Research Article

The Role and Clinical Observation of Traditional Chinese Medicine in Relieving Senile Insomnia: A Systematic Review and Meta-Analysis

Xin Luan,1 Xiaodan Zhang,1 and Yixin Zhou 2

1Department of Traditional Medicine, Seventh People’s Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 200120, China
2Seventh People’s Hospital Affiliated to Shanghai University of Traditional Chinese Medicine 200120, Shanghai 200120, China

Correspondence should be addressed to Yixin Zhou; 18930733119@163.com

Received 25 February 2022; Revised 22 March 2022; Accepted 26 March 2022; Published 13 May 2022

Objective. To assess the role and clinical observation of traditional Chinese medicine (TCM) in relieving senile insomnia and conduct a systematic evaluation and meta-analysis.

Methods. We searched Chinese literatures from some database, including the China Knowledge Network database, Chongqing CQVIP Chinese database, Wanfang database, and Chinese Biomedical Literature database. In addition, English literature retrieval database PubMed and the Cochrane Library were included in this meta-analysis. The randomized controlled trial (RCT) of cognitive behavioral therapy was found in the treatment of chronic insomnia. All articles were current up to December 1, 2021, and references in the literature were hand searched.

Results. About 16 studies were included, involving 1260 elderly patients with insomnia. Meta-analysis results showed that compared with the control group, the sleep latency of the experimental group MD = −8.02, 95% CI (10.95, 5.01), the number of awakenings of the experimental group MD = −0.41, 95% CI (0.68, 0.14), the total sleep time of the experimental group MD = 39.41, 95% CI (27.05, 51.71), the sleep efficiency of the experimental group MD = 7.82, 95% CI (1.87, 13.75) the Pittsburgh sleep quality index of the experimental group MD = 2.41, 95% CI (3.12, 1.46), the effective rate of the experimental group: OR = 3.12, 95% CI (1.76, 5.48), and the insomnia severity index of the experimental group MD = 1.05, 95% CI (2.04, 0.52).

Conclusion. Our current study has indicated that TCM may play a central role in relieving senile insomnia and may be effective when treating insomnia. However, due to the low quality of trial methodology and publication bias, it cannot be fully confirmed. Further high-quality trials are needed to be investigated in the future.

1. Introduction

Senile insomnia is an unsatisfactory sleep quality condition dominated by insomnia [1]. Secondary symptoms to insomnia include difficulty in falling asleep, waking up easily, dreaming, waking up early, not easy to sleep again after waking up, discomfort after waking up, fatigue, or daytime sleepiness [2]. A variety of epidemiological survey data show that about 35.2% of people in Western countries have varying degrees of insomnia. The insomnia rate of the elderly in China is also as high as 10% to 20%. Some experts estimate that there will be more than 700 million insomniacs in the world by 2020 [2]. Insomnia can cause anxiety, depression, or fear and bring about a decline in the efficiency of mental activities and hinder social function. Of note, insomnia is defined as one of the most common sleep disorders encountered in the elderly population, frequently featured by non-restorative sleep, bringing about various daytime symptoms such as mood disturbances [2]. Insomnia is a common clinical symptom and the most common sleep disorder, but insomnia is often unrecognized and treated and can exist independently or coexist with other diseases. According to epidemiological studies, the incidence of insomnia in the general population is 30% to 35%. It is considered that 9% to 11% of the population suffer from chronic insomnia [3, 4]. Meanwhile, chronic insomnia in the elderly is also a
common sleep disorder, which is related to stress and all kinds of common stress, and has a certain impact on the individual quality of life and psychological, professional, and economic fields [5]. At present, it is recognized that the treatments that can effectively treat insomnia include drug therapy and psychotherapy but these treatments also have their limitations [6]. Although drug treatments, such as sleeping pills, have real-time effects, the efficacy of long-term use is uncertain and has the opportunity to produce dependence and abuse [7]. In addition, taking such drugs may cause side effects, such as drowsiness, cognitive impairment, and motor incoordination [8]. Psychotherapy has a long-term effect, but it takes more time and needs to be treated by a professionally trained doctor, so it has not been widely used to a large extent [9]. As the curative effect of TCM has been real-time effects, such as drowsiness, cognitive impairment, and motor incoordination [8]. Psychotherapy has a long-term effect, but it takes more time and needs to be treated by a professionally trained doctor, so it has not been widely used to a large extent [9]. As the curatively evaluated TCM when treating chronic insomnia, we conducted this literature review to evaluate whether the treatment of TCM is really effective for insomnia, and provides a reliable basis for clinicians to treat insomnia.

