CHINESE HERBAL MEDICINE FOR INSOMNIA:

EVIDENCE AND EXPERIENCE

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Statement of Authentication

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

Yoann Birling

Contents

Abstract

Background

Insomnia, a condition with significant medical consequences, is becoming more and more prevalent worldwide. Hypnotic drugs are associated with dependence, adverse reactions and long-term risks. Psychotherapy is time- and resource-consuming and largely unavailable. As such, many people who present with insomnia also look for alternative treatments. Recent studies show that Chinese herbal medicine (CHM), a traditional herbal medicine based on holistic theories, could be a potential alternative.

Aims and research questions

The aims of this doctoral research were to explore the potential benefits of CHM for the treatment of insomnia and provide guidance in the treatment of insomnia with CHM. For practical reasons, the empirical aspect of the investigation focuses on one specific CHM product, which is Zao Ren An Shen (ZRAS). The research questions include: (1) Is ZRAS a safe and effective treatment for insomnia disorder? (2) How do Chinese medicine clinicians diagnose and treat insomnia with CHM?

Methods

This doctoral research consists of a narrative review and three major studies: one systematic review, one randomised, placebo-controlled trial and one clinical experience synthesis.

In the systematic review, clinical trial that assessed the efficacy and/or safety of ZRAS for insomnia were systematically searched and screened. Primary outcomes were sleep quality assessed with the Pittsburgh Sleep Quality Index (PSQI) and number of adverse events at post-treatment. The risk of bias was assessed with the Cochrane Collaboration's tool and meta-analyses were performed where possible.

In the clinical trial, after one week of placebo run-in, 85 participants with insomnia disorder were randomly allocated to either take ZRAS capsule or placebo for four weeks. Insomnia severity, psychological status, fatigue levels, quality of life, subjective sleep parameters, objective sleep

parameters, and adverse events were assessed through the intervention period and at a four-weeks follow-up. Both the investigator and the participants were blind to the treatment allocation.

In the clinical experience synthesis (CES), clinical experience reports published in the literature, which described treatment of insomnia with CHM, were systematically reviewed and screened. Data relevant to the diagnosis and treatment of insomnia with CHM was collected and analysed using a method driven from thematic and content analyses. The data were quantified where possible.

Results

A total of 18 studies (1,710 participants) were included in the systematic review. The effect of ZRAS on sleep quality (MD [95% CI], p, number of trials, number of participants) was found better than placebo (-0.90 [-1.56, -0.24], 0.007, 1, 60) and similar to benzodiazepine receptor agonists (BzRAs) (0.17 [-0.29, 0.64], 0.46, 7, 642). The number of adverse events (RR [95% CI], p, number of trials, number of participants]) was lower for ZRAS than BzRAs (0.16 [0.12, 0.23], <0.001, 10, 1003). An overall high risk of bias was found in the selected studies, especially for performance and detection risk of bias.

In the randomised clinical trial, the primary outcome of insomnia severity was found to be no different between the two groups at post-treatment (md = 0.7 points; p = 0.161). However, secondary outcomes of subjective sleep onset latency was significantly shorter (md = 12.2 min; p = 0.023) at post-treatment in the active group. The differences were not significant (p > 0.05) for all other outcomes. No serious adverse event occurred and the number of adverse events was similar in the active and placebo groups (p = 0.443). In the active group, all participants completed the intervention and the adherence to treatment was 96.8%.

The CES showed a complex diagnostic and therapeutic process in which the signs and symptoms of the patient, the cause of the disease, the characteristics of the patient (gender, age, comorbidities), the mechanism and features of the disease, the location and the time are taken into account to provide a treatment in which not only the prescription (i.e., ingredients), but also the treatment modality and the methods of preparation and administration are adapted to the situation. The intervention is not limited

to a prescription but encompasses psychological aspects, health recommendations and self-help interventions, and integration with other therapies.

Discussion and conclusions

The systematic review shows that ZRAS is safe and effective for insomnia. The randomised trial support ZRAS capsule as a safe and acceptable treatment, yet failed to improve significantly insomnia severity in insomnia patients. These differences may be explained by the poor quality of the studies included in the systematic review. The studies included in the systematic review and the randomised trial both used a standardised intervention approach. However, Chinese medicine clinician recommend an individualised approach, which may contribute to improved outcomes across a broader range of measures.

Acknowledgement

I would like to acknowledge the incredible emotional support of my fiancée Mingxian Jia. Her warm smile was one of the driving forces that pushed me through the difficulties of the doctoral journey. Mingxian took part actively in each aspect of the thesis, including the systematic review, the clinical trial and the clinical experience synthesis.

Great thanks to Pr. Xiaoshu Zhu, my principal supervisor, who encouraged my move to Australia to undertake this doctoral study in the first place. For me, Xiaoshu is not only an academic mentor but a life mentor as well, and I share deep affection with her. Pr. Alan Bensoussan, my second supervisor, was extremely helpful on both the technical aspect and the emotional aspect of undergoing a doctoral thesis. I respect and admire his leadership, and feel grateful for his help and support. I would like to thank Dr. Caterina Tannous, who kindly helped me understanding the depth and scope of qualitative analysis and whose support was essential to build the methodology for the clinical experience synthesis. The expertise of Pr. Jerome Sarris, who was a supervisor in the early stages of the thesis, was extremely useful in the design and conduction of the clinical trial. Great thanks also to Dr. Nicole Avard who selflessly provided her medical expertise. Her help was essential in the conduction of the project.

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I would like to thank all the clinicians who shared their clinical experience via the clinical experience reports. Finally, and importantly, I would like to thank all the participants who joined the clinical trial. Their dedication to give their time for science and to help other patients is a great inspiration.

Declarations

The candidate is a recipient of a Blackmores-NICM Higher Degree Research Scholarship. The product tested in the clinical trial conducted as part of this doctoral thesis is not currently marketed by Blackmores.

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List of abbreviations

AASM = American Academy of Sleep Medicine

AE = adverse event

ARAS = ascending reticular activating system

BDZ = benzodiazepines

BzRAs = benzodiazepine receptor agonists

CAM = complementary and alternative medicine

CBT = cognitive-behavioural therapy

CBT-I = cognitive-behavioural therapy for insomnia

CEQ = Credibility and Expectancy Questionnaire

CER = clinical experience report

CES = clinical experience synthesis

CGI-S = Clinical Global Impressions – Severity scale

CHM = Chinese herbal medicine

CM = Chinese medicine

CNKI = Chinese National Knowledge Infrastructure

CQVIP = Chong Qing VIP

CSD = Consensus Sleep Diary

DSM = diagnosis and statistical manual

DFA = difficulty falling asleep

ECG = electrocardiogram

EEG = electro-encephalogram

EMA = early morning awakenings

EMG = electromyogram

EOG = electro-oculogram

FA = frequent awakenings

FD = frequent dreams

GABA = gamma-butyric acid

GABAA = GABA type-A

HARS = Hamilton Anxiety Rating Scale

Heart-Gall Qi Def = heart-gallbladder qi deficiency

HREC = Human Research Ethic Committee

H-S Def = Heart and Spleen Deficiency

ICD = international classification of diseases

ICSD = international classification of sleep disorders

ISI = Insomnia Severity Index

Liver Stag = Liver Stagnation

LPS = latency to persistent sleep

L-S Dis = Liver-Spleen Disharmony

LTE = List of Threatening Events

NAWAK = number of awakenings

Non-Int Bet Heart-Kid = non-interaction between heart and kidney

NREM = non-rapid eye movement

NRS = non-restorative sleep

PMR = progressive muscle relaxation

PR = participant-rated

PSQI = Pittsburgh Sleep Quality Index

PSG = polysomnography

QoL = quality of life

REDCap = Research Electronic Data Capture

REM = rapid eye movement

RCT = randomized controlled trial

SCN = suprachiasmatic nucleus

SCT = stimulus control therapy

SDRS = Sleep Dysfunction Rating Scale

SE = sleep efficiency

SES = socio-economic status

SJW = St John’s Wort

SOL = sleep onset latency

SRSS = Self-Rating Scale of Sleep

SRT = sleep restriction therapy

SSs = signs and symptoms

SWS = slow-wave sleep

TAU = treatment as usual

TIB = time in bed

TST = total sleep time

VAS = Visual Analogue Scale

VLPO = ventrolateral preoptic nucleus

WASO = wake after sleep onset

Yin-Def-Fire = Yin Deficiency with Effulgent Fire

ZRAS = Zao Ren An Shen

Introduction

Complementary and alternative medicine (CAM) are becoming increasingly popular worldwide. One third of Americans now use at least one type of CAM every year in the US for example [1]. The increase in the use of CAM has been followed by the recognition of various CAM as part of the medical system. This is also true for Chinese medicine, one of the most ancient and influential CAM, which has been recognised in Australia as early as 2000 with the Chinese Medicine Registration Act. CAM are increasingly integrated to the conventional medical system. Conventional medicine students and doctors have nowadays a better understanding and a more positive attitude towards CAM [2, 3]. Research in the field of CAM is expanding. Integrative medicine is developing. However, the integration of CAM with conventional medicine is not without difficulties [4].

In China, the modernisation and standardisation of Chinese medicine (CM), which has been developed for thousands of year through clinical experience and academic discussion, has led to serious debates and conflicts [5]. The debate crystallises on the evidence-based paradigm. There is an urge from governmental bodies, insurance companies and part of the public opinion to produce evidence of efficacy. According to this paradigm, only treatments with the best available evidence should be used. Some scholars argue that this one-size-fits-all approach is incompatible with the principles of CM, which has a holistic approach and adapts treatments according to the specificities of the patient [5]. Despite the growing availability of evidence from experimental studies, most of CM textbooks and guidelines are still based on reviews of ancient literature and clinical experience from the authors [6, 7].

In the evidence-based medicine era, there is increasing pressure for any therapy or medicine to prove evidence of efficacy through experimental studies, especially randomised-controlled trials. Double-blind randomised-controlled trials and systematic reviews of these trials provide high-quality evidence to the clinician (especially to the primary care clinician), that treatments are safe and effective [8]. However, experimental studies may not be able to provide enough guidance for clinicians about the implementation of individualised treatments, as is typically required in CM [9]. As such, for CM, there appears to be a gap in available evidence to support practitioner decision-making in practice.

The “clinical experience synthesis (CES)”, a systematic synthesis of clinical experience reports from hundreds of clinicians, is suggested in this thesis as a way of addressing this gap by providing guidance about the individualisation of CM treatments for insomnia.

Insomnia disorder is a chronic condition that can persist for years and impairs the patient’s quality of life [10]. Although it can have severe consequences on the long term, the direct risk is low compared to life-threatening conditions such as strokes and cardiovascular diseases. Concern over adverse reactions, long-term risks and dependence leads insomnia patients to avoid the use of conventional drugs [11]. Cognitive-behavioural therapy for insomnia, the major alternative, is resource-consuming, burdensome and not widely available. As such, insomnia disorder appears to be particularly suited for CAM treatment. Chinese herbal medicine (CHM) is already used by many insomnia patients, especially in ethnic Chinese populations and increasingly in Asian and Western populations as well [12, 13]. A better understanding of CHM as a treatment of insomnia is warranted.

This thesis focus on two aspects of the treatment of insomnia with CHM. The first uses a quantitative experimental approach in order to assess the efficacy and safety of Zao Ren An Shen (ZRAS), a Chinese herbal patent medicine, for the treatment of insomnia. The second uses a qualitative experiential approach in order to synthesise the documented clinical experience of hundreds of clinicians regarding the treatment of insomnia with CHM. As such, quantitative methods and a deductive process are used in combination with qualitative methods and an inductive process in order to provide a deep and rigorous understanding of the treatment of insomnia with CHM.

The thesis starts with a review of the literature, including background knowledge about the physiology of sleep (Chapter 1), the definition and management of insomnia (Chapter 2) and the current knowledge on the treatment of insomnia with Chinese medicine (Chapter 3). A systematic review was conducted (Chapter 4) to assess the current evidence regarding the efficacy and safety of ZRAS. A clinical trial was conducted in order to assess the efficacy and safety of ZRAS for insomnia (Chapter 5 to 7). Finally, a CES was conducted about the treatment of insomnia with Chinese medicine (Chapter 8 to 10). The structure of the thesis is shown in Figure 0.1.

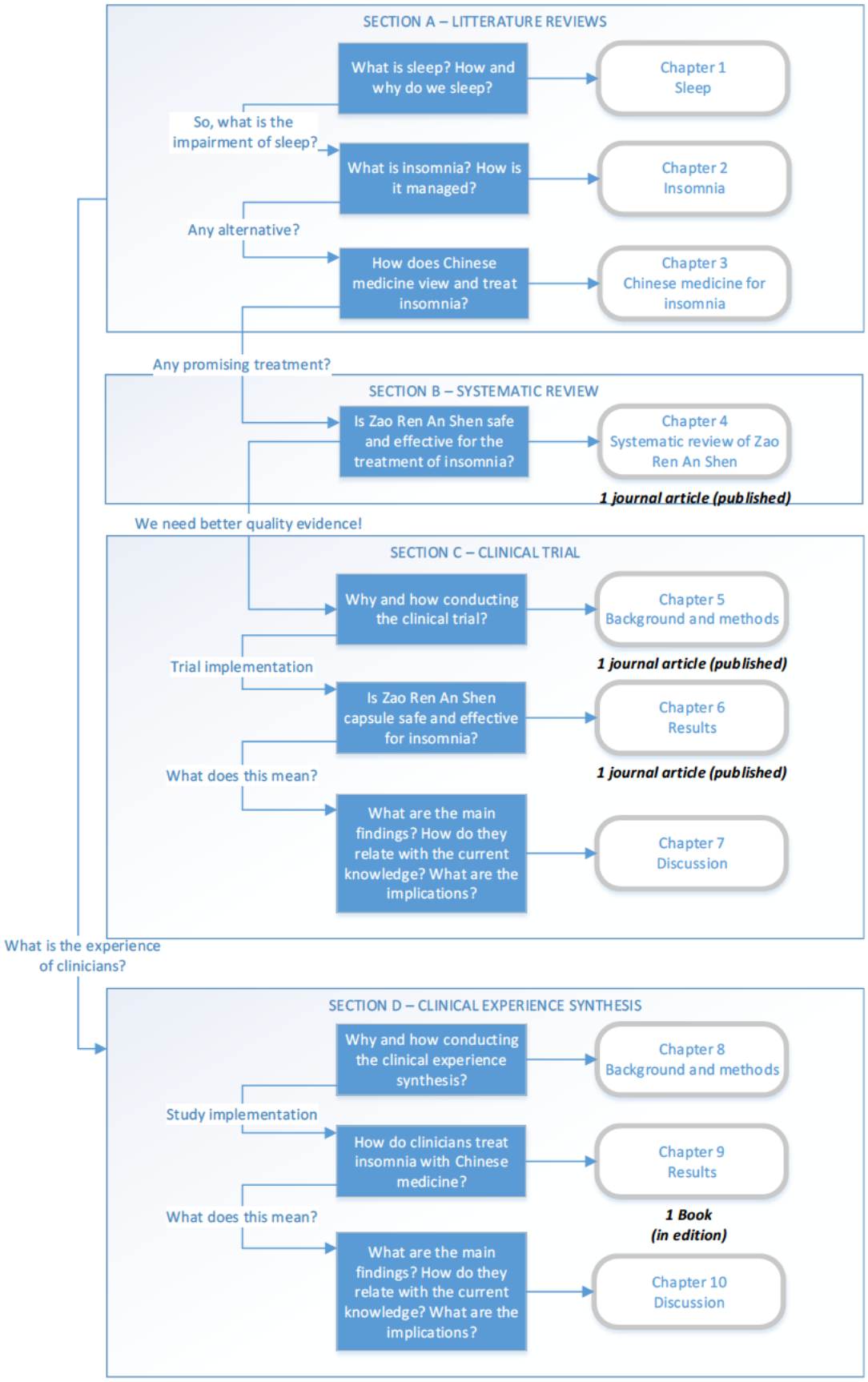
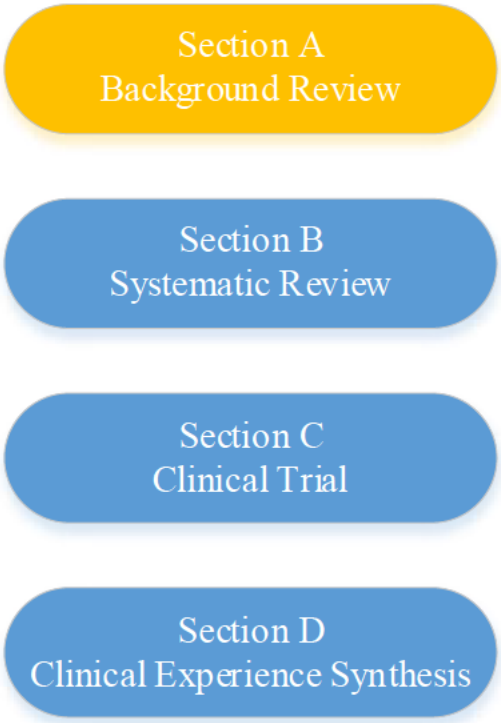


