or hypnotics for patients with epilepsy, and there is a risk of exacerbating seizures [15]. For example, some first-generation antidepressants, especially tricyclic antidepressants, are reported to have a very high risk of seizure occurrence [15, 17]. Currently, even though depression in epilepsy is mainly treated with selective serotonin reuptake inhibitors (SSRIs), the FDA warns patients with seizures against taking them [18].

Thus, in a situation where reliable evidence regarding the effective and safe use of these drugs would help treatment decisions, we need to find evidence for the selection of antidepressants with the lowest risk of seizure exacerbation. Recently, herbal medicines, with fewer side effects, have been in the spotlight [19], among which, the Shugan Jieyu capsule (SJC) has been licensed since 2008 and is widely prescribed, especially for depression [20], but also anxiety, insomnia, stroke, and schizophrenia [21-24]. Shugan Jieyu is composed of *Acanthopanax senticosus* and *Hypericum perforatum* [25]. *Acanthopanax senticosus* has been traditionally used to treat brain diseases such as stroke and nervous breakdown [26] and has been reported to improve depressive disorder, ischemic stroke, and fatigue in previous clinical trials [26-28]. *Hypericum perforatum* is clinically effective against depression [29] and has been reported to have sedative effects in preclinical studies in rodents [30].

Based on these facts, we will conduct a preliminary study to analyze the effectiveness and safety of the SJC against psychiatric symptoms, mainly depression, anxiety, and insomnia, in epilepsy by synthesizing results from individual trials. Accordingly, the aims of this study are to

I) Assess the effectiveness of SJC alone or in combined administration on psychiatric symptoms,

II) Evaluate the seizure frequency when SJC is administered alone or in combination,

III) Determine the quality of life when SJC is administered alone or in combination,

IV) Describe the adverse effects when SJC is administered alone or in combination.

MATERIALS AND METHODS

This systematic review was registered on PROSPERO with CRD 42021238804 (available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021238804). This protocol was conducted according to the Preferred Reporting Item for Systematic Review and Meta-analysis (PRISMA-P) list. The detail of the PRISMA-P checklist can be found in the supplementary file.

Since the eligible study was previously approved by the local ethics committee and the subjects had signed the informed consent form for each study, ethical approval was not necessary for this review.

1. Inclusion criteria

1) Types of studies

All randomized control trials (RCTs) of SJC for the treatment of psychiatric symptoms in epilepsy patients will be included without publication status restrictions. Here, psychiatric symptoms are limited to depression, anxiety, and insomnia. We

will include publications in English, Korean, Chinese, and Japanese.

2) Types of participants

Participants should meet the following criteria: (1) patients diagnosed with epilepsy (any type); (2) patients who met any criteria for each psychiatric symptom (e.g., depression, anxiety, insomnia) in the questionnaire or validated tools. For example, the Patient Health Questionnaire 9-item Depression and Hamilton Depression Rating Scale will be included. There will be no restrictions with sex, age, or race.

3) Types of interventions

Studies that used SJC or modified SJC were included. The modified SJC is prescribed according to personal differentiation by adding or subtracting herbs to the original formula and has almost the same effects as the original prescription.

There are no restrictions on the dosage, frequency, duration, or follow-up time of interventions. In addition, we included the studies in which SJC was used alone or with conventional treatment as an intervention.

4) Types of comparators

All types of control, including placebo, conventional treatment, and no treatment, will be included in this review. Studies using acupuncture or other herbal medicines as comparators will be also included.

5) Type of outcome measurements

(1) Primary outcomes

The outcomes of psychological symptoms will be measured by the change in the validated scale from baseline to the endpoint.

1. Depression: An overall reduction in depression occurring during trials, measured using a depression scale, such as the Hamilton Depression Rating Scale, Chinese-Neurological Disorders Depression Inventory for Epilepsy, or Patient Health Questionnaire 9-item Depression.

2. Anxiety: An overall reduction in anxiety occurring during trials, measured using an anxiety scale, such as the Hamilton Anxiety Rating Scale or State-Trait Anxiety Inventory.