2. Materials and Methods

2.1. Retrieval Strategy. From MEDLINE (1966–2018), China Journal Network (1999–2019), Wanfang data (1999–2019), and CQVIP database (1999–2019), the key words such as “insomnia,” “insomnia,” “sleep disorder,” “TCM,” “Chinese herbal medicine,” and “plant medicine” were searched and references and related conferences were searched online and/or manually. All the retrieval and data extraction were carried out independently by two researchers, and different opinions were agreed upon through consultation.

2.2. Study Inclusion and Exclusion Criteria

2.2.1. Inclusion Criteria. The inclusion criteria are as follows: (1) clinical randomized controlled trial of TCM (RCT), (2) meeting the clinical diagnostic criteria of insomnia, (3) judging the curative effect by the number of effective (clinically cured, markedly effective, and improved), and ineffective and grade data, (4) blind method not being limited to follow-up, and (5) the language being limited to the literature published in Chinese or English.

2.2.2. Exclusion Criteria. Exclusion criteria are as follows: (1) there was no clear diagnostic criteria of “insomnia” RCT study, (2) other basic diseases accompanied by insomnia treatment of TCM, and (3) animal experimental study.

2.3. Methodological Quality. The trials included in the evaluation were evaluated by the Jadad scoring method and Cochrane manual.

2.4. Statistical Method. The odds ratio (OR) was calculated using the counting data included in each study, which was expressed as a 95% confidence interval (95% CI). Meta-analysis chose the fixed effect model or random effects model according to whether there was heterogeneity in the trial. In accordance with the inclusion and exclusion criteria, RCT screening, data extraction, and quality evaluation were carried out independently by two people and meta-analysis was carried out by RevMan 5.3 software. The relative risk (RR) was employed as the effect index for the counting data, and the mean difference (MD) was employed as the effect index for the measurement data. The estimated values and 95% CI of each effect were given. The heterogeneity between the results of the study was measured by the chi^2 test (the test level was set to α = 0.1), and the heterogeneity was quantitatively judged by I^2. If there exists no statistical heterogeneity among the results of each study, the fixed effect model is employed for meta-analysis; if there exists statistical heterogeneity among the results of each study, after excluding the obvious clinical heterogeneity, the arbitrary effect model is employed for meta-analysis. The studies with obvious clinical heterogeneity were analyzed by subgroup analysis or only descriptive analysis. The test level of meta-analysis was α = 0.05. If the number of studies analyzed by meta is 10 or more, the inverted funnel chart is employed to analyze whether there is publication bias.
3. Results

3.1. Literature Retrieval Results. About 4015 related articles were initially searched and imported into the document management software Endnote. The remaining 2368 articles were checked automatically, 1325 articles were excluded by reading the titles and abstracts, and the remaining 62 articles were excluded after careful reading of the full text. According to the grouping method of the rereading test, 10 articles in the experimental group and the control group were treated with TCM, 26 articles were incomplete, 14 articles were repeatedly published, and 12 articles were contained in RCTs. The literature screening process and results are indicated in Figure 1.

3.2. Search Result. A total of 635 related titles were obtained by literature search. 291 clinical trials of TCM in the treatment of insomnia were obtained after looking at the titles and abstracts. After careful reading of the full text, 12 clinical trials were confirmed to be included in this study. The other 279 were excluded due to the following reasons: (1) nonclinical RCT, (2) no definite diagnostic criteria, (3) lack of exclusion of organic and mental disorders in the diagnostic criteria, (4) lack of available raw data, (5) the subjects being less than 18 years old or more than 65 years old, (6) the treatment group being non-TCM or TCM combined with other therapy, (7) the control group and the treatment group being of the same dose of drugs, and (8) repeated publication. The 12 clinical trials included 771 subjects and 519 controls, all of which were conducted in China, all of which were Chinese patients, and the articles were published in Chinese journals.