Figure 0.1. Overview of the thesis structure with research questions, link between chapters, and publications

Section A

Literature reviews



This section presents a review of the literature regarding sleep, insomnia disorder, the management of insomnia with Chinese medicine and the evidence on ZRAS as a treatment of insomnia.

The first objective of this section is to present the background knowledge and the key concepts relevant to the topic of the thesis. It allows the reader to grasp the context of the thesis. The second objective is to present the current knowledge about Chinese medicine as a treatment for insomnia disorder and the evidence on a specific Chinese herbal treatment called ZRAS. This sets the basis for further development in the Sections B, C and D.

Chapter 1: Sleep

1.1. Definition of sleep

Before understanding what insomnia is, one needs to understand first what sleep is. Sleep can be defined as a naturally recurring bio-psychological state characterised by altered consciousness, reduced sensory and motor activities, and reduced interactions with surroundings. It is different from a state of coma as in sleep the alteration of consciousness is temporary and recovers spontaneously. Sleep is a complex biological process which involves different parts of the brain such as the hypothalamus, the brain stem, the thalamus, the pineal gland, and the basal forebrain [14]. Sleep is influenced by behaviour, affect and external factors such as light [15], and has an influence on almost every type of tissue and system in the body [14].

In Chinese medicine, sleep is characterised as a state in which "the *yang* penetrates the *yin*". The *yin* state of sleep, with *yin* features of calm and passivity and *yin* functions of collecting and conserving, is opposed to the *yang* state of wakefulness, which is an active state of consumption. Yet, there is no consensus on *what* is collected during sleep: *yin* or *yang*? From the perspective of brain functions, memory and mood regulation, sleep seems to be conserving and consolidating blood and essence. Yet from the perspective of energy conservation and immune system sleep seems to be conserving and consolidating *yang* and *qi.* Both aspects are likely to be involved.

The main characteristics of sleep are automaticity and plasticity [15]. Automaticity refers to the fact that sleep is automatically triggered by processes independent of consciousness and decision [16]. These processes, the homeostatic drive and the circadian drive, will be discussed in the section "1.2. Mechanism of sleep". As a matter of fact, active seeking of sleep is one of the most important factors of insomnia, and the discontinuation of this active seeking one of the main strategies to treat insomnia [17]. Plasticity refers to the fact that the timing, length and structure of sleep is adapted to the needs of the person and the surrounding environment [16]. For example, in mammals, sleep is not only influenced by the sleep homeostasis (i.e., the "need" for sleep, see section "1.2. Mechanism of

sleep"), but also by hunger drive [18, 19], the presence of predators or predator cues [20-22], the motivation to mate [23], and long flight [24, 25].

Sleep is not a unique state, on the opposite sleep is composed of different stages which have different characteristics. There are four different stages of sleep, the rapid eye movement (REM) sleep, the non-rapid eye movement (NREM) stage 1, the NREM stage 2 and the NREM stage 3 [26]. Sometimes NREM 3 is divided into a NREM stage 3 and NREM stage 4 (Figure 1.1). These different sleep stages are differentiated based on their electrophysiological signature based on electro-encephalogram (EEG) measurements [27]. These electrophysiological signatures are shown in Figure 1.2.

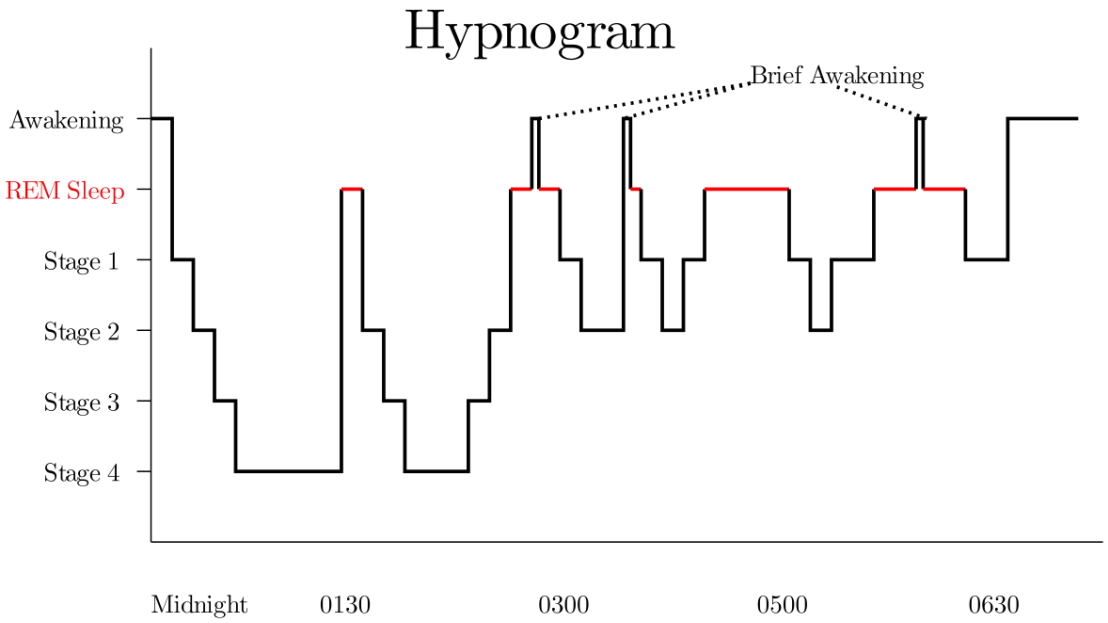


Figure 1.1. Different stages of sleep.

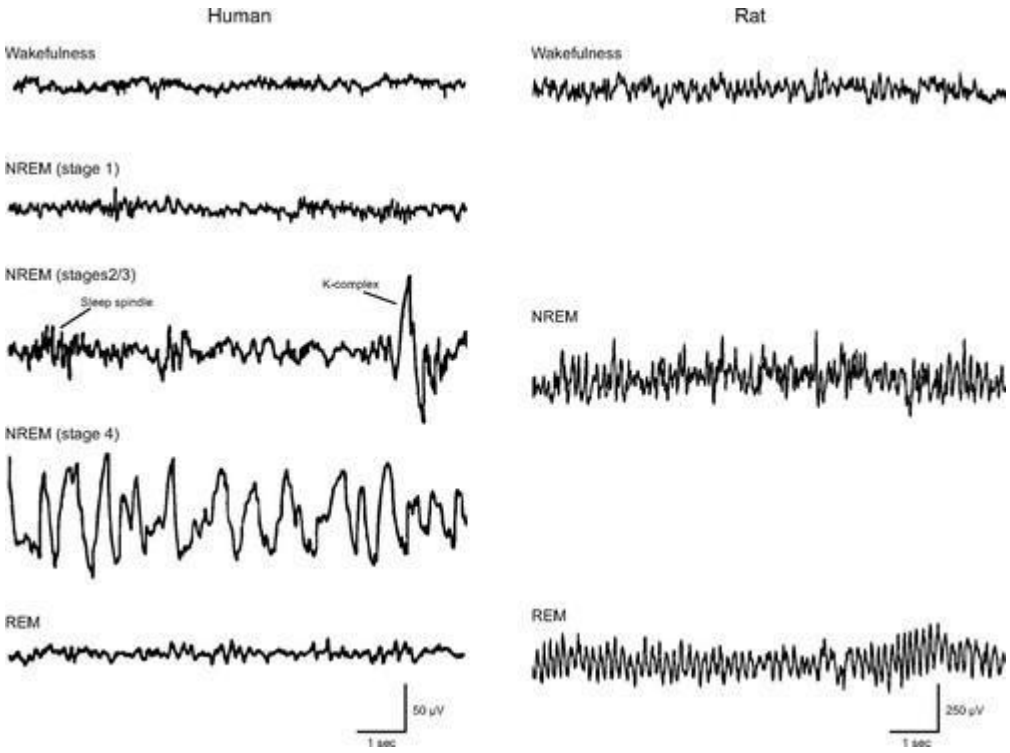


Figure 1.2. Electrophysiological signature of the different stages of sleep in the human and the rat [28].

REM and NREM stage sleep are fundamentally different brain states which are controlled by specific neural circuits [29]. REM sleep is characterised by low-voltage high-amplitude activity, which is a feature of wakefulness, rapid eye movements, and a complete loss of muscle tone [28]. It means that the brain is awake yet disconnected from the rest of the body. Most of dreams occur in the REM stage of sleep. In contrast, NREM sleep is characterised by high-amplitude low-frequency EEG and decreased muscle tone [28]. NREM stage 1 and NREM stage 2 are termed together as light sleep, as during these stages the sensory threshold is relatively lower and the muscle tone relatively higher than during deep sleep [30]. NREM stage 3 and NREM stage 4 are collectively termed as deep sleep or slow-wave sleep (SWS), as the EEG readings are dominated by slow oscillations during these stages [31].

In Chinese medicine, there is no clear differentiation between light and deep stages of sleep. Nonetheless, dreams (which are the markers of REM sleep) are considered as manifestations of the ethereal spirit or *hun*, which is controlled by the liver. When the liver is impaired, the hun is not

concealed properly which leads to frequent dreams [32]. It is important to understand that *experiencing* dreams is part of a normal REM sleep (which happens several times every night) but *remembering* dreams (which is what we really mean by "frequent dreams") is a feature of low sleep quality (i.e., waking up too often and for a period long enough to create memory).

1.2. Mechanism of sleep

Sleep is not an active process but rather the inhibition of wakefulness. Wakefulness is maintained by the activity of the ascending reticular activating system (ARAS) [28]. The ARAS is a part of the reticular formation composed of neural circuits connecting the dorsal part of the anterior pons and posterior midbrain to the cerebral cortex via the thalamus and hypothalamus [33]. The neurons of the thalamic pathway are principally cholinergic neurons in the pontine tegmentum, whereas the neurons of the hypothalamic pathway release principally dopamine, norepinephrine, serotonin, and histamine [34]. The entire system is regulated by the orexin neurons of the lateral hypothalamus, which innervate every component of the ARAS [33, 35]. The main function of the ARAS is to maintain wakefulness and consciousness via constant firing to the cerebral cortex [36]. The ARAS is also involved in the process of attention [37].

In Chinese medicine, the *dumai* has a key role in controlling the *yang* and nurturing the brain [32]. From its position and function, the *dumai* shares many similarities with the ARAS. The balance of the *yang* is also crucial in the maintaining of a healthy sleep-wake schedule. In Chinese medicine wakefulness, consciousness and alertness, which are related with the cerebral cortex in biomedicine, are a manifestation of the *shen* or spirit which is controlled by the heart [38]. An excess of wakefulness and alertness, which is called "agitation *(fanzao)*", is related with excessive heart fire/heat [39]. Wakefulness and consciousness are also related with the concept of "clear orifice *(qingqiao)*". When the clear orifice is blocked, consciousness is impaired (for example in case of severe infection, stroke or coma).

As said previously, sleep is the inhibition of the wakefulness rather than an active process. This inhibition is mainly due to two sleep drives, the homeostatic drive and the circadian drive [40, 41].

The homeostatic drive or sleep-wake homeostasis is the most basic regulation system of sleep and wake. This system is mainly driven by the ventrolateral preoptic nucleus (VLPO), which is situated in the hypothalamus. During prolonged periods of wakefulness, the depletion of glycogen and the accumulation of adenosine in the forebrain disinhibits the VLPO [42]. The neurons of the VLPO then inhibits the ARAS via the action of gamma-butyric acid (GABA) and galanin [43], therefore promoting sleep. There is a mutual inhibition between the ARAS and the VLPO. During wakefulness, the ARAS is active and inhibits the VLPO while during sleep the VLPO is active and inhibits the ARAS [43, 44]. This mutual inhibition is further stabilised by orexin neurons from the lateral hypothalamus [44]. This sleep "switch" prevents intermediate states between sleep and wake [43].

In Chinese medicine, this process can be understood from the perspective of *yinyang* theory. The rise of *yang* (i.e., energy consumption) when we are active during the day leads eventually to the rise of *yin* (i.e., energy conservation) when the energy is consumed completely [45].

The second drive is the circadian rhythm, which is a biological rhythm that regulates biological activities such as heart rate, oxidative stress, cell metabolism, and immune and inflammatory responses on a 24-hours basis. The markers of this 24-hours rhythm are melatonin level (which is higher during night time), cortisol level (which is higher during daytime) and body temperature (which is higher during daytime) [46, 47]. The circadian rhythm is regulated by the suprachiasmatic nucleus (SCN), which is located in the hypothalamus. The neurons of the SCN show a 24h-rhythm pattern in their neural output which arise from self-sustaining molecular feedback loops of clock gene expression [48]. The circadian rhythm is primarily influenced by light, which is the most important zeitgeber (in German: time-giver). Light travels from the retina to the SCN via the retinohypothalamic tract. In the absence of light, the SCN sends signals to the pineal gland to secrete melatonin, which then acts on the MT-1 and MT-2 receptors of the SCN to synchronise the circadian rhythm [49, 50]. The SCN has direct and indirect projections to the VLPO, which in turns inhibit the ARAS and therefore promotes sleep [50].