3. Insomnia: An overall reduction in insomnia occurring during trials, measured using an insomnia scale, such as the Pittsburgh Sleep Quality Index or Insomnia Severity Index.

4. Frequency of epileptic seizures: To identify antidepressants with the lowest risk of seizure exacerbation, the frequency of monthly epileptic seizures will also be measured.

(2) Secondary outcomes

1. Adverse effects: Assessed based on the incidence of adverse events.

2. Quality of life: Assessed using a valid scale.

2. Exclusion criteria

Participants who took antipsychotic drugs, such as antianxiety drugs or antidepressants, for at least 2 weeks or who received treatment related to psychiatric symptoms will be excluded. Patients with psychiatric disorders other than depression, anxiety, and insomnia will also be excluded. If the full text cannot be obtained despite contacting the original author, it will be also excluded.

3. Databases and search strategy

We will conduct an investigation of published RCTs in the following academic electronic databases: MEDLINE (PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). We will also search the following Korean databases: Korean Traditional Knowledge Portal, the Korean Medical Database (KMBASE), and OASIS. The following Chinese and Japanese databases will also be included: CiNii and China National Knowledge Infrastructure (CNKI).

We will combine keywords (e.g., 'Shugan Jieyu' AND 'depression' AND 'epilepsy') to find trials that met the criteria mentioned above. Considering the characteristics of the database, the search strategy can slightly differ for each database, and we will conduct a comprehensive search. Furthermore, the reference lists of all collected articles will be checked to collect accurate information.

This study will be restricted to articles written only in English, Korean, Japanese, or Chinese. In addition, we will find existing studies published from database inception to January 2021.

4. Study selection

We will put all collected studies into EndNote X9 software for data selection. Two reviewers (YNK and SJK) will check the studies to ensure that they meet the criteria mentioned above.

 https://doi.org/10.3831/KPI.2023.26.1.38

They will select the exam independently by checking the details of the title and abstract. If there is a potentially eligible study, the full text will be obtained, and two reviewers will independently assess their eligibility. Any disagreement on the eligibility of the study will be resolved by discussion. The PRISMA flow chart of the study selection will be used to show the screening process of the study [31].

5. Data extraction

Two independent reviewers (SJK and YNK) will extract the data from the individual studies using a pre-specified data extraction form that includes the author, title, journal, year of publication, study design, intervention, comparison, follow-up, outcome measurements, results, and adverse events. We will contact the authors of the studies for further information, if necessary.

Two reviewers will crosscheck the results of data extraction. Any disagreement on the results of the study will be resolved through discussion.

6. Assessment of risk of bias

Two reviewers (SJK and YNK) will independently assess the risk of bias using the risk-of-bias tool (ROB) by Cochrane. It includes random sequence generation, allocation concealment, blinding of participants, blinding of personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each category can be evaluated in three stages: low risk of bias, high risk of bias, and unclear risk of bias. Any disagreement on the results of the RoB will be resolved through discussion.

7. Data analysis

We will use Cochrane Collaboration's software program Review Manager (RevMAN) for Windows to execute all statistical analyses. Continuous data will be indicated using mean differences (MDs) with 95% confidence intervals (CIs). When we analyze the difference between the control and intervention groups, the above method is applied. Standardized mean differences will be adopted if there is high heterogeneity between studies. Dichotomous data will be expressed using relative risks (RRs) with 95% CIs.

A chi-square test will be performed to assess statistical heterogeneity (p-value < 0.10). An additional I^2 test will be carried out to determine the degree of heterogeneity, regardless of the number of studies. I^2 < 50% will be considered to indicate statistical homogeneity, where an overall estimate can be obtained by integrating the data from individual studies.

8. Subgroup analysis

Subgroup analyses can be conducted if the reviewers are aware of any factors that potentially affect heterogeneity, for example, when the difference in the frequency of treatment or follow-up period is large. However, this will be possible only if a sufficient number of studies are retained for the review.

9. Publication bias

RevMAN software will be used to confirm publication bias. A funnel plot will be used to detect potential reporting biases and publication bias will be checked by visually examining and statistically assessing the asymmetry of the funnel plot.