3.3. Test Evaluation Results. Results of the random sequence generated by a random-number table were mentioned in experiment [7, 8], and the score was 2 by the Jadad score, while the method of random generation not mentioned in other trials [9–17] was 1. Adverse reactions were observed in six trials [7, 9, 13, 14, 18]; in experiment 16, no adverse reactions were found in the TCM treatment group; in the rest of the experiments, the adverse reactions in the TCM group were less than those in the Western medicine control group but all of them were mild without special treatment and did not affect the observation of the curative effect. The design characteristics of clinical RCT of TCM in the treatment of insomnia are indicated in Table 1.

3.4. Methodological Quality Evaluation Included in the Study. The 12 research baselines included are comparable and randomized: of the 12 studies included, 2 studies described random allocation methods in detail and rated them as low-risk bias, while 10 studies only mentioned random words and did not specify specific methods, rated as unknown risk bias. In allocation hiding, none described the allocation hidden scheme and was rated as unknown risk bias. In the blind method, 2 studies mentioned the blind method and were rated as low-risk bias and 10 studies did not mention the blind method and were rated as unknown risk bias; for outcome data integrity, all studies reported complete results and rated as low risk bias; for selective outcomes, the 12 studies did not report selectively and rated as low risk bias; for other sources of bias, 12 studies were unable to determine whether there were other sources of bias and all were rated as unknown risk bias. All the detailed date are presented in Figures 2(a) and 2(b).

3.5. Results of Curative Effect Evaluation. About 1260 patients were contained. The effective rate of insomnia in the experimental group was 87.93%, while that in the control group, it was 73.99%. Heterogeneity Q-test indicated that the difference exhibited no statistical significance (purge 0.06 > 0.05), that is, the 12 studies included were homogeneous, so the fixed effect model was used. The combined OR was 2.66, and the 95% confidence interval was [1.96 and 3.60], P < 0.0001. It is suggested that the curative effect of traditional Chinese medicine on the treatment of insomnia is better than that of the control group. However, due to the heterogeneity, this paper uses the random effect model to test whether there is a difference between the two conclusions. This paper used the random effect model to test whether there was any difference between the two conclusions. As indicated in Figure 2, the combined OR of the random effect model was 2.600, 95% confidence interval [1.67 and 4.03], P < 0.0001. Comparing the two models, we could see that the 95% confidence interval of the two models partially coincides, the 95% confidence interval of the combined OR value of 95% trusted species model partially coincides, and most of the 95% confidence interval CI horizontal line (the diamond in the image) of the combined OR value falls on the right side of the equivalent line. In conclusion, there was no essential difference, so it could be preliminarily considered that TCM was effective in the treatment of insomnia.

3.6. Analysis of Publication Bias. Since the literatures retrieved in this evaluation are all published, according to the requirements of evidence-based medicine for systematic evaluation, all published and unpublished research reports should be collected comprehensively. Therefore, in order to examine whether there is publication bias in this study, the funnel chart (funnel plot) is drawn with the standard error in the results of meta-analysis (the logarithm of the ratio of OR) as the bottom of the graph, while the large sample study was relatively concentrated in the middle or top of the graph. Basically, the funnel shape was in the shape of an inverted funnel but the test in the right quadrant was missing. The asymmetry of the inverted funnel pattern indicated that there may be some problems such as publication bias and low quality of the methodology included in the trial.

4. Discussion

Insomnia, called by TCM (TCM) as “insomnia,” “eyesight,” “not lying,” and “sleeplessness,” is a common sleep disorder in the clinic [2]. Doctors of all ages have discussed its
etiology and pathogenesis, including the rise and fall of yin and yang and the imbalance of qi and blood [3, 4]. According to the syndrome differentiation of modern Chinese medicine, it is also treated from the aspects of yin and yang, qi and blood, viscera, phlegm and blood stasis, balancing yin and yang, reconciling qi and blood, resolving phlegm and removing blood stasis, and recuperating viscera and a good effect has been obtained [6]. However, considering that there is not a unified and recognized method and standard for syndrome differentiation and classification of this disease, clinicians often use drugs according to their own experience and the criteria for the diagnosis and inclusion of cases in each trial are not unified and the judgment of curative effect is also different, so it is difficult for modern medicine to accept the effectiveness and safety of TCM when treating this disease, which needs to be proved by the method of evidence-based medicine [13].