In Chinese medicine, the circadian rhythm is related to the movement of the protective *qi (weiqi)*, which according to the Neijing makes 25 rounds in the *yang* during the day and 25 rounds in the *yin*

during the night [45]. This underlying philosophy behind this understanding is the union between humans and their environment *(tianren heyi)*. According to traditional theories, the *yang* starts to rise after midnight, grows in the morning, is the strongest at noon and declines during the afternoon and evening, following the movement of the sun (which light regulates the circadian cycle in biomedicine) [51].

The homeostatic drive and the circadian drive are biological processes that are facilitated by behavioural sleep conditioning. As time passes, the neutral stimuli such as the bed, the bedroom or night time get associated with sleep, becoming sleep stimuli [52]. The strength of the stimulus (i.e., its ability to induce sleep) depends on the number of activities associated with the stimulus, i.e. the stimulus becomes stronger when associated with sleep only and weaker when associated with other activities such as watching TV, eating or worrying [52].

Besides that, many biological and behavioural factors can have an impact on sleep. The reticular formation, which includes the ARAS, is located in the brainstem and has strong connections to every ascending and descending neural pathways which connect the body and the brain. Sensations caused by light, noise, etc. can activate the ARAS and facilitate wakefulness [52]. Stress due to emotions or medical conditions can also promote wakefulness via the activation of the ARAS [53]. The use of substances such as nicotine, alcohol, caffeine and many recreational and pharmacological drugs can affect sleep as well [54, 55].

1.3. Functions of sleep

The main difference between rest and sleep is that during rest the muscle are relaxed yet the brain is still fully active, while in sleep (and especially slow-wave sleep) the brain activity is reduced considerably. Indeed, brain recovery is considered the main function of sleep [56]. During sleep, essential molecules and fuel substrates of the central nervous system are replenished [57, 58] and waste products that accumulate during the waking state are removed [59]. Meanwhile, a global downscaling of synapses resulting from waking neuronal activity enables the processing of new information the next day [60, 61].

Learning and memory consolidation are also important functions attributed to sleep [62, 63]. These functions are mainly related with SWS and REM sleep. Studies in animals and humans revealed that neurons activated during the previous waking episodes in relation to specific tasks are reactivated during SWS, which facilitates the consolidation of memory [64]. As mentioned previously, the brain is activated during REM sleep. This activation, which is also related with dreams, allows the processes of memory consolidation, especially for procedural memory [65, 66].

We know from previous studies on sleep deprivation that sleep maintains and improves the immunity [67, 68]. A low sleep efficiency (i.e., the ratio of time asleep on time in bed) is also associated with a significant increase in cold susceptibility [69]. However, this association between sleep and the immune system is not unilateral. The activation of the immune system can also provoke changes in the sleep architecture [70]. This bilateral relation is furthermore complicated by the role of the circadian rhythm as a mediator of the interaction between sleep and the immune system [71].

1.4. Summary

Many questions about what is sleep and what are its functions have not been answered yet. Sleep, which is characterised by altered consciousness and reduced interaction with the environment, is composed of four different stages that have different mechanisms, electro-physiological signatures and functions. The regulation of sleep results from the interaction of the wake-promoting system using serotonin, acetylcholine, norepinephrine, histamine, dopamine, glutamate and orexin, and the sleep-promoting system using GABA and galanin. The need for sleep and the timing of the circadian rhythms are the basic factors inducing sleep, and many other behavioural and biological factors can influence sleep. Sleep, and especially the SWS and REM stages of sleep, may have important roles in brain recovery, learning and memory, and strengthening of the immune system.

Chapter 2: Insomnia disorder

2.1. Definition, epidemiology and aetiology of insomnia disorder

2.1.1. Definition and categories

The term “insomnia” describes a difficulty to sleep, perceived or observed, and can refer to a symptom as well as a disorder [72-74]. Insomnia disorder is usually diagnosed using international criteria with strict requirement of insomnia symptoms consequences (i.e. distress or impairment), duration and frequency. The most recognised diagnostic standards of insomnia disorder are the classifications of the different versions of the Diagnosis and Statistical Manual (DSM), the International Classification of Sleep Disorders (ICSD) and the International Classification of Diseases (ICD), which all evolved according to the advances of sleep medicine.

In Chinese medicine, there is no strict definition of insomnia disorder. The disease diagnosis of “insomnia *(bumei)*” includes difficulty falling asleep, waking up frequently, early morning awakenings, light sleep and frequent dreams, regardless of the frequency and duration of these symptoms [75].

Insomnia disorder has been traditionally divided in primary insomnia and secondary insomnia. Primary insomnia is defined as a sleep disturbance that “does not occur exclusively during the course of another sleep disorder or mental disorder” [76]. This diagnosis has been challenged, the causal relation between insomnia and a comorbid disorder was seen as unclear and variable [73], maladaptive cognitions and behaviours can be found and successfully addressed in both primary and secondary insomnia [77], and the reliability and viability of the primary insomnia diagnosis were challenged in several studies [78, 79]. The distinction between primary and secondary was finally abandoned in both the DSM-V [73] and the ICSD-3 [72].

The development of polysomnography (PSG) allowed the differentiation of objective insomnia and subjective insomnia. In a recent study in Brazil, objective criteria of insomnia assessed with PSG was met by only 37% of insomnia complainers and as much as 23% of self-reported good sleepers [80]. The perception of insomnia symptoms without evidence of objective insomnia was identified as “sleep state misperception” or paradoxical insomnia with a distinctive diagnosis criterion in the ICSD-

2. However, the clinical relevance of the distinction between subjective and objective insomnia has been challenged, providing that “sleep time misperceptions are ubiquitous among primary insomnia sufferers” [81], that insomnia symptoms are instable and may not be caught by punctual PSG recordings [82], and that underlying mechanisms may be similar in both objective and subjective insomnia [83]. Following this evolution, the diagnosis of paradoxical insomnia was abandoned in the ICSD-3.

The distinction between acute and chronic insomnia is not only one of the earliest [84] but also the most stable in insomnia nosology. Both the DSM-V [73] and the ICSD-3 [72] use a 3-months threshold to define chronic insomnia (the term “insomnia disorder” is used for the DSM-V). This distinction is clinically useful as acute insomnia is considered to be mainly caused by physiological, psychological and social precipitating factors whereas chronic insomnia is mainly maintained by behavioural and cognitive perpetuating factors [85]. Espie [86] proposed that the transition from acute or “adjustment” insomnia to chronic or “psychophysiologic” insomnia occurs when the selective attention of the patient shifts from stressors to insomnia symptoms themselves. It is unnecessary to point out that this shift does not always occur at the 3-months threshold.

Another way of classifying insomnia is by symptoms subtypes, i.e. difficulty falling asleep, difficulty maintaining sleep, early-morning awakenings and non-restorative sleep [87]. However, a longitudinal study on insomnia subtypes [88] found that for most of patients the insomnia symptom subtype changes over a 4-months period, questioning the relevance of this classification in cross-sectional studies. This classification is also challenged by the fact most insomnia patients show at least two subtypes at the same time [89, 90]. Additionally, a PSG study [91] showed that non-restorative sleep (NRS) can occur independently of other components of insomnia and a 5-years follow-up study [92] suggested that NRS has its own longitudinal course and association with mental and medical outcome, leading the DSM-V to separate NRS from the insomnia disorder diagnosis.

It is important to distinguish insomnia from sleep deprivation. Sleep deprivation is an objective lack of sleep. For example, if someone who needs seven hours of sleep to feel refreshed has only six hours of sleep, this is sleep deprivation. Sleep deprivation is usually caused by a busy schedule (i.e., no time

for sleep) or some conditions such as sleep apnoea, in which sleep is impaired by biological processes. Sleep deprivation can be observed in insomnia patients but is not a typical feature of insomnia. The main features of insomnia are frustration and worries about sleep. The objective sleep of the large majority of people who report trouble sleeping is not shorter than for people who report having a good sleep. Insomnia patient feel tired and believe their cognitive functions (e.g., memory, attention) are impaired but objective test on sleepiness (i.e., the propensity to fall asleep) and cognitive functions do not support this claim (or at least they are much less sleepy and cognitively impaired than people with sleep apnoea for example).

In Chinese medicine, sleep deprivation is associated *yangqi*, blood or essence deficiency [45]. As we will see in the Chapter 9, deficiency is not a main feature of insomnia pathology (except for the Heart-Spleen Deficiency pattern). Stagnation and heat, which are related to stress reaction and hyperarousal, are much more common in insomnia patients.

2.1.2. Epidemiology

In a review of 50 epidemiological studies on insomnia, Ohayon [93] found an overall insomnia prevalence rate of 4.4- 48%. The amplitude of this range highlights the heterogeneity of the methodology and the choice of insomnia criteria in the epidemiological studies. Indeed, the prevalence rate of insomnia can be as high as 30-48% when participants are asked if they have insomnia symptoms, but decreases to 8-18% if frequency or severity criteria apply, and falls to approximately 6% when using a diagnosis criterion as the DSM-IV [93]. More recent studies based on international diagnosis criteria show a higher prevalence rate of 7.9-15% in the general population [80, 87, 94], which is consistent with the increase of insomnia prevalence observed in the beginning of the 21th century [95].

A systematic review including more than one million participants [96] found that females are more prone to contract insomnia than males, with an overall risk ratio of 1.41 [95% confidence interval: 1.28–1.55]. This is consistent with the gender tendency of many mental disorders such as depression and anxiety [73]. The male/female ratio peaks around 50 years old, which is usually explained by menopause [90, 95].

Due to menstruation, pregnancy, labor, and lactation, females are more prone to blood deficiency than males. In Chinese medicine the liver, which drains the *qi* movements and emotions, uses blood to function. Relative blood deficiency explains why female are more prone than males to mood disorders. The lack of blood is temporary accentuated before the menstruations, after birth and at the time of menopause, which are periods in which mental disorders are common. Blood deficiency disturbs the draining function of the liver, leading to insufficient draining (*qi* stagnation) or excessive draining (liver fire), sometimes both alternatively. In the section D, we will see that blood deficiency is not a main pattern of insomnia but is rather a central mechanism in the pathology of insomnia.

The relation between insomnia and age is not as clear as the one with gender. Most of epidemiologic studies [95, 97-99] have found a positive correlation between age and insomnia, but this relation was not linear in all studies. Some studies [80, 90, 98] found a decrease in prevalence among the elderly. This could be explained by a less stressful lifestyle after retirement and a decrease of sleep expectations. Other studies [80, 94, 98] have found a peak around 30 years old, which could be explained by the stress of starting a career and raising children at the same time in modern society.

In the CERs we have analysed, two sociodemographic subgroups of insomnia were the focus of attention of the clinicians: perimenopausal women and older adults (see Chapter 9). Both types of insomnia were associated with the *yin* deficiency and fire pathological system compared to insomnia in younger patients which was associated with the liver *qi* stagnation pathological system. Insomnia in perimenopausal women was associated with blood deficiency, kidney deficiency and fire, which is typical of perimenopausal constitution. Insomnia in older adults was associated with kidney deficiency and coldness, but not blood stasis.

Divorced, separated and widowed marital statuses were found to be risk factors for insomnia [90, 97, 98]. Higher prevalence rate was found for singles in a study in Canada [98] and for married subjects in a study in China [90]. This could be explained by the cultural differences among the two countries, i.e. marriage for love in Western countries opposed to marriage for the society in Asian countries. Insomnia was also associated with low education level [80, 87, 97] and unemployment or shift work [80, 90, 98, 100]. The relationship between insomnia and socio-economic status (SES) is more

ambiguous. While some epidemiological studies [80, 87, 97] have found a higher prevalence rate in the lower SES, which was explained by exposition to stress factors and lower mental health, other studies [95, 98] have found a higher prevalence rate in the middle SES, which was explained by cultural specificities.

Cross-sectional studies also found a correlation between lifestyle and insomnia rate. Poor lifestyle habits such as smoking, drinking alcohol, watching TV, physical inactivity and obesity are risk factors for insomnia [87, 90, 94, 101]. The direction of this association was explored in a recent longitudinal study [102] that showed an association between insomnia symptom and subsequent alcohol consumption and inactivity as well as an association between alcohol consumption and subsequent insomnia symptoms, but no longitudinal association with smoking or unhealthy food habits when adjusted for socio-demographic characteristics.

According to Chinese medicine a sedentary lifestyle, lack of physical activity, excessive diet and drinking harm the spleen, causing spleen deficiency [51]. According to the clinical experience synthesis, spleen deficiency is a key factor in the pathological mechanism of insomnia. Spleen deficiency is more closely associated with Heart-Spleen Deficiency pattern and Phlegm-Heat pattern but is widely present as a background feature in most patterns. Indeed, the atypical stomach disharmony pattern of insomnia spreads across several typical patterns of insomnia, including the Yin Deficiency and Fire pattern. Protecting the spleen and stomach is also one of the main concern of herbalists. Chinese medicine theory allows us to understand the importance of non-sleep-related lifestyle factors in the mechanism of insomnia.

2.1.3. Aetiology and pathology

2.1.3.1. Physiological hyperarousal

Insomnia disorder has long been conceptualized as an arousal disorder as evidence of physiological hyperarousal was found in insomnia patients. Early studies using electromyogram (EMG), body temperature measurements, electrocardiogram (ECG) and skin conductance measurements showed a higher degree of arousal for bad sleepers compared to good sleepers [103-105]. This point of view provided an explanation on the way stressors can induce insomnia and a rationale for the therapeutic

effect of relaxation on insomnia. The hyperarousal was first found on a somatic level, then following the progress in sleep sciences was also observed on emotional, cognitive and cortical levels. More recently, Espie [15] proposed that insomniacs actually show an inhibition of the de-arousal process normally associated with sleep rather than an hyperarousal. Coherent with this view, the rodent model of insomnia conceptualizes insomnia as an imbalance between the sleep promoting system enhanced by the homeostatic and circadian drives and the arousal system enhanced by stress [52]. The hyperarousal model has been used to support the use of pharmacological inhibitors as benzodiazepines. However, a study using caffeine-induced hyperarousal [106] found that the effect produced by caffeine on metabolism and sleep continuity decreases over time, showing that the physiological arousal can provide a good pathological model for acute insomnia but not for chronic insomnia.

From a Chinese medicine perspective, the concept of cortical hyperarousal can be related with excessive heart yang or heart fire disturbing the *shen*. The most common symptom of heart fire is agitation *(fanzao) [39]*, which corresponds to the elevated wakefulness and awareness associated with cortical hyperarousal. We will see in the Chapter 9 that agitation is a common symptom in every type of insomnia except the Heart-Spleen Deficiency type. Although Chinese medicine does not traditionally recognise stress reaction, it considers that emotions are associated with *qi* movements regulation. Excessive emotions are associated with liver *qi* stagnation and liver fire. It is not hard to find correspondence between the manifestation of stress reaction and the signs of liver *qi* stagnation and liver fire, such as thoracic pressure, palpitations, agitation, stomach distension, etc [39]. As we will see in the Chapter 9, liver *qi* stagnation and liver fire are core mechanisms of insomnia. These mechanisms can lead to heart fire and *shen* disturbance.