RESULTS

The systematic review and meta-analysis will be reported following the PRISMA-P statement.

DISCUSSION

Although psychiatric symptoms aggravate epilepsy, they cannot be aggressively treated due to a lack of evidence for conventional sedatives in epilepsy. Moreover, there are no criteria for tranquilizer administration for patients with epilepsy. In this context, our study may suggest an effective and safe treatment with SJC, an herbal medicine.

According to this protocol, we will rigorously evaluate the quality of the included studies for SJC. This is the first study to evaluate the possibility of using SJC for the treatment of psychiatric symptoms in epilepsy. We expect this review to systematically and scientifically assess the efficacy and safety of SJC, a potential AED candidate, and provide high-quality evidence that can contribute to establishing clinical guidelines for patients with epilepsy. Furthermore, we expect to help develop a natural medicine that is specific to each psychiatric symptom and has fewer side effects.

CONCLUSION

This protocol for systematic review aimed to set a method to evaluate the efficacy and safety of SJC for the treatment of psychiatric symptoms in epilepsy. We anticipate that this study will provide a clinically applicable rationale for patients with epilepsy when choosing treatment.

ACKNOWLEDGMENT

Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2020R1F1A1067569) supported this work. Thank you for the Undergraduate Research Program (URP) grant of Kyung Hee University College of Korean Medicine, Republic of Korea.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

All authors declare that they have no competing financial interests or personal relationships with which this study could have an impact.

AUTHORS' CONTRIBUTIONS

KSJ, KYN, and CSH conceptualized the study and formulated the research aims. KSJ and KYN developed the methodology for this study. KSJ wrote the original draft and KYN helped edit the manuscript. KYN and CSH critically revised the manuscript. CSH supervised the research. The final manuscript was read and approved by all authors.

FUNDING

Not applicable.

ORCID

Sejin Kim, https://orcid.org/0000-0001-5649-3172
Yunna Kim, https://orcid.org/0000-0003-2286-1242
Seung-Hun Cho, https://orcid.org/0000-0002-0627-768X

REFERENCES

1. Michaelis R, Tang V, Nevitt SJ, Wagner JL, Modi AC, LaFrance WC Jr, et al. Psychological treatments for people with epilepsy. Cochrane Database Syst Rev. 2020;8(8):CD012081.
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342(5):314-9.
3. Fiest KM, Dykeman J, Patten SB, Wiebe S, Kaplan GG, Maxwell CJ, et al. Depression in epilepsy: a systematic review and meta-analysis. Neurology. 2013;80(6):590-9.
4. Kennedy SH. Core symptoms of major depressive disorder: relevance to diagnosis and treatment. Dialogues Clin Neurosci. 2008;10(3):271-7.
5. Kanner AM. Depression and epilepsy: a bidirectional relation? Epilepsia. 2011;52 Suppl 1:21-7.
6. Danzer SC. Depression, stress, epilepsy and adult neurogenesis. Exp Neurol. 2012;233(1):22-32.
7. Hesdorffer DC, Ishihara L, Mynepalli L, Webb DJ, Weil J, Hauser WA. Epilepsy, suicidality, and psychiatric disorders: a bidirectional association. Ann Neurol. 2012;72(2):184-91.
8. Quigg M, Gharai S, Ruland J, Schroeder C, Hodges M, Ingersoll KS, et al. Insomnia in epilepsy is associated with continuing seizures and worse quality of life. Epilepsy Res. 2016;122:91-6.
9. Tellez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia. 2007;48(12):2336-44.
10. Macêdo PJOM, Oliveira PS, Foldvary-Schaefer N, Gomes MDM. Insomnia in people with epilepsy: a review of insomnia prevalence, risk factors and associations with epilepsy-related factors. Epilepsy Res. 2017;135:158-67.
11. Stephen LJ, Wishart A, Brodie MJ. Psychiatric side effects and antiepileptic drugs: observations from prospective audits. Epilepsy Behav. 2017;71(Pt A):73-8.
12. Zhang LL, Zeng LN, Li YP. Side effects of phenobarbital in epilepsy: a systematic review. Epileptic Disord. 2011;13(4):349-65.
13. Foldvary N, Perry M, Lee J, Dinner D, Morris HH. The effects of lamotrigine on sleep in patients with epilepsy. Epilepsia. 2001;42(12):1569-73.
14. Trivedi MH, Kurian BT. Managing depressive disorders in patients with epilepsy. Psychiatry (Edgmont). 2007;4(1):26-34.
15. Maguire MJ, Weston J, Singh J, Marson AG. Antidepressants for people with epilepsy and depression. Cochrane Database Syst Rev. 2014;2014(12):CD010682.
16. Guo Y, Ding XY, Lu RY, Shen CH, Ding Y, Wang S, et al. Depression and anxiety are associated with reduced antiepileptic drug adherence in Chinese patients. Epilepsy Behav. 2015;50:91-5.
17. Curran S, de Pauw K. Selecting an antidepressant for use in a patient with epilepsy. Safety considerations. Drug Saf. 1998;18(2):