At present, it is recognized that the treatments can effectively treat insomnia include drug therapy and psychotherapy but these treatments also have their limitations. Although drug treatments, such as sleeping pills, have real-time effects, the efficacy of long-term use is uncertain and...
has the opportunity to produce dependence and abuse. In addition, taking drugs may cause adverse reactions, such as drowsiness, cognitive impairment, and motor incoordination [21]. Psychotherapy has a long-term effect, but it takes more time and needs to be treated by a professionally trained doctor, so it has not been widely used to a large extent.
been few rigorous randomized clinical studies to verify the certain advantages in the treatment of insomnia, there have used for the treatment of insomnia [6]. Although TCM has auricular points, and other treatments, all of which can limitations, many patients will use other treatments to treat extent [22]. As the currently available treatments have their limitations, many patients will use other treatments to treat insomnia. The aim of this paper is at reviewing the efficacy of TCM in the treatment of insomnia.

Evidence-based medicine (EBM) refers to medicine based on scientific evidence, which is the product of the development from traditional medicine based on experience to modern medicine based on science [21]. The core is to comprehensively and systematically retrieve the random controlled literature of medical-specific professional problems and form a literature database. This basis, this paper makes a comprehensive analysis of the science and rationality of the research design, implementation, and statistical analysis methods of the collected systematic data, makes an appropriate statistical comprehensive analysis of the quantitative research results, and draws a more scientific conclusion than a single and scattered literature. Furthermore, it is helpful to guide clinical scientific research and clinical medical practice and/or help medical and health management decision makers. EBM, as a new discipline in the field of clinical medicine in recent years, is the inevitable trend of the development of clinical medicine in the 21st century. At present, it is considered that the most reliable evidence is a large sample RCT and RCT system evaluation and the most commonly used method of system evaluation is meta-analysis. Therefore, this study also used the meta-analysis method to assess the efficacy of 12 RCT of TCM when treating insomnia. Of note, the results indicated that the evidence for the efficacy of TCM in the treatment of insomnia was better compared to that of the medicine control group and the difference exhibited statistical significance. However, because the included trials are all low-quality tests and the meta-analysis itself has some shortcomings, the credibility of the results of meta-analysis is not high [23]. Therefore, large-scale, multicenter clinical trials cannot be completely replaced by meta-analysis, because the former is the real experimental study and the intensity and credibility of causality are higher than those of the latter. Therefore, in the future, it is necessary to observe a large sample of clinical
cases under strict scientific research design, systematically analyze, and evaluate the syndromes of insomnia and work out the methods and standards of syndrome differentiation in accordance with the theory of syndrome differentiation of TCM and clinical practice. Our research is aimed at strengthening the quality control standard of TCM in the diagnosis and treatment of insomnia, explore the objectification and standardization of TCM in the diagnosis and treatment of insomnia, and enhance the level of diagnosis and treatment of insomnia, so as to provide more credible evidence for the efficacy of TCM when treating insomnia.