2.1.3.2. Behavioural factors

With the development of behavioural psychology, scholars started to look for the behavioural factors associated with insomnia. Bootzin [107] proposed that sleep was normally induced by a conditioning of the sleep environment (i.e. the bed and the bedroom) and the physiological process of sleep. As insomniacs stay in bed while awake, stimulus associated with sleep become associated with insomnia,

which maintains the symptoms and leads to chronic insomnia. In order to restore the normal conditioning of sleep, Bootzin [107] proposed the stimulus-control therapy, in which patients are asked to stay in the sleep environment only while asleep. Later on Spielman, Caruso, and Glovinsky [108] proposed a more integrative model based on Bootzin's theory, the 3P model also known as the Spielman's model. In this model, chronic insomnia is the fruit of the interaction between three types of factors, i.e. predisposing factors, precipitating factors and perpetuating factors. The predisposing factors are long-term bio-psycho-social factors such as a sensible sleep system or personality trait which cannot induce insomnia alone. On the basis of these factors, precipitating factors, which are short-term bio-psycho-social factors such as emotional stress or caffeine, are able to induce acute insomnia. In order to cope with acute insomnia symptoms, the patients adopt maladaptive behaviours such as staying in bed while awake or getting to bed earlier. These maladaptive behaviours known as perpetuating factors maintain insomnia symptoms and lead to chronic insomnia. A combination of stimulus-control therapy and sleep restriction therapy, which allows a time in bed equal to the sleep capacity of the patient, was then proposed to eliminate perpetuating factors [108].

2.1.3.3. Cognitive factors

The perpetuating factors of insomnia where first thought to be behavioural. The shift of focus from behavioural psychology to cognitive psychology helped to understand dysfunctional beliefs that could maintain insomnia. Among them were found misattribution about sleep causes, unrealistic expectations about sleep, worry about the consequences of poor sleep, lack of confidence in the control of sleep, and unhelpful beliefs about sleep-promoting behaviours [109-111]. Just as the behavioural factors, these dysfunctional are induced by the distress caused by insomnia symptoms, but tend to maintain insomnia as they increase the worry, rumination and dysfunctional behaviours of insomnia patients. More recently, Espie [112] proposed an alternative view on the development of chronic insomnia. Noting that normal sleep was based on automaticity, i.e. the largely involuntary nature of the well-adjusted sleep schedule, they proposed that selective attention on sleep, including monitoring of the environment for sleep-related threats, can disrupt the automaticity of sleep and cause insomnia. This selective attention would be followed by an intention and efforts to sleep [112]. In other words, the patient cannot sleep because he is trying to sleep.

In Chinese medicine, cognitions and emotions are entangled into a unique system of seven *qingzhi [51]*. Thinking *(si)*, which is associated with earth and the centre, functions as a pivot to shift emotions. Negative thinking and emotions tend to make the *qi* going inward and create stagnation [38]. As the function of the liver is to drain *qi* movements and emotions, this stagnation is often called "liver *qi* stagnation". This *qi* stagnation can produce heat and fire, which correspond to the physiological arousal associated with insomnia. As we will see in the Chapter 9, emotion-induced liver *qi* stagnation is one of the core features of insomnia pathology.

2.1.3.4. Summary

The mechanism of insomnia is complex and not fully understood. Physiological hyperarousal, which can be caused by biological or psychological causes, prevents the normal inhibition of the sleep-promoting system (i.e. the ARAS), but is not limited to it. The perpetuation of insomnia into a chronic stage is due to dysfunctional behaviours and cognitions, which result from the symptoms of insomnia and furthermore aggravate them.

2.1.4. Comorbidities and consequences

In the literature, insomnia has been consistently associated with mental diseases, especially anxiety and depression [80, 94, 97, 113, 114]. As anxiety and depression were found to be risk factors for future insomnia [99, 115, 116], insomnia was long considered as a symptom of anxiety and depression disorders, the insomnia disorder being then called "secondary". However, others studies [99, 117-119] highlighted that insomnia could also be a risk factor for the development of anxiety and depression. Linking these two observations, a more recent longitudinal study [120] suggested a bidirectional association between, on one hand, anxiety and depression and, on the other hand, insomnia. Besides anxiety and depression, there is also a strong comorbidity between insomnia and other mental disorders such as eating disorders, personality disorders and schizophrenia [121-123]. There is a lack of longitudinal studies about the association between these mental disorders and insomnia, therefore the causal relation cannot be clearly established.

Poor physical health was also associated with insomnia, although the association was found to be less strong than with mental health [113, 124, 125]. The range of physical and systemic diseases related to

insomnia encompasses hypertension, heart diseases, arthritis, lung and ear–nose– throat diseases, stomach problems, and diabetes mellitus [87, 126]. As longitudinal studies suggested, somatic health problems and insomnia may be related in a bidirectional way [127, 128]. One of the main somatic factors associated with insomnia is pain, which can not only disturb sleep but might be also caused by previous insomnia [99]. In a 12-years prospective study [129], insomnia was found to be associated with mortality in univariate analysis, but this association disappeared when adjusting for systemic diseases and depression, which leads to think insomnia itself does not increase mortality but participates in the degradation of global health.

As Chinese medicine is a holistic medicine that treats not only the disease but the person as a whole, the question of comorbidities is primordial in the treatment of insomnia with Chinese medicine. We will see in the chapter 9 that the relationship between insomnia and the comorbidity is complicated, yet the comorbidity is more often considered the cause than the other way around. Pattern theory adds a level to the pathological mechanism of diseases. The treatment often targets the unique underlying mechanism of both insomnia and the comorbidity, i.e. the pattern. Nonetheless treatment strategies are complex and include treating the “primary” condition alone, treating insomnia alone, or treating both with different combinations of treatment.

Despite the fact that sleep loss can cause sleepiness in experimental conditions [130], chronic insomniacs do not have higher levels of daytime sleepiness [131]. This counter-intuitive finding can be explained by the higher level of arousal experienced by insomniacs during night-time as well as daytime [53]. As there is a strong association between insomnia, anxiety and depression, the “fatigue” experienced by chronic insomniacs might then refer to mental strain and not sleepiness [125]. Beside daytime fatigue, individuals with insomnia report impaired memory, attention and concentration, and awakening headaches as direct consequences of insomnia symptoms [80, 89, 132, 133]. However, neuropsychological tests show limited differences in cognitive and psychomotor functions [134], leading to think these consequences are mainly subjective.

Insomnia has also been associated with higher rates of absenteeism, increased rates of accidents and decreased productivity at work [135-138]. The cost of this absenteeism and decreased productivity,

associated with other insomnia-related expenses, was evaluated at $5010 per person per year in Canada [139].

In summary, insomnia disorder has to be considered in the light of complex relations with medical and psychological disorders, dysfunctional behaviours and the professional and financial situation. The problem is not only about sleep but rather about all the factors surrounding sleep. Interestingly, objective sleep might be the only aspect of life that is not genuinely impaired.

2.2. Management of insomnia disorder

2.2.1. Assessment

Insomnia is assessed with a clinical interview including sleep characteristics, daytime behaviours, medical-psychiatric history, symptoms of other sleep disorders, and medications [140]. Several tools can help in the assessment of insomnia in clinical and research settings, including polysomnography (PSG), actigraphy, sleep diary, questionnaires, and neuropsychological tests.

2.2.1.1. Polysomnography

Polysomnography is a multi-parametric test used to monitor biophysiological changes that occur during sleep. Its origin can be found in the recording of brain wave during sleep using EEG [141] and it nowadays consists of a montage usually composed of EEG, ECG, EMG, electro-oculogram (EOG), and oximeter. As it allows for a precise recording of sleep parameters such as sleep onset latency (SOL), latency to persistent sleep (LPS), wake after sleep onset (WASO), total sleep time (TST), and sleep efficiency (SE), it is often considered as the gold standard for sleep assessment [124]. As the conditions of sleep at the laboratory are different from the ones at home, subjects undergoing PSG may experience a “first-night effect” or a “reverse first-night effect” [142], therefore two or more consecutive nights of recording are usually required [124]. In addition to its cost and burden on subjects, PSG is a poor predictor of subjective sleep quality [143, 144] and does not allow distinguishing insomniacs from good sleepers sensitively [145], it is thus not indicated in the routine evaluation of chronic insomnia [140]. It is however indicated for differential diagnosis purpose when breathing or movement disorders are suspected [140].

2.2.1.2. Actigraphy

Actigraphy is a method of monitoring human activity, usually using a wrist-watch-like device containing a small actigraph unit that can detect gross motor activity. As gross motor activity is significantly different during sleep state, actigraphy allows to measure the time spent asleep, and even to differentiate between light and deep sleep stages. When compared to PSG, actigraphy provides reasonably accurate estimates of objective sleep parameters [146]. As an objective and relatively non-invasive monitoring method, its use is appealing in insomnia treatment studies [124]. However, it does not allow measuring the subjective perception of sleep and is not as accurate as PSG in detecting wake [146], therefore actigraphy is not indicated for routine evaluation of chronic insomnia but only to characterize circadian rhythm patterns or sleep disturbances in individuals with insomnia [140].

2.2.1.3. Sleep diary

Sleep diary is a self-report table used to measure subjective sleep parameters. The subject is asked to record every day his bedtime, number and duration of awakenings, arising time, etc. Because of its relatively unobtrusive nature and its ability to record perceived sleep, is the most widely used outcome measurement tool in insomnia treatment studies [124]. It is also a helpful tool in the evaluation and differential diagnosis of insomnia as well as in assessing treatment efficacy in clinical setting [140, 147]. As chronic insomniacs often present a high night-to-night sleep pattern variability, when using sleep diary for treatment efficacy assessment it is recommended to average baseline data using one to two weeks' records, and to continue the recording throughout treatment and follow-ups periods. In order to avoid heterogeneity, a standardized sleep diary has been designed by a group of expert [148].

2.2.1.4. Questionnaires

Self-report questionnaires are widely used to assess insomnia symptoms, related factors and comorbid conditions. The Pittsburgh Sleep Quality Index (PSQI) [149], one of the oldest self-rating scale used in insomnia assessment, is composed of 19 items about sleep quality and disturbances. As it provides assessment for various sleep disorders, the questionnaire is relatively long and lack specificity about insomnia severity. The Insomnia Severity Index (ISI) [150] was designed to overcome this defect. ISI is a brief 7-item scale assessing perceived insomnia severity and consequences in accordance with

DSM-IV and ICSD-2 insomnia criteria. The Athens Insomnia Scale (AIS) [151] was designed to assess insomnia according to another standard, the ICD-10 criteria. Other questionnaires, such as the Insomnia Symptom Questionnaire, Leeds Sleep Evaluation Questionnaire, the St Mary's Hospital Sleep Questionnaire, and the Sleep Problems Scale can be used to assess insomnia symptoms [124]. Additionally, the Sleep Disturbance Questionnaire, the Dysfunctional Beliefs and Attitudes about Sleep, the Pre-Sleep Arousal Scale, and the Sleep Hygiene Awareness and Practice Scale can be used to assess etiological factors and related pathological process of insomnia. Questionnaires measuring fatigue, daytime functioning, psychological symptoms, and quality of life are also recommended for insomnia assessment [140].

2.2.1.5. Neuropsychological tests

In order to assess the consequences of insomnia, several neuropsychological tests can be used in addition to questionnaires, including the Multiple Sleep Latency Test (MSLT), pupillometry, the Digit Span, the Wechsler Memory Scale, the Continuous Performance Test, and the Trail Making Test. These tests, used to assess various cognitive and neurological performances as vigilance, memory, and attention, are sometimes used in insomnia clinical trials to show improved daytime functioning or that hypnotic drugs do not produce daytime residual [124]. However, due to the complexity of their implementation, these tests are not recommended as routine insomnia assessment methods [140].

2.2.1.6. Summary

The objective (i.e., measured by instruments) and subjective (i.e., perceived by the person) aspects of sleep are fundamentally different. Sleep-related questionnaires are a good option for intervention testing as they represent the subjectivity of sleep and are relatively used-friendly. Actigraphy and sleep diaries can be used in routine insomnia testing and clinical trials in order to understand the objective and subjective aspects of sleep, respectively. Due to its cost, polysomnography is recommended only for differential diagnosis purposes, and can be used to detect precisely objective sleep parameters. Questionnaires and neuropsychological tests can be useful to understand the surrounding aspects of sleep (psychological wellbeing, sleepiness, fatigue, cognitive functions) but are not necessary for routine assessment.

2.2.2 Conventional treatments

The objectives of insomnia treatment are to improve quantitative and qualitative aspects of sleep, to reduce the psychological distress associated with poor sleep, and to improve daytime functioning [140]. Insomnia treatment recommended by current guidelines includes pharmacotherapy and psychotherapy [140, 152-155]. Various alternative treatments are also used for insomnia, often on a self-medication basis.

2.2.2.1. Pharmacotherapy

Pharmacotherapy is currently the most commonly used treatment for insomnia. Pharmaceutical drugs used to improve sleep are often called “hypnotics”; they include barbiturates, benzodiazepine receptor agonists, antihistamines, and melatonin. Some non-hypnotics drugs are also used in the treatment of insomnia.

2.2.2.1.1. Barbiturates

This family of central nervous system depressant drugs was the first type of pharmaceutical drug used to treat insomnia, its clinical use dating from 1903. Barbiturates are allosteric modulators and agonists of gamma-aminobutyric acid (GABA). GABA is the most abundant inhibitory neurotransmitter in the central nervous system [156]. GABAergic neurotransmission is involved in many physiological functions including sleep regulation [157, 158]. Barbiturates can bind to the GABA type-A (GABAA) receptor and potentiate the effect of GABA at this receptor [159]. From the 1950s, reports on barbiturates adverse effects and dependence started to influence their clinical use, being progressively replaced by benzodiazepines (BDZs), which were considered safer than barbiturates. Nowadays, although barbiturates are still used for anaesthetic purposes and to treat certain neurological disorders, they are not recommended in the treatment of insomnia [140].

2.2.2.1.2. Benzodiazepine receptor agonists

Benzodiazepine receptor agonists (BzRAs) have dominated the pharmacologic treatment of insomnia since the 1960s [160]. They are composed of two groups, the benzodiazepines and the newer “nonbenzodiazepines” drugs. Although chemically distinct, they all bind to the benzodiazepine site on the GABAA receptor and potentiate the action of GABA through a similar mechanism [156]. Benzodiazepine medications include triazolam, temazepan, flurazepam, estazolam, and quazepam,

and the nonbenzodiazepines include zolpidem, zolpidem CR, zaleplon, and eszopiclone. The BzRAs are by far the insomnia medications that have the strongest empirical support for their use in insomnia patients [161]. Double-blind placebo-controlled trials provide evidence of efficacy in adults, older adults and children with primary insomnia, as well as efficacy for insomnia comorbid with major depressive disorder, generalized anxiety disorder, rheumatoid arthritis, chronic obstructive pulmonary disease, and menopause [160]. As the efficacy of BzRAs is broadly accepted in the medical field, research on pharmacologic treatment has decreased over the past few years [162]. However, BzRA hypnotics can induce a large range of adverse effects, including morning sedation, anterograde amnesia, anxiety, falls, undesired sleep behaviour, somatic symptoms, and drug interactions [140]. These adverse events have even been found to outweigh the beneficial effects of BzRAs for insomnia in older adults [163]. A longitudinal matched cohort study [164] also found a higher risk of mortality and cancer in patients receiving hypnotics medication, even occasionally. Insomnia patient who take BzRAs have also a higher risk to develop cancer and dementia [164-166]. Dependence is also a common concern about BzRAs use, particularly in patients with abuse history [167, 168]. Indeed, BzRAs have been associated with rebound insomnia and withdrawal symptoms [145], and are often used for years by chronic insomnia patients.