125-33.
18. Gilliam FG, Black KJ, Carter J, Freedland KE, Sheline YI, Tsai WY, et al. A trial of sertraline or cognitive behavior therapy for depression in epilepsy. Ann Neurol. 2019;86(4):552-60.
19. Wani M, Polshettiwar SA, Parakh SR, Chopade VV. Herbal medicine and its standardization. Pharm Rev. 2007;5(6):1-2.
20. Sun X, Chen A, Xu X, Zhang H, Tang Q, Zhang H. Randomized, double blind, placebo-controlled trial of Shuganjieyu capsule in the treatment of mild or moderate depression. Chin J New Drugs. 2009;18:413-6.
21. Si C, Wang H, Luo M, Xie J, Chen Y, Guan H, et al. A control study on treatment of vasovagal syncope with mild-to-moderate depression and anxiety by Shugan Jieyu capsules, Flupentixol and Melitracen tablets. World Sci Technol Mod Tradit Chin Med. 2015;17(6):1230-4.
22. Deng H, Adams CE. Traditional Chinese medicine for schizophrenia: a survey of randomized trials. Asia Pac Psychiatry. 2017;9(1):e12265.
23. Fan M, Guo D, Tian Y, Liu Y, Zhao J. Efficacy and safety of Shugan Jieyu capsule in the treatment of essential hypertension with insomnia, anxiety or depression: a protocol for systematic review and meta-analysis. Medicine (Baltimore). 2021;100(8):e24856.
24. Gong L, Yang X, Feng Y, Fei Z, Wang M, Qin B, et al. The efficacy of integrative anti-depressive therapy on motor recovery after ischemic stroke - a randomized clinical trial. Eur J Integr Med. 2020;35:101102.
25. Yao G, Li J, Wang J, Liu S, Li X, Cao X, et al. Improved resting-state functional dynamics in post-stroke depressive patients after Shugan Jieyu capsule treatment. Front Neurosci. 2020;14:297.
26. Li W, Liu M, Feng S, Wu B, Zhang S, Yang W, et al. Acanthopanax for acute ischaemic stroke. Cochrane Database Syst Rev. 2009;(3):CD007032.
27. Zhang X, Kang D, Zhang L, Peng L. Shuganjieyu capsule for major depressive disorder (MDD) in adults: a systematic review. Aging Ment Health. 2014;18(8):941-53.
28. Kuo J, Chen KW, Cheng IS, Tsai PH, Lu YJ, Lee NY. The effect of eight weeks of supplementation with Eleutherococcus senticosus on endurance capacity and metabolism in human. Chin J Physiol. 2010;53(2):105-11.
29. Ng QX, Venkatanarayanan N, Ho CY. Clinical use of Hypericum perforatum (St John's wort) in depression: a meta-analysis. J Affect Disord. 2017;210:211-21.
30. Rezaei A, Rezaei-Dorostkar K, Pashazadeh M, Ahmadizadeh C, Jafari B. A comparative study of sedative and anxiolytic effects of the Hypericum perforatumin and diazepam on rats. Zahedan J Res Med Sci. 2012;13(8):e93758.
31. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.