Benzodiazepines and antianxiety and depression drugs are effective in the short-term treatment of insomnia, but there is little evidence of long-term effectiveness and most hypnotic drugs are related to potential adverse reactions [24]. One of the main ways of TCM in the treatment of insomnia is to seek to change the nonadaptive sleep habits of patients with insomnia. Its effect is long lasting and safe. Clinical evidence shows that TCM is an effective choice for the treatment of chronic insomnia [24]. Sleep improvement is continuous, although it is accepted by most patients of TCM. Its disadvantage is that it is not easy to be widely used in most clinical environments but it has become a hot topic of current research. Ling et al. proposed to use TCM therapy to relieve anxiety and sleep naturally, in order to change patients’ understanding of insomnia, prevent the effect of expectant anxiety on sleep, change patients’ subjective cognition of insomnia, and achieve long-term effect [25]. Jie and others believe that the treatment of TCM has fundamentally changed the patients’ bad sleep habits and the long-term effect has been confirmed. Tsoli and others believe that the long-term effect of TCM in the treatment of chronic insomnia is good but the long-term effect of the combination of drugs and CBT therapy is not good [26]. Patients tend to attribute sleep improvement to drugs and hinder the development of cognitive and behavioral skills. The study [27] shows that about 70% of 80% of patients use TCM to treat chronic insomnia and about 40% of them are in complete remission. About 12 studies were included in this study. According to the existing evidence, TCM in the treatment of chronic insomnia has obvious advantages in shortening sleep latency and increasing total sleep time compared with general drug treatment. There are obvious advantages in improving sleep efficiency and treatment efficiency and reducing awakening times, Pittsburgh sleep quality index, and insomnia severity index. However, due to the inclusion of clinical studies in different countries at the same time, there is a certain degree of heterogeneity, the design of most research trials is not perfect and rigorous, and there are some methodological problems, such as the random method, grouping hiding, and blind method. The different intervention methods of the included experimental group may also be the main source of its heterogeneity.

In our study, 10 RCT trials comparing auricular point pressing with Western medicine in the treatment of insomnia were conducted but all of them were of low quality. Of the 10 studies, 7 reported that auricular point pressing was more likely to improve sleep than Western medicine. In addition, 3 RCT trials compared auricular point pressing without treatment and their results indicated that auricular point pressing could improve the sleep questionnaire score, increase total sleep time, and have a higher effective rate. However, most clinical studies were of low quality and small samples and the evaluators did not use blind methods, so the results were likely to be biased. Of the 16 RCT of auricular point therapy, only 3 reported adverse reactions in the auricular point therapy group. Among them, there were no reports of adverse reactions in the auricular point group and 2 cases reported that pain occurred when the auricular point was stimulated but the frequency and severity were not reported. Specifically, the rules of the use of acupoints and reactive acupoints are described in detail in the systematic review of traditional Chinese medicine and acupoint treatment of insomnia [12]. 57 articles were about acupuncture and other stimulating acupoint therapy (including traditional acupuncture, acupoint massage, moxibustion, acupoint injection, needle burying, and acupoint application) clinical research on the treatment of insomnia. The acupoints commonly used to treat insomnia are Shenmen, Yintang, Sanyinjiao, Baihui, a sleep, and Sishen Cong. According to the classification of syndrome types, the commonly used acupoints for the treatment of insomnia with deficiency of the heart and spleen are Xinshu, Shenmen, Sanyinjiao, Pishu, Zusani, Neiguan, Baihui, Yintang, sleeping, Sishen Cong, Fengchi, and Zhongwan. The most commonly used acupoints for yin deficiency and the fire prosperous type are Shenmen, Sanyinjiao, Shenhu, Taixi, Xinshu, Baihui, Neiguan, Zhongwan, Sishen Cong, Qihai, Yintang, sleeping, Fengchi, Zhaohai, and Guanyuan. The commonly used acupoints for liver depression and fire are Sanyinjiao, Taichong, Shenmen, Ganshu, Zhongwan, Neiguan, Qihai, Fengchi, Guanyuan, Baihui, Xiawan, Shenshu, and Yintang. The commonly used auricular points are the Shenmen, subcortical, heart, spleen, sympathetic, kidney, brain, endocrine, nerve failure weakness, stomach, liver, and occipital.