2.2.2.1.3. Melatonin

Melatonin, a hormone produced by the pineal gland, is involved in the entrainment of the circadian rhythms including sleep-wake timing [169]. As it appeared to cause few side effects, melatonin seemed an appropriate alternative of BzRA drugs for the treatment of insomnia. Despite being effective for delayed sleep phase syndrome, exogenous melatonin was found to be unable to improve sleep in patients with primary and secondary insomnia [170, 171]. It was suggested that melatonin actually acts to reset the endogenous circadian pacemaker rather than acting directly on somnogenic structures of the brain. Ramelteon, a melatonin receptor agonist that has similar properties to endogenous melatonin, has yet been found to reduce sleep latency and increase total sleep time in older adults with chronic insomnia, but the effects on WASO were inconsistent [172].

2.2.2.1.4. Antihistamines

First-generation antihistamines such as diphenhydramine, doxylamine, and hydroxyzine are able to pass the brain-blood-barrier and disturb the histaminergic pathways of sleep regulation [173]. Because of their sedative effect, antihistamines are widely used as an over-the-counter medication for insomnia [140]. However, the evidence of antihistamines efficacy for insomnia in adults is limited to a 1983 placebo-control trial using diphenhydramine [174], and there is no available study using recent methodology [175]. In addition, due to their anticholinergic effects, antihistamines can cause side effects such as cognitive impairment, blurred vision, dry mouth, constipation, and urinary retention [176]. Furthermore, there are potential interactions with other medications, alcohol, and CAM substances [175].

2.2.2.1.5. Orexin receptors antagonists

As mentioned previously, orexin neurons of the lateral hypothalamus are involved in the regulation of sleep. Their role is to enhance the activity of the ARAS and therefore maintain wakefulness. Suvorexant, a dual orexin receptor antagonist that selectively binds to orexin-1 and -2 receptors, have been found effective to improve sleep, though adverse events such as somnolence, fatigue, and abnormal dreams exist [177].

2.2.2.1.6. Non-hypnotic drugs

Antidepressants such as trazodone, amitriptyline, doxepin, nortriptyline, and mirtazapine, antipsychotic such as quetiapine and olanzapine, and anticonvulsant such as gabapentin, pregabalin, valproic acid, and tiagabine are commonly used for insomnia [160]. In 2002, the most prescribed medications for insomnia in the United States were antidepressant, not hypnotics [178]. This tendency may be caused by unsubstantiated beliefs among prescribers that antidepressant and antipsychotics are reliably effective, safer than hypnotics, and that hypnotics would be needed for a duration of time that outstripped their indication [179]. However, the evidence for the efficacy of these drugs on insomnia is limited [180] and they are currently prescribed “off-label” [161, 178]. These treatments can cause serious adverse effects, especially antipsychotic drugs [179]. Therefore, antidepressants, antipsychotics and anticonvulsants are not recommended as a first-line treatment for insomnia [140].

2.2.2.1.7. Summary

Although not recommended as a first-line treatment, pharmacotherapy (and especially BzRAs) is still the primary treatment of insomnia in clinic. Beside the availability and easiness of use, the strong evidence for efficacy the efficacy of BzRAs might be one of the reasons of this choice. However, they suffer severe limitations such as dependence issue and adverse reactions. These limitations are partially overcome by more recent drugs such as ramelteon and suvorexant. The clinical efficacy of other medications such as melatonin, anti-depressant and anti-histamine drugs is, to date, unproven, and they are therefore not recommended.

2.2.2.2. Psychological interventions

2.2.2.2.1. Sleep hygiene education

Sleep hygiene refers to the daily activities and environmental factors that may influence sleep quality and quantity. Sleep hygiene education is perhaps the most widely used psychological intervention for insomnia [181]. It consists in instructions about good sleep hygiene habits, e.g. avoiding caffeine intake, adjusting the temperature of the sleep environment or avoiding intensive exercising just before bedtime. The rationale of this therapy is that lifestyle and environmental factors are involved in the cause and maintenance of insomnia [182]. However, patients with primary insomnia have been found to not have poorer sleep hygiene practices than good sleepers [181]. Even though multicomponent treatment packages including sleep hygiene instructions are effective for insomnia [183], sleep hygiene education as a monotherapy does not reliably produce significant benefit [184, 185]. It is often used as a control intervention for psychological treatment in controlled trials for insomnia [186, 187].

2.2.2.2.2. Relaxation training

Relaxation was one of the first behavioural interventions used to treat insomnia. As stated earlier, insomniacs have been found to have higher levels of somatic and cognitive arousal than good sleepers. The rationale of relaxation training is to teach the patient a method to reduce the somatic and/or cognitive arousal, thereby increasing the probability that he will fall asleep. There are mainly four types of relaxation therapy, i.e. progressive muscle relaxation (PMR), diaphragmatic breathing, autogenic training, and imagery training [188]. PMR consists in alternatively tensing and relaxing different muscle groups through the body, often in a specific order. Diaphragmatic breathing consists

in a form of breathing that is slower, deeper, and mechanically driven from the abdomen as opposed to the thorax. Autogenic training is a method using auto-suggestion of warmth and heaviness in the limbs in order to increase peripheral blood flow. Imagery training entails the patient focusing on a relaxing image and engaging with it from a multisensory perspective. The patient is not only guided by the therapist into relaxation, but he has to learn the method in order to be able to use it independently. Other behavioural interventions involving relaxation include hypnosis, biofeedback, yoga, and meditation [189]. There is strong empirical support for the efficacy of PMR [190] but there is a lack of evidence for the use of other techniques as single treatments for insomnia [189].

2.2.2.2.3. Stimulus control therapy

The proposition of stimulus control therapy (SCT) by Bootzin in 1972 [107] was a milestone in the development of behavioural treatments for insomnia. This therapy is based on the application to sleep of the behavioural theory of conditioning. The spatiotemporal sleep environment cues (e.g. the bed, the bedroom or bedtime) are normally stimuli associated with a de-arousal reaction. In chronic insomniac, these cues are associated with arousal and not de-arousal, which maintains the symptoms of insomnia. The rationale of SCT is to strengthen the bed and bedroom as cues for sleep and not arousal [189]. It consists in six instructions on sleep behaviours, i.e. going to bed only when sleepy; using the bed only for sleep and sexual activities; getting up and going into another room if unable to fall asleep; going back to bed only if feeling sleepy and getting up again if necessary; getting up at the same time every morning; not napping during daytime [189]. A 1999 meta-analysis [191] concluded that SCT can significantly improve sleep and the American Academy of Sleep Medicine (AASM) considers it is an “effective and recommended therapy in the treatment of chronic insomnia” [190]. A new form of SCT, intensive sleep retraining, was designed in order to accelerate the conditioning of the bed environment with sleep [192]. After 40 hours of sleep deprivation, participants are given 50 opportunities to fall asleep during a 25-hours period, and are being awaken after four-minutes sleep [192]. The efficacy of this weekend of intensive intervention was found to be similar to four weeks of SCT [186, 192].

2.2.2.2.4. Sleep restriction therapy

Advances in knowledge of the influence of sleep deprivation, the role of attitudes and anxiety about sleep, and the importance of circadian rhythm led to the development of sleep restriction therapy (SRT) in 1987 [189]. The rationale for restricting the sleep of people who long to sleep more is that restricting time in bed (TIB) allows an increase of sleep homeostatic drive and addresses insomnia perpetuating factors such as anticipatory anxiety about sleep, disturbed sleep conditioning, and broken circadian cycle [189]. In order to determine his ideal time in bed duration, the patient is asked to record his sleep parameters using a sleep diary. The average total sleep time, which reflects the patient's sleep capacity, is increased by 30 minutes to obtain the prescribed TIB [193]. A standard wake-up time and earliest bedtime are the chosen by the patient in accordance with the prescribed TIB. TIB is then adjusted every week according to the patient's sleep efficiency until achieving a reasonably ideal total sleep time. Even though SRT is usually used in combination with other psychological intervention such as SCT, SRT has been proven effective as a stand-alone treatment in number of studies [189] and is recommended in the treatment of insomnia by the AASM [190]. A retrospective study on 90 patients who had completed 12-month follow-up after a clinical trial [194] found that the combination of SCT and SRT was a predictor of clinical improvement in sleep latency and night-time wakefulness. An alternative to SRT is sleep compression. This technique consists in gradually compressing time in bed by delating bedtime or advancing wake time until the ideal TIB is reached. This approach is useful for patients who cannot tolerate the suddenness of SRT [188].

2.2.2.2.5. Cognitive therapy

Following the development of cognitive therapy in the 1980s, more and more cognitive components were added to the behavioural treatment of insomnia. As the term cognition encompasses different aspects of thinking such as memory, attention, and beliefs, the range of cognitive therapies for insomnia is extensive, including cognitive restructuring, cognitive control, mindfulness, and paradoxical intention [195]. Cognitive restructuring is based on the finding that insomniacs present more dysfunctional beliefs and attitudes about sleep such as beliefs about the negative consequences of insomnia, fear of losing control of sleep, and helplessness about its unpredictability [111]. It aims at replacing these beliefs with alternative beliefs that are more compatible with sleep using either

sleep education or Socratic questioning. Cognitive control rationale is to teach patients strategies to cope with intrusive thoughts in order to decrease cognitive arousal during sleep time [195]. Articulatory suppression and imagery training are two techniques that can be used to block or distract the individual from these intrusive thoughts.

Mindfulness has been more recently added to the palette of psychological interventions for insomnia. In accordance to the principles of mindfulness, which are nonjudgement and acceptance, patients are asked to acknowledge passively their thoughts, emotions, and feelings without judgement rather than trying to suppress or control them, breaking the cycle of emotional and cognitive arousal [196]. It has been proposed that specific attention for sleep cues, and intention and efforts to fall asleep are the cornerstone of chronic insomnia mechanism [86]. Instead of focusing on trying to fall asleep, paradoxical intention teaches patients to try to stay awake for as long as possible, breaking the attention-intention-effort pathway, and finally resulting in a more autonomous sleep pattern [195]. As cognitive therapy tends to change inner beliefs that influence sleep quality indirectly through behavioural changes, its efficacy is slower but more sustained than behavioural therapy [197].

Cognitive therapy is usually combined with other psychological interventions, and the efficacy of cognitive therapy as a monotherapy for insomnia was only assessed by one open trial without control group [198], therefore the evidence base for cognitive interventions is limited.

2.2.2.2.6. Phototherapy

Although light therapy is not strictly speaking a form of psychotherapy, it comports some behavioural aspects and is often used in combination with psychological interventions, therefore it is included in this section. Patients are exposed to white light produced by a phototherapy device emitting in average 2500 lux while they are reading, eating or during similar activities [199]. This exposure, which simulate exposure to sun light, can affect the SCN and readjust the circadian rhythms [200]. Although it has been proved effective for circadian rhythm disorders [200], the results of studies focusing on chronic insomnia are mixed [199]. Moreover, phototherapy can cause side effects such as jumpiness or jitteriness, headache, and nausea. It is therefore not recommended as a first-line treatment for insomnia [188].

2.2.2.2.7. Multicomponent cognitive-behavioural therapy for insomnia

Cognitive and behavioural interventions for insomnia are more effective when used combined than separated [197]. Therefore, they are usually combined into a multicomponent therapy including SCT, SRT, cognitive therapy, sleep hygiene, and relaxation. The cognitive and behavioural techniques used to treat insomnia are similar to the more general cognitive-behavioural therapy (CBT) as it is based on the same pathopsychological model (i.e. mental disorders are caused by cognitive and behavioural maintaining factors) and as the goal of the therapist is to teach to the patient self-help techniques in order to make him independent. However, methods such as SCT and SRT are quite specific to the treatment of insomnia and the term "cognitive-behavioural therapy for insomnia (CBT-I)" is often used to refer to this set of methods. New treatment modalities of CBT-I have been developed, such as group therapy [201, 202], internet-based treatment [203], television program [204], telephone-based treatment [205], and self-help treatment [206, 207]. After decades of clinical research on CBT-I, the efficacy of multicomponent CBT for primary and comorbid insomnia is well established [145]. The effects of CBT-I on sleep have even been found to be better and/or more sustained than pharmacotherapy [208-210]. However, due to a lack of trained practitioners and the time-consuming and burdensome nature of CBT-I, pharmacotherapy is still the most widely used therapy for insomnia [211]. In addition, insomniacs may lack of willingness or ability to change maladaptive behaviours, especially patients with comorbid conditions [212].

2.2.2.2.8. Summary

A long distance has been travelled since the start of the use of behavioural techniques to treat insomnia in the seventies. The efficacy of psychological interventions for insomnia has been proven and CBT-I is now widely recommended as a first-line treatment for insomnia disorder. CBT-I is generally used as a multi-component therapy including educational, behavioural and cognitive components. The main limitation of CBT-I remains in its psychological nature. Psychological interventions need trained therapists, an appropriate setting and the active involvement of the patient.

2.2.3. Alternative treatments

Because of the long-held misconception of insomnia as "not a disease", many insomnia sufferers do not report their condition to their physician [89]. Even for patients looking for treatment, because of

the fear of adverse events and dependence there is a preference for non-pharmaceutical approaches [11]. However, CBT-I is often unavailable in primary care settings [212], leading a large proportion of insomnia sufferers to resort to self-help methods and CAM to improve their sleep [98]. In the United states, 45% of insomniacs reported using CAM in 2007 [213]. About a half of the people using CAM to treat insomnia report that the therapy helped their condition a great deal [214]. These CAM include western herbal medicine, homeopathy, aromatherapy, music therapy, massage, physical exercise, yoga, dietary supplements, and Chinese medicine. The use of Chinese medicine and related interventions for insomnia will be specifically addressed in the next section.

2.2.3.1. Western herbal medicine

Herbal products are the most popular CAM among adults with insomnia in Western countries [213]. In the West, herbs are typically used individually in the form of herbal tea or plant extract. Valerian is probably the most commonly used individual herb to improve sleep. The sedative effects of this herb are attributed to the valepotriates and sequiterpenes in the volatile oil [215] and its biochemical action may involve GABA metabolism and reuptake as well as 5HT1a and adenosine receptors [216]. Reviews of clinical evidence for the use of valerian to treat insomnia are mixed and inconclusive [217-219]. Valerian has been found to be generally safe in a systematic review of clinical studies [219]. Another herb, St John's Wort (SJW), has been traditionally used for its sedative effects [220]. A Cochrane review including 5489 patients from 29 randomized-controlled trial found SJW as effective as standard antidepressants for major depression [221]. However, the empirical evidence of the efficacy of SJW for insomnia is very limited [175]. Hops, which are also used to drew beer, have been found to improve sleep parameters in association with valerian [222], but their efficacy as an individual herb is unclear. Kava Kava has been found to have hypnotics effects in uncontrolled studies [175]. Chamomile is also used for insomnia, but its effects on sleep were found to be mixed [223, 224]. Other herbs such as passionflower, skullcap, Jamaica dogwood, lavender, wild lettuce, California poppy, and lemon balm are marketed as natural remedies for insomnia, though there is only little evidence supporting their efficacy and safety [225].

2.2.3.2. Homeopathy

The rationale of homeopathy, one of the oldest CAM, is the similitude principle, i.e. to use a substance that would normally provoke in healthy individuals the symptoms that are aimed at [226]. For instance, coffea cruda (coffee), which is able to produce insomnia symptoms, can be used as a homeopathic treatment for insomnia [227]. Usually homeopathic remedies have to be diluted and succussed (vigorously shaken) in order to be more effective, which is called the potentiation process [228]. Although homeopathy is commonly used in certain countries to treat insomnia [229], only a few randomized trials with poor methodology are available and they have showed insignificant effects compared to placebo [230].

2.2.3.3. Aromatherapy

Aromatherapy, a rapidly growing subfield of CAM, is a therapy using plant essential oils via the skin or the respiratory system [231]. Several essential oils are considered to have sedative effects, including Bergamot, Roman Chamomile, Jasmine, Lavender, Mandarin, Marjoram, Melissa, Neroli, Patchouli, Egypt Rose, Ylang-Ylang, and Vetiver [232]. A few studies on animals or healthy individuals support the sleep promoting effects of Lavender and Sandalwood essential oils [233, 234], however no randomized controlled trial assessing aromatherapy for insomnia is yet available [235].

2.2.3.4. Massage

Massage is a therapy involving multiple techniques of manipulation of the soft tissues either manually or with instruments. Massage is considered to have sedative effects through the reduction of somatic and/or cognitive arousal [199], and has been found effective for improving sleep of cancer patients and healthy infants [236, 237]. Massage therapy has also been found to improve the subjective sleep quality of postpartum and postmenopausal women with insomnia [238, 239]. Clinical research focusing on the efficacy of massage on primary insomnia patients is needed.

2.2.3.5. Physical exercise

Longitudinal studies showed that physical inactivity is a predictor of insomnia and physical activity a predictor of good sleep [240, 241]. The effects of physical exercise on sleep might be explained on one hand by sleep-wake homeostasis and on the other hand by the thermodynamics hypothesis [199].

There is evidence that moderate to intense physical exercise can improve sleep quality in a normal population [242, 243]. There is a need of randomized trial focusing on insomniac population.

2.2.3.6. Yoga

Yoga is a spiritual practice originating from ancient India. It has been popularized in the second half of the 20th century in the West as a mind-body practice consisting in series of postures (asanas) involving the awareness of breath (pranayama) and thought processes [199]. As yoga can reduce the somatic, emotional and cognitive arousal related to stress, this technique as a potential as a treatment for insomnia. However, the empirical evidence of yoga's efficacy in the treatment of insomnia is limited. Only one randomized controlled trial found that yoga was effective to improve self-rated sleep measures in a normal older adults' population [244].

2.2.3.7. Dietary supplements

As poor sleepers have a degraded health and quality of life (QoL), they are more prone to vitamin use than good sleepers [245]. However, the impact of dietary supplements on sleep is uncertain. Some supplements such as magnesium, nicotinamide, and vitamin B12 have been found to have potential sleep improvement effects [246-248], but no randomized trial was found to support their efficacy on insomnia [175].

2.2.3.8. Summary

There is a plethora of CAM treatments for insomnia, ranging from mind-body therapies such as yoga to biological treatments such as herbal medicine. These treatments are generally considered safe, however a lack of high-quality research prevents them from being recommended and widely applied in clinical settings.

Chapter 3: Chinese medicine for insomnia

In Chapter 1 and Chapter 2 we presented the current knowledge on sleep and insomnia from a sleep medicine perspective. As this thesis has a focus on Chinese medicine, we interpreted some of this knowledge from a Chinese medicine perspective. In the present chapter we will present a more systematic and comprehensive view of sleep and insomnia from the point of view of Chinese medicine.

3.1. Theory, diagnostic and treatment of insomnia with Chinese medicine

3.1.1. Basic theory of Chinese medicine

Chinese medicine is one of the oldest medicines still in use nowadays. The fundamental theory of Chinese medicine takes root in the antique Chinese philosophy and fortuitous discoveries about the healing properties of herbs or body points. This theory has evolved through clinical practice for thousands of years, inference of clinical findings leading to clinical experimentation of the new theories and vice versa. Chinese literature rich academic literature was a breeding ground for the development and critic of new theories, the academic disputes culminating in the Jin and Yuan dynasties (1115-1368 A.D.). The philosophical theories that compose the foundation of Chinese medicine include the yin-yang theory and the five elements (*wu xing* 五行) theory. The *yin-yang* theory proposes that things can have either *yin* (i.e., cold, inhibition, and structure) properties or *yang* (i.e., warmth, excitement, and function) properties, these being relative [249]. The four relations between *yin* and *yang* include interdependence, opposition, mutual consuming, and intertransformation [249]. The five elements theory proposes that things evolve through five phases, which have directions related to five elements (e.g., the direction of growth, elevation, is related to the "wood") [249]. The body is divided into five systems whose heart is the five organs. The five organs (i.e., the liver, the heart, the spleen, the lung, and the kidney) do not refer to substantial organs but to global functions. For example, the "spleen" refers to the metabolic and digestive functions of the whole body. Chinese medicine holistic view of the body tends to not separate the material body (*xing* 形), the "*qi*" or energy/functions (*qi* 气), and the spirit (*shen* 神) [250]. The therapeutic techniques set of CM includes herbal medicine, acupuncture, tuina massage, qi gong, tai chi, and food therapy [251].

3.1.2. Diagnosis of insomnia

There are four different diagnosis and treatment approaches in Chinese medicine, namely the disease approach, the pattern approach, the constitution approach, and the symptom approach.

In the disease approach, the specificities of the patients are not taken in account and the treatment is based on the disease, i.e. insomnia, or its equivalent CM diagnosis the "not-sleeping syndrome (*bu mei zheng* 不寐症)" [45]. As the core mechanism of insomnia is considered to be an excess of *yang* (i.e., excitation, heat, energy) coupled with a lack of *yin* (i.e., inhibition, cold, liquids) that leads to an impossibility for the *yang* to "penetrate into the *yin*", the principle of the treatment is to inhibit the *yang*, clear the heat, and nurture the *yin* [45]. This approach is similar to the hyperarousal model of insomnia and the subsequent treatment with neurological inhibitors.

The pattern and the constitution approaches are similar in that they consider the specificities of every patient and tend to an individualised treatment. The difference is that the pattern approach considers the global state of the patient at a particular time, while the constitution approach focuses on the long-term biological and psychological characteristics of the patient [252]. As much as 69 different patterns were reported in insomnia patients, with the top three patterns covering more than a half of the subjects [253]. The constitution approach can be considered as a treatment on the predisposing factors of the 3P model.

Finally, a symptomatic approach focuses on treating the symptoms of insomnia. This technique is called "to appease the spirit (*an shen* 安神)", and is embodied by acupuncture points such as shen men (HT 7) or an mian (EX-HN-8) and herbs such as *suanzaoren* (Ziziphi Spinosae Semen) or *fuling* (Poria) [254].

3.1.3. Treatment of insomnia

3.1.3.1. Acupuncture

Acupuncture, as a therapeutic system, consists in using various techniques such as needling, bleeding, cupping, warming with moxa or lamps, and digital pressure on acupuncture points and "meridians" located in the whole body. The mechanism of insomnia treatment with acupuncture may involve the autonomic nervous system, the regulation of GABA and melatonin, and the concentration of beta-

endorphins [255-258]. A Cochrane review published in 2012 [259] found that acupuncture might increase the proportion of people with improved sleep quality when added to another treatment. However, the overall quality of the studies led the author to conclude the evidence is insufficient to support or refute acupuncture for treating insomnia [259].

3.1.3.2. Tuina massage

Tuina consists in various techniques of massage, two of them namely "pushing (*tui* 推)" and "grabing (*na* 拿)" composing the name of this therapy. As Tuina is considered to not have side effects and dependence issue [260], it is broadly used as an alternative therapy for insomnia in Chinese populations [13]. A narrative review published in 2011 found several studies showing the efficacy of Tuina for insomnia, thought the lack of standardization of the intervention, the size of the samples, and the poor methodology of these studies were pointed out [261]. A systematic review published in Chinese [262] could only find one high-quality randomized-controlled trial assessing the efficacy of Tuina for insomnia.

3.1.3.3. Tai Chi

Originally developed in China as a martial art, tai chi is nowadays used worldwide as a type of moving meditation [263]. It usually consists in series of movements accomplished in accordance to philosophic principles such as the yin-yang theory. Tai chi can have a positive impact on the causes and consequences of insomnia as a session of tai chi was found to be able to decrease subjects' anxiety, depression, and fatigue levels [264]. Two randomised-controlled trials [265, 266] reported a significant improvement of subjective sleep measures in older adults with moderate sleep complaints. Another study found that tai chi performed better than the control but not as good as CBT [267]. Clinical trials for a more general population of insomniacs are needed.

3.1.3.4. Qigong

Qigong, which could be roughly translated by "work on the energy", encompasses various mind-body practises rooted in the ancient Chinese philosophy. During qigong exercises, which can be static or mobile, the adjustments of the body, the mind, and the breath are emphasized [268]. As qigong practice has been found to decrease autonomic activity and brain activity, it has been proposed as a potential treatment for insomnia [268]. A recent meta-analysis [269] found that baduanjin, a form of

qigong, was effective to improve subjective sleep quality in insomnia patients, though the improvement was not maintained at follow-up. The lack of appropriate behavioural control and the absence of recognised diagnostic criteria for insomnia in the studies limit the validity of these findings.

3.1.3.5. Food therapy

As Chinese medicine tends to not only treat illnesses but also to balance the body in order to prevent diseases, food therapy is an important part of the Chinese medicine set of techniques [270]. Unlike Western food therapy, Chinese medicine's approach of food therapy is not nutritive but functional, the effects of food on the body being considered from a Chinese medicine theory point of view including the five organs and the yin-yang theory [271]. The rationale of food therapy is to provide an individualised diet to the patient with consumption of beneficial food and avoidance of harmful food [271]. The research in the field of Chinese medicine food therapy is limited as only one randomized controlled trial (RCT) published in English is available, the study in question assessing the impact of food therapy on hypertensive patients [272]. A few studies published in Chinese [273, 274] found the combination of food therapy with other therapies efficient for insomnia, however the role of food therapy alone is unclear.

3.1.3.6. Chinese herbal medicine

Chinese herbal medicine (CHM) is one of the most common treatments for insomnia in Chinese populations [12, 13] and its use is increasing in Western countries [275]. Although it is called herbal medicine, it includes materials arising from mineral and animal sources. A typical CHM prescription consists in a formula of two or more single herbs that have additive or synergistic effects. The formula is usually taken as a decoction, powder, granules or tablets.

The active components of CHM herbs used for insomnia, including alkaloids, terpenoids and volatile oils, flavonoids, lignanoids and coumarins, and saponins, are thought to play sedative effects through regulating central neurotransmitters, influencing sleep-related cytokines, and improving the structure of the central nervous system [276].

In a systematic review including 217 studies Yeung et al. [277] found that CHM has similar effects but less adverse events than biomedicine pharmaceutical medications. However, due to the poor methodology of the studies, the evidence was considered insufficient to support the efficacy of CHM for insomnia [277]. Setting more stringent inclusion criteria, Ni et al. [278] found 79 randomized-controlled trials in an update of the systematic review. The meta-analysis showed that CHM was more effective than placebo or BDZs to improve subjective sleep quality measured with PSQI [278]. The efficacy in terms of self-reported sleep parameters was found higher for CHM than placebo and higher or equivalent than BDZs. The frequency of adverse events induced by CHM was found to be not significantly different from placebo and lower than for BDZs [278]. However, the risk of bias from these studies does not allow for any clear conclusion and further well-designed RCT with proper blinding are needed in order to insure the efficacy and safety of CHM for insomnia [279].

3.2. Zao Ren An Shen, a patent herbal medicine for insomnia

3.2.1. Overview of the formula

Zao Ren An Shen (ZRAS) is a Chinese herbal medicine formula composed of three herbs, i.e. *suanzaoren* (Ziziphi Spinosae Semen), *wuweizi* (Schisandrae Chinensis Fructus) and *danshen* (Salviae Miltiorrhizae Radix et Rhizoma). The name of the formula, Zao Ren An Shen 枣仁安神, means "appeasing the spirit with *suanzaoren*". Li Peisong, a senior Chinese medicine pharmacist from Beijing Medicinal Herbs Company, designed this formula for the treatment of insomnia based on his clinical experience [280]. Originally manufactured as a solution [280], the formula exists also in form of capsule [281] and granule [282]. Other formulas with the same or a similar name such as Zao Ren An Shen decoction [283, 284], Huang Qi Zao Ren An Shen decoction [285], compound Zao Ren An Shen capsule [286], Zao Ren An Shen tablet [287], and Quick-effect Zao Ren An Shen capsule [288] have actually different ingredients and should not be confused with ZRAS. According to the Chinese Pharmacopeia, the effect of ZRAS is to "nurture the blood and appease the spirit" and it is indicated for insomnia, memory loss, dysphoria, dizziness, and for neurasthenia [289]. Besides insomnia, the efficacy of ZRAS has been positively assessed for anxiety and depression in patients with coronary heart disease [290, 291], neurasthenia [292, 293], schizophrenia [294], post-traumatic reaction [295], and post-stroke major depressive disorder [296].

3.2.2. Ingredients of the formula

3.2.2.1. *Suanzaoren*

Suanzaoren (Ziziphi Spinosae Semen) is the dried mature seed of the spine date, whose Latin name is Ziziphus jujuba Mill. var. spinosa (Bunge) Hu ex H. F. Chou. According to the Chinese pharmacopeia, it is indicated for dysphoria, insomnia, fright, palpitation, excessive dreams, excessive perspiration, and thirst [289]. The major known chemical constituents of *suanzaoren* are alkaloids, triterpene saponines, and flavonoids [297]. Pharmacological studies showed that *suanzaoren* has sedative, analgesic, anticonvulsant, antiarrhythmic, and can also decrease the body temperature, decrease the blood pressure, decrease blood lipids level, prevent atherosclerosis, increase the resistance to hypoxia, reduce the effects of burning, and strengthen immunity [298]. *Suanzaoren* is considered relatively safe as toxicology studies in rats showed no death even with 50g/kg of oral

intake of *suanzaoren* decoction [298]. The recommended dosage of the Chinese pharmacopeia for *suanzaoren* is 10 to 15g of raw herb per day for oral intake [289].