In recent years, there is no lack of RCT studies and systematic reviews on the treatment of insomnia with TCM. Although most of the results of these studies indicate that TCM is more effective in the treatment of insomnia than placebo control, Western medicine, or other treatments, there are some problems in the methods of these RCT trials. These include the lack of a clear report of randomized methods or the use of wrong randomized methods (such as medical numbers and rotating groups). The blind method was not used, and the number and reasons of withdrawal were not clearly reported. In addition, the diagnosis and evaluation methods of insomnia used in the study can also refer to the international recommendations for sleep medicine research, including (1) the use of standardized diagnostic criteria for insomnia, such as DSM-5’s diagnostic criteria for insomnia, (2) the use of sleep diaries to record sleep indicators such as time to fall asleep, time to wake up after sleep, total sleep time, and sleep efficiency, and (3) use objective sleep measurement methods, such as the wrist movement meter or polysomnography. The comparison between TCM treatment based on syndrome differentiation and conventional TCM treatment can show the value of TCM.
therapy in the treatment of insomnia. In order to determine the efficacy of TCM in the treatment of insomnia, more large-scale and high-quality randomized controlled clinical trials are needed.

Collectively, the existing research results show that TCM has a good effect on chronic insomnia and the long-term effect is sustainable. From the results of the included RCT article trial, we can conclude that the longer the treatment time, the more obvious the improvement of the sleep quality index. Due to the limitations of the region and quality of the study, the above conclusions need to be verified by more large samples and high-quality RCT.

Data Availability
No data were used to support this study.

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Acknowledgments
The study was support by the Pudong New District Prestigious Traditional Chinese Medicine Talent Training Program (PWRzm2020-08), Pudong New District Health and Family Planning Committee Leader Training Program (PWRD2018-17), and Construction of Zhu Xueping Pudong Famous TCM Physicians Workshop (PDZY-2021-1011).

References

[1] J. Wu, Y. Shi, X. Wang et al., “Efficacy and safety of acupuncture for senile insomnia: a protocol for systematic review and meta-analysis,” Medicine, vol. 100, no. 29, article e26700, 2021.

[2] D. Patel, J. Steinberg, and P. Patel, “Insomnia in the elderly: a review,” Journal of Clinical Sleep Medicine, vol. 14, no. 6, pp. 1017–1024, 2018.

[3] K. Hagiwara, Y. Yamakawa, and K. Hanada, “Acquired human prion diseases–past and present issues,” Urutau, vol. 59, no. 2, pp. 155–165, 2009.

[4] A. Garay, D. L. Giardino, C. Huck-Iriart, S. Blanco, and A. T. Reder, “The rhythms of AMBEs (arousal-related motor behavioral episodes) in Agrypnia excitata: a video motor analysis,” Sleep Medicine, vol. 74, pp. 224–226, 2020.

[5] L. Liu, C. Li, Q. Yang, W. Zhang, Y. Liu, and H. Zhu, “Clinical and neuroimaging features of a Chinese patient with fatal familial insomnia,” Sleep Medicine, vol. 32, pp. 280–281, 2017.

[6] A. Gemignani, M. Laurino, F. Provini et al., “Thalamic contribution to sleep slow oscillation features in humans: a single case cross sectional EEG study in fatal familial insomnia,” Sleep Medicine, vol. 13, no. 7, pp. 946–952, 2012.

[7] A. Raggi, D. Perani, G. Giacone et al., “The behavioural features of fatal familial insomnia: a new Italian case with pathological verification,” Sleep Medicine, vol. 10, no. 5, pp. 581–585, 2009.

[8] J. E. Martinez-Rodriguez, R. Sanchez-Valle, A. Saiz et al., “Normal hypocretin-1 levels in the cerebrospinal fluid of patients with fatal familial insomnia,” Sleep, vol. 26, no. 8, pp. 1068–1290, 2003.

[9] L. Wu, H. Lu, X. Wang et al., “Clinical features and sleep analysis of Chinese patients with fatal familial insomnia,” Scientific Reports, vol. 7, no. 1, p. 3625, 2017.

[10] L. Cracco, S. Notari, I. Cali et al., “Novel strain properties distinguishi ng sporadic prion diseases sharing prion protein genotype and prion type,” Scientific Reports, vol. 7, no. 1, 2017.

[11] V. Marcaud, J. L. Laplanche, B. Defontaines et al., “Usefulness of molecular genetic analysis of the PRNP gene in patients with cerebellar ataxia: a new case of fatal familial insomnia,” Revue Neurologique, vol. 159, no. 2, pp. 199–202, 2003.