3.2.2.2. *Danshen*

Danshen (Salviae Miltiorrhizae Radix et Rhizoma) is the dried rhizome and root of the Salvia miltiorrhiza Bge, a specie of salvia. Its indication is chest tightness, heart pain, stomach pain, abdominal pain, pain in hypochondria, masses, hot join pain, dysphoria, insomnia, irregular menstruation, dysmenorrhea, amenorrhea, and sores [289]. The major known chemical constituents of *danshen* are quinones, diterpene ketones and diterpene lactones, and phenols [297]. It has mixed effects on the cardiac function, can lower the blood pressure, improve cardiac circulation, brain circulation, and the microcirculation, decrease blood lipids level, prevent atherosclerosis, increase the resistance to hypoxia, improve immunity, protect the liver, protect the stomach mucosa, improve renal function, promote fracture healing, and has also anticoagulation, fibrinolysis, antithrombotic, anti-inflammatory, anti-allergic, anticancer, sedative, analgesic, anti-oxidation, and antibacterial effects [298]. Toxicology studies on rat found a median lethal dose of 80.5 (±3.1)g (raw herb)/kg [298]. The recommended dosage of the Chinese pharmacopeia for *danshen* is 10 to 15g of raw herb per day for oral intake [289].

3.2.2.3. *Wuweizi*

Wuweizi (Schisandrae Chinensis Fructus) is the dried mature fruit of the Chinese magnoliavine, more specifically the Schisandra chinensis (Turcz.) Baill. and the Schisandra sphenanthera Rehd. & Wils. species. *Wuweizi* is indicated for chronic cough, dyspnea, nocturnal emission, urinary incontinence, frequent urination, chronic diarrhoea, spontaneous perspiration, nocturnal perspiration, thirst, palpitations, and insomnia [289]. Its major known chemical constituents are various volatile constituents, lignin compounds, glycosides, and organic acids [297]. Pharmacological studies showed that *wuweizi* and its constituents have central nervous system inhibition, respiratory system excitation, cardiac output increase, coronary blood flow increase, anti-shock, liver protection, anti-oxidation, body adaptability increase, anti-ulcer, antibacterial, and anticancer effects [298]. A toxicology study in which 5g/kg of *wuweizi* aqueous suspensions was administered to rats found no death nor

poisoning [298]. The recommended dosage of the Chinese pharmacopeia for *suanzaoren* is 2 to 6g of raw herb per day for oral intake [289].

3.2.3. Evidence of efficacy and safety

Only one RCT has compared ZRAS to placebo, showing a significantly lower score for the ZRAS group than for the placebo group after three weeks of treatment [299]. Twelve RCTs [299-310] and one non-randomized controlled [281] trial assessed the efficacy of ZRAS for insomnia compared to a BzRA drug. These studies found similar or better outcomes for ZRAS compared to BzRA drugs in term of self-reported sleep quality and insomnia severity, therapist-rated clinical efficacy, and sleep parameters measured with PSG. However, these studies present an overall high risk of bias, including selection, performance and attrition risks of bias. Moreover, except for one study [306] in which self-reported anxiety level was measured, psychological status, quality of life, fatigue, performance, and self-reported sleep parameters were not assessed, despite it is recommended by the guidelines for clinical trials on insomnia [311]. Other studies show that ZRAS can be efficient for insomnia in combination with acupuncture [312, 313] or another Chinese herbal patent medicine [314], though the contribution of ZRAS alone is not clear. ZRAS has also been showed to improve significantly the efficacy of BzRAs for insomnia as an additional treatment [282].

Safety was assessed with a standardized tool in only two studies in which ZRAS was used alone. Patients treated with ZRAS reported mild adverse reactions such as fatigue, stomach discomfort, diarrhoea, acid reflux, and lips numbness. In the studies comparing ZRAS to BzRAs, adverse reactions were significantly less reported by patients in the ZRAS group, 0-10.67% of the patients taking ZRAS reporting adverse reactions compared to 14.1-86.7% of those who took BzRAs. As adverse reactions were not reported in the only study in which ZRAS was compared to placebo, it is difficult to conclude on the absolute safety of the formula. Moreover, the impact of ZRAS on liver and kidney functions is unclear as it was not measured in these studies. As one case of paroxysmal sinus tachycardia induced by ZRAS capsule has been reported in 1993 [315], more research is needed to assess the safety of ZRAS.

3.2.4. Rationale for choosing the formula

The reasons for which ZRAS was chosen among many other CHM formulas are:

- The main ingredient of ZRAS, *suanzaoren* (Ziziphi Spinosae Semen), was found to be the most commonly used CHM individual ingredient for insomnia [254] and is also used across a variety of different patterns [316].

- As the formula does not have a significant tendency (i.e. neither very yin nor very yang), it can be used on insomnia patients presenting various types of pattern.

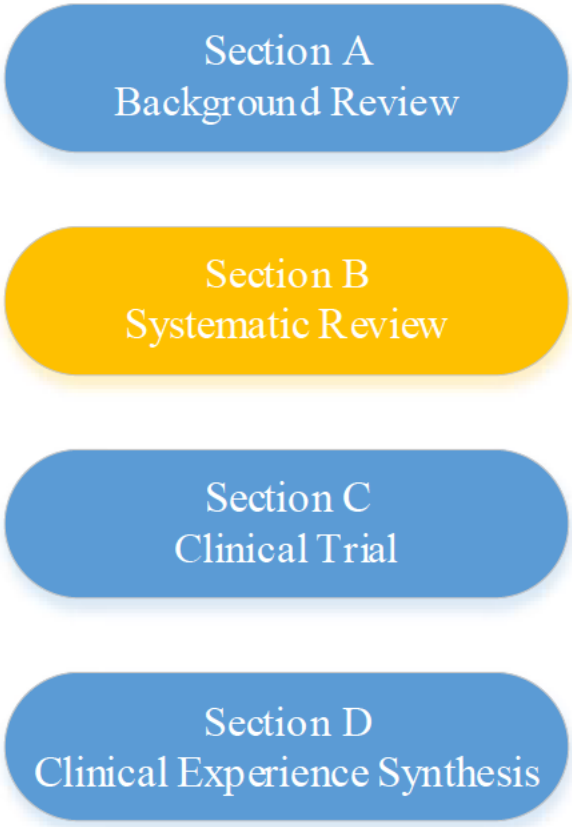
- The formula has already been used in clinic for 30 years and its efficacy is recognised as it was used as a control intervention in several studies on other treatments [317-321].

- Based on toxicological studies on individual herbs and their constituents as well as clinical studies on the formulation, ZRAS can be considered as being relatively safe.

- This formula, composed of only three herbs, is relatively small, allowing for conjecturing about its potential mechanism.

Section B

ZRAS for insomnia: A systematic review



This section presents a systematic review in which clinical trials testing the efficacy and safety of ZRAS for insomnia were systematically collected, analysed and assessed.

The objective of the review was to assess the evidence on the efficacy and safety of ZRAS capsule as a treatment of insomnia disorder.

This section is composed of a unique chapter, Chapter 4, which presents the background for the review, the methods and the results of the systematic review.

This section was the basis for the conduction of the clinical trial presented in section C.

Chapter 4: A systematic review on the safety and efficacy of ZRAS for insomnia disorder

The content of this chapter was published as a journal article in the journal Sleep Medicine [322].

4.1. Introduction

CHM is one of the most popular alternative treatments for insomnia [12, 13, 214]. A recent systematic review [278] supports the use of CHM as a whole for insomnia, whilst calling for an evaluation of the evidence for individual formulas. ZRAS is a CHM formula composed of three ingredients: *suanzaoren* (*Ziziphi spinosae* Semen), *wuweizi* (*Schisandrae chinensis* Fructus) and *danshen* (*Salviae miltiorrhizae* Radix et Rhizoma). Produced in forms of solution, capsule and concentrated extract granules, ZRAS is not only one of the oldest Chinese herbal manufactured product [323], but also one of the most used and studied [324-326]. The main ingredient of the formula, i.e. *suanzaoren*, is the most commonly used CHM individual herb for insomnia [316]. Pharmacology studies showed that both ZRAS granule and the three components of ZRAS (i.e., *suanzaoren, danshen and wuweizi*) exert sedative and hypnotic effects [327-331], potentially mediated through the GABA-ergic and serotoninergic systems [328, 332]. Alkaloids [332, 333], triterpene saponin glycosides, jujubosides [334], flavonoids [335] and schisandrin [336] are purported to be the active constituents of ZRAS. These compounds may enhance the activity of GABA by selectively binding to the $GABA_A$ receptors as agonists [337-339] or regulate serotonergic systems [336, 340, 341]. ZRAS is currently widely used for insomnia despite clear evidence of effectiveness and safety. Thus there is a need to review systematically the effectiveness and safety of ZRAS for insomnia.

4.1.4 Study objectives

The aim of this systematic review is to assess the effectiveness and safety of ZRAS for insomnia compared to placebo or a positive control, or as an add-on treatment. The primary outcomes are sleep quality measured with the PSQI for effectiveness and the number of adverse events for safety. The primary comparison of interest is ZRAS compared to placebo or conventional treatments (i.e., BzRAs or CBT-i). Secondary outcomes are sleep quality or similar outcomes (not measured with PSQI),

objective and subjective sleep parameters, clinical severity, fatigue and sleepiness levels, psychological distress levels, and QoL.

4.2. Methods

4.2.1 Study design

This study is a systematic literature review with a meta-analysis. The two review authors, MJ and YB, conducted a literature database search and screened the studies found in a two-step process. After data collection, the risk of bias of the included studies was assessed and a meta-analysis of the results was conducted. This systematic review has been registered in PROSPERO (registration number CRD42019126113).

4.2.2 Search strategy

Four international databases, i.e. EMBASE, PubMed, the Cochrane library, and PsycINFO, and three Chinese databases, i.e. Chinese National Knowledge Infrastructure, Wanfang and Chong Qing VIP (CQVIP) were searched from their inception to the 6 November 2018. The use of Chinese databases was based on the high number of studies published in Chinese in recent systematic reviews in the field of Chinese medicine [342]. The searched terms used were ("zaorenanshen" OR "zaoren anshen" OR "zaoren an shen" OR "zao ren an shen") AND ("clinical study" OR "investigation" OR "trial") AND ("sleep" OR "insomnia"). The databases were all searched with keywords both in English and Chinese in the full text (when possible) and the searches were adapted to each database. Search results from the databases were imported into Endnote (Figure 4.1). The reference list of the included reports and the articles using the included reports as references were also searched for any additional study.

4.2.3 Eligibility criteria

The eligibility of the studies found was assessed according to the following criteria:

Inclusion criteria:

1. RCT or Controlled Clinical Trial (CCT) with or without blinding.

2. Participants diagnosed with insomnia by the researcher or a competent health care provider, regardless of the diagnosis process and comorbidities.

3. Using Zao Ren An Shen, i.e. a formula using the combination of Suan zao ren, Dan shen and Wu wei zi, as the experimental intervention, regardless of the administration type, dose or intervention duration.

4. Using an intervention whose effectiveness is internationally recognised (i.e., pharmacotherapy or CBT-I) [153-155] or a placebo as a control, or using ZRAS in combination with the same intervention used in the other group.

5. At least one outcome relevant to insomnia (i.e., sleep quality, sleep parameters or similar outcomes) [134, 311] or to safety (i.e., number of adverse events).

Exclusion criteria

1. The study focuses on adolescent or child participants (i.e., age < 18 years old).

2. ZRAS is used in both the experimental group and in the control group.

3. ZRAS is used in combination with another treatment that is not used in the other group.

4. The full text of the report is not accessible and the missing information could not be sought from the authors.

4.2.4 Screening process

After combining the results of the searches in Endnote, the duplicates were removed (Figure 4.1). The reports were then screened by YB using the title and the abstract (Figure 4.1). The title/abstract screening was over-inclusive in order to avoid missing relevant reports [343]. The full text of the selected reports was retrieved and screened independently by YB and MJ. A high degree of agreement (Kappa = 0.84) was reached, and all disagreements were resolved by discussion followed by consensus, with XZ being able to arbitrate in cases of study inclusion disagreement. Reports on the same study were combined as studies were chosen as the unit of interest [343].

4.2.5 Data collection

Data concerning the study design, the participants type, age, gender, sample size, the interventions regimen, outcomes types and measurements, and outcome data were collected by YB with a data collection form [343]. The outcome data collected were sleep quality or similar outcomes measured with a questionnaire (e.g., PSQI), objective and subjective sleep parameters such as SOL, TST, Number of AWAKenings (NAWAK) or SE, clinical severity, fatigue and sleepiness levels, psychological distress levels, and QoL [124] for effectiveness, all measured with a validated measurement only, and number of participant-reported adverse events, regardless of the collection procedure. The authors were contacted when relevant data were missing.

4.2.6 Risk of bias assessment

The risk of bias was assessed independently by YB and MJ for every study using the Cochrane Collaboration's tool [344]. Individual studies were assessed at the study level. Agreement was reached by consensus after discussion between the two review authors. The risk of bias was exported to RevMan 5.3. and reported with a risk of bias summary [344].

4.2.7 Statistical analysis

Results from studies using the same outcome measurement and the same comparison were combined and meta-analyses were performed using RevMan 5.3. every time the I-square was inferior to 85%, the primary meta-analytic outcomes being the sleep quality measured with PSQI and the number of adverse events. In case of heterogeneity due to one or two outlying studies with results that conflict with the rest of the studies and obvious reasons for the outlying results, the outlying studies were removed from the meta-analysis [345]. For the primary outcomes, sub-analyses were performed for different modalities of ZRAS (e.g., granule, capsule) and different types of BzRAs (i.e., benzodiazepines and Z-drugs). Dichotomous data were analysed with the Peto odds ratio and a fixed effects model, and continuous data with the inverse variance method and a random effects model. Results were reported in terms of mean difference (for continuous data) or risk ratio (for dichotomous data), 95% confidence interval, *p* value, number of trials and number of participants.

4.3. Results

4.3.1 Studies characteristics

We found 19 studies focused on ZRAS for insomnia (Figure 4.1) [346-364]. These studies included in total 1,780 participants. Sixteen studies used a randomized controlled design and three studies used a non-randomized controlled design (Table 4.1). The population studied was adults or older adults with insomnia, with two studies focusing on people with schizophrenia and hypertension, respectively, and one study focusing on people with insomnia with a specific Chinese medicine pattern. ZRAS was compared with both BzRAs and placebo in one study, with BzRAs in thirteen studies, used in combination with BzRAs compared with BzRAs alone in three studies, and used in combination with Treatment As Usual (TAU) compared with TAU alone in two studies. In all the studies ZRAS was used orally once a day before bedtime, with a dose of five capsules (2.45g) for ZRAS capsule, 5g for ZRAS granule and 20ml for ZRAS solution.