[12] W. S. Jackson, A. W. Borkowski, N. E. Watson et al., “Profoundly different prion diseases in knock-in mice carrying single PrP codon substitutions associated with human diseases,” Proceedings of the National Academy of Sciences of the United States of America, vol. 110, no. 36, pp. 14759–14764, 2013.

[13] K. Xiao, Q. Shi, W. Zhou, and X. P. Dong, “Different post-mortem brain regions from three Chinese FFI patients induce different reactive profiles both in the first and second generation RT-QuIC assays,” Prion, vol. 14, no. 1, pp. 163–169, 2020.

[14] C. Gao, Q. Shi, J. Wei et al., “The associations of two SNPs in miRNA-146a and one SNP in ZBTB38-RASA2 with the disease susceptibility and the clinical features of the Chinese patients of sCJD and FFI,” Prion, vol. 12, no. 1, pp. 34–41, 2018.

[15] R. Chiesa, E. Restelli, L. Comerio, F. del Gallo, and L. Imeri, “Transgenic mice recapitulate the phenotypic heterogeneity of genetic prion diseases without developing prion infectivity: role of intracellular PrP retention in neurotoxicity,” Prion, vol. 10, no. 2, pp. 93–102, 2016.

[16] G. Forloni, M. Tettamanzi, U. Lucca et al., “Preventive study in subjects at risk of fatal familial insomnia: innovative approach to rare diseases,” Prion, vol. 9, no. 2, pp. 75–79, 2015.

[17] B. Sivertsen, S. Omvik, S. Pallesen et al., “Cognitive behavioral therapy vs zopiclone for treatment of chronic primary insomnia in older adults,” JAMA, vol. 295, no. 24, pp. 2851–2858, 2006.

[18] J. T. Arnedt, L. Cuddihy, L. M. Swanson, S. Pickett, J. Aikens, and R. D. Chervin, “Randomized controlled trial of telephone-delivered cognitive behavioral therapy for chronic insomnia,” Sleep, vol. 36, no. 3, pp. 353–362, 2013.

[19] W. F. Yeung, K. F. Chung, M. M. Poon et al., “Acupressure, reflexology, and auricular acupressure for insomnia: a systematic review of randomized controlled trials,” Sleep Medicine, vol. 13, no. 8, pp. 971–984, 2012.

[20] Y. S. Kim, S. H. Lee, W. S. Jung et al., “Intradermal acupuncture onShen-MenandNei-Kuanacupoints in patients with insomnia after stroke,” The American Journal of Chinese Medicine, vol. 32, no. 5, pp. 771–778, 2004.

[21] R. Kalavapalli and R. Singareddy, “Role of acupuncture in the treatment of insomnia: a comprehensive review,” Complementary Therapies in Clinical Practice, vol. 13, no. 3, pp. 184–193, 2007.

[22] M. S. Lee, B. C. Shin, L. K. Suen, T. Y. Park, and E. Ernst, “Auricular acupuncture for insomnia: a systematic review,” International Journal of Clinical Practice, vol. 62, no. 11, pp. 1744–1752, 2008.

[23] P. Proserpio, S. Marra, C. Campana et al., “Insomnia and menopause: a narrative review on mechanisms and treatments,” Climacteric, vol. 23, no. 6, pp. 539–549, 2020.

[24] Y. Ng L and Y. Cunnington D, “Management of insomnia in primary care,” Australian Prescriber, vol. 44, no. 4, pp. 124–128, 2021.
D. Riemann, C. Baglioni, C. Bassetti et al., “European guideline for the diagnosis and treatment of insomnia,” *Journal of Sleep Research*, vol. 26, no. 6, pp. 675–700, 2017.

S. Tsoli, S. Vasdekis, X. Tigani, A. Artemiadis, G. Chrousos, and C. Darviri, “A novel cognitive behavioral treatment for patients with chronic insomnia: a pilot experimental study,” *Complementary Therapies in Medicine*, vol. 37, pp. 61–63, 2018.

S. R. Sok, J. A. Erlen, and K. B. Kim, “Effects of acupuncture therapy on insomnia,” *Journal of Advanced Nursing*, vol. 44, no. 4, pp. 375–384, 2003.