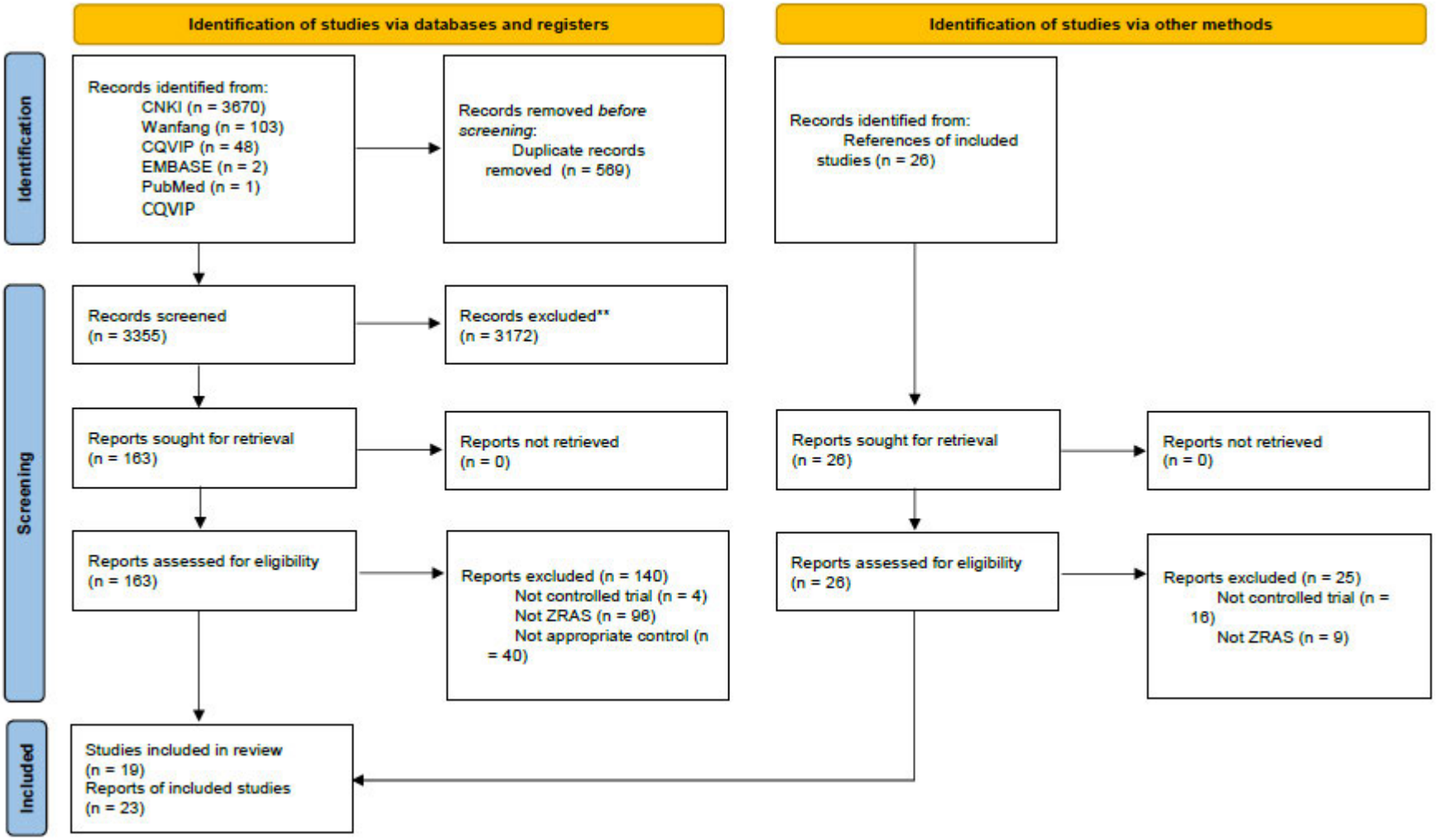


Figure 4.1. Flow diagram. Adapted from the PRISMA statement [365]. CNKI = Chinese National Knowledge Infrastructure, CQVIP = Chong Qing VIP

First author (Year)	Design	Participant type, mean age, nb females/total	Interventions; duration	Outcomes (measurement), unit	Results at post-treatment (M±SD or nb events/total)
Qin (2007)	RCT	Adults, 36.1, 77/125	(a) ZRAS capsule, 5 capsules qn; (b) Clonazepam, 1 mg qn; 15d	(1) Sleep quality (SRSS) (2) Adverse events	(1) 19.2±4.2 (a), 18.8±4.3 (b) (2) 6/63 (a)*, 43/62 (b)
Ren (2007)	RCT	Older adults, 68.0, 52/100	(a) ZRAS capsule, 5 capsules qn; (b) Estazolam, 1 mg qn; 16d	(1) Sleep quality (SDRS) (2) Anxiety (HARS) (3) Clinical severity (CGI-S) (4) Adverse events	(1) 11.3±5.4 (a), 14.5±8.2 (b) (2) 7.8±5.6 (a), 6.8±5.3 (b) (3) 2.4±1.1 (a), 2.3±1.2 (b) (4) 0/50 (a), 20/50 (b)
Liu (2009)	RCT	Adults, 37.3, 52/90	(a) ZRAS capsule, 5 capsules qn; (b) Estazolam, 1 mg qn; (c) Placebo, 5 capsules qn; 21d	(1) Sleep quality (PSQI)	(1) 5.9±1.3 (a)[#], 4.5±1.2 (b), 6.8±1.3 (c)
Tian (2010)	RCT	Older adults, 67.8, 74/120	(a) ZRAS capsule, 5 capsules qn; (b) Alprazolam, 0.8 mg qn; 28d	(1) Sleep quality (PSQI) (2) Adverse events	(1) 5.9±1.3 (a), 5.7±1.6 (b) (2) 8/60 (a)*, 32/60 (b)
Xu (2011)	RCT	Adults, 36.1, 82/150	(a) ZRAS capsule, 5 capsules qn; (b) Zopiclone, 7 mg qn; 14d	(1) Sleep quality (SRSS) (2) Adverse events	(1) 19.2±4.2 (a), 18.8±4.3 (b) (2) 8/75 (a)*, 38/75 (b)
Li (2012)	RCT	Adults, 37.6, 32/60	(a) ZRAS capsule, 5 capsules qn; (b) Estazolam 1 mg qn; 14d	(1) Sleep quality (PSQI) (2) Adverse events	(1) 6.3±1.1 (a), 6.5±1.6 (b) (2) 3/30 (a)*, 26/30 (b)
Huang (2013)	RCT	Adults, 37.4, 47/90	(a) ZRAS capsule, 5 capsules qn; (b) Estazolam, 1 mg qn; 14d	(1) Sleep quality (SDRS) (2) Adverse events	(1) 10.7±8.1 (a), 10.3±6.9 (b) (2) 0/ 45 (a)*, 13/45 (b)
Chen (2014)	RCT	Adults with blood deficiency, 45.4, 79/120	(a) ZRAS granule, 5g qn; (b) Zopiclone, 7.5 mg qn; 28d	(1) Sleep quality (PSQI) (2) Adverse events	(1) 6.5±2.9 (a), 6.9±2.9 (b) (2) 2/60 (a)*, 16/60 (b)
Hu (2015)	RCT	Adults, 47.9, 41/93	(a) ZRAS granule, 5g qn, and Estazolam, 1-2 mg qn; (b) Estazolam, 1-2 mg qn; 21d	(1) Sleep quality (PSQI) (2) Adverse events	(1) 5.1±1.8 (a)*, 7.9±2.3 (b) (2) 7/50 (a)*, 20/43 (b)
Qin (2015)	RCT	Adults, 45.2, 36/62	(a) ZRAS capsule, 5 capsules qn; (b) Alprazolam, 0.8 mg qn; 7d	(1) SOL (PSG), min (2) NAWAK (PSG), times (3) TST (PSG), min (4) SE (PSG), %	(1) 28.2±12.7 (a), 27.4±12.9 (b) (2) 1.9±0.5 (a), 1.9±0.5 (b) (3) 368.1±40.0 (a)*, 347.9±38.3 (b) (4) 88.0±6.4 (a), 86.0±6.5 (b)
Wu (2015)	RCT	Schizophrenia patients, 34.7, 27/66	(a) ZRAS capsule, 2.25 g qn, and Quetiapine, 400 mg qd; (b) Quetiapine, 400 mg qd; 14d	(1) SOL (PR), min (2) TST (PR), h	(1) 20.4±4.3 (a)*, 48.5±5.2 (b) (2) 12.3±2.5 (a)*, 5.4±2.2 (b)

Zhang (2015)	RCT	Older adults with hypertension, 63.4, 34/60	(a) ZRAS capsule, 5 capsules qn, and Amlodipine, 5 mg qd; (b) Amlodipine, 5 mg qd; 56d	(1) SOL (PR), min (2) TST (PR), h (3) SE (PR), % (4) Sleep quality (PSQI) (5) Adverse events	(1) 37.2±14.7 (a)*, 68.2±17.1 (b) (2) 6.7±0.9 (a)*, 5.2±1.0 (b) (3) 81.3±8.8 (a)*, 66.1±11.2 (b) (4) 4.47±2.0 (a)*, 11.4±3.4 (b) (5) 3/30 (a), 0/30 (b)
Liang (2016)	RCT	Older adults, 68.1, 42/80	(a) ZRAS capsule, 5 capsules qn; (b) Estazolam, 1 mg qn; 28d	(1) Sleep quality (PSQI) (2) Adverse events	(1) 5.9±1.3 (a), 5.8±1.6 (b) (2) 6/40 (a)*, 21/40 (b)
Zhang (2016)	RCT	Adults, 43.5, 37/68	(a) ZRAS capsule, 5 capsules qn; (b) Estazolam, 1-2 mg qn; 21d	(1) Adverse events	(1) 2/34 (a)*, 8/34 (b)
Liu (2017)	CCT	Older adults, 64.4, 64/120	(a) ZRAS capsule, 5 capsules qn; (b) Esomezolpine, 1 mg qn; 14d	(1) Sleep quality (PSQI)	(1) 6.2±1.2 (a), 6.6±1.5 (b)
Wang (2017a)	RCT	Adults, 56.9, 43/82	(a) ZRAS capsule, 2.25 g qn; (b) Estazolam, 1 mg qn; 21d	(1) Sleep quality (PSQI) (2) Adverse events	(1) 6.8±1.8 (a), 6.4±1.2 (b) (2) 5/41 (a)*, 18/41 (b)
Wang (2017b)	RCT	Adults, 42.6, 51/128	(a) ZRAS capsule, 5 capsules qn; (b) Eszopiclone, 3 mg qn; 28d	(1) Sleep quality (PSQI) (2) Adverse events	(1) 5.3±0.4 (a)*, 7.8±0.7 (b) (2) 2/64 (a)*, 9/64 (b)
Yan (2018)	CCT	Adults, 47.2, 37/70	(a) ZRAS capsule, 5 capsules qn and Estazolam, 1 mg qn; (b) Estazolam, 1 mg qn; 28d	(1) Sleep quality (PSQI) (2) TST (PSG), h (3) SOL (PSG), min (4) NAWAK (PSG), times (5) Adverse events	(1) 4.2±1.1 (a)*, 8.0±3.2 (b) (2) 6.3±0.3 (a)*, 5.8±0.3 (b) (3) 24.8±3.2 (a)*, 26.5±4.3 (b) (4) 1.8±0.9 (a)*, 1.9±0.8 (b) (5) 2/35 (a)*, 9/35 (b)
Zhong (2018)	CCT	Adults, 42.4, 54/96	(a) ZRAS capsule, 5 capsules qn and Oxazepam, 15-30 mg tid; (b) Oxazepam, 15-30 mg tid; 28d	(1) Sleep quality (PSQI)	(1) 5.6±0.8 (a), 8.8±0.9 (b)

Table 4.1. Characteristics of the selected studies. * Favoured this group with $p<0.05$. RCT = Randomized Controlled Trial; CCT = Controlled Clinical Trial; ZRAS = Zao Ren An Shen; SRSS = Self-Rating Scale of Sleep; SDRS = Sleep Dysfunction Rating Scale; HARS = Hamilton Anxiety Rating Scale; CGI-S = Clinical Global Impressions – Severity scale; PSQI = Pittsburgh Sleep Quality Index; SOL = Sleep Onset Latency; PSG = PolySomnoGraphy; NAWAK = Number of AWAKenings; TST = Total Sleep Time; SE = Sleep Efficiency; PR = Participant-Rated.

4.3.2 Outcomes of the selected studies

The outcomes assessed in the selected studies were sleep quality measured with the PSQI, the Sleep Dysfunction Rating Scale (SDRS) and the Self-Rating Scale of Sleep (SRSS), sleep parameters measured with Polysomnography (PSG) or participant-rated (PR), clinical severity measured with the Clinical Global Impressions – Severity scale (CGI-S), anxiety levels measured with the Hamilton Anxiety Rating Scale (HARS), and the number of adverse events. The PSQI [149], the SDRS [366] and the SRSS [367] are self-rated scales measuring sleep quality with a range of respectively 0-21 points, 10-50 points and 0-40 points, and for which a lower score is better. Sleep parameters included SOL (i.e., the time spent trying to fall asleep), TST (i.e., the total duration of sleep during the night), NAWAK (i.e., the number of awakenings, regardless of the duration) and SE (i.e., the ratio between TST and the total time spent in the bed). The CGI-S is a clinician-rated, Likert-style scale ranging from 1 to 7, a higher score meaning a higher severity [368]. The HARS is a clinician-rated scale ranging from 0 to 56 and for which a higher score a higher anxiety level [369]. The studies included in this review did not report how the adverse events were assessed.

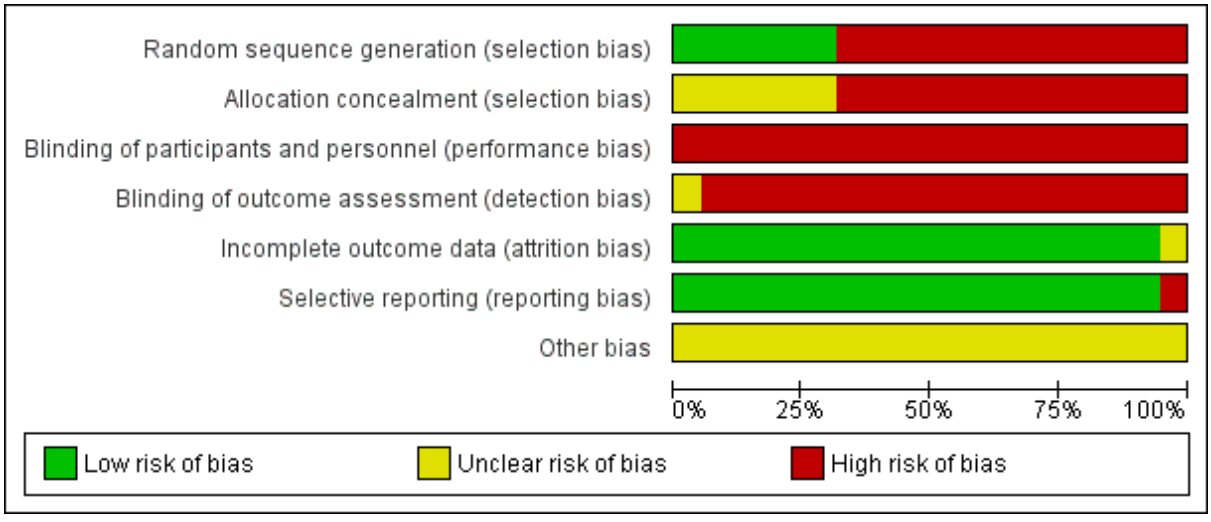


Figure 4.2. Overall risk of bias of the 19 included studies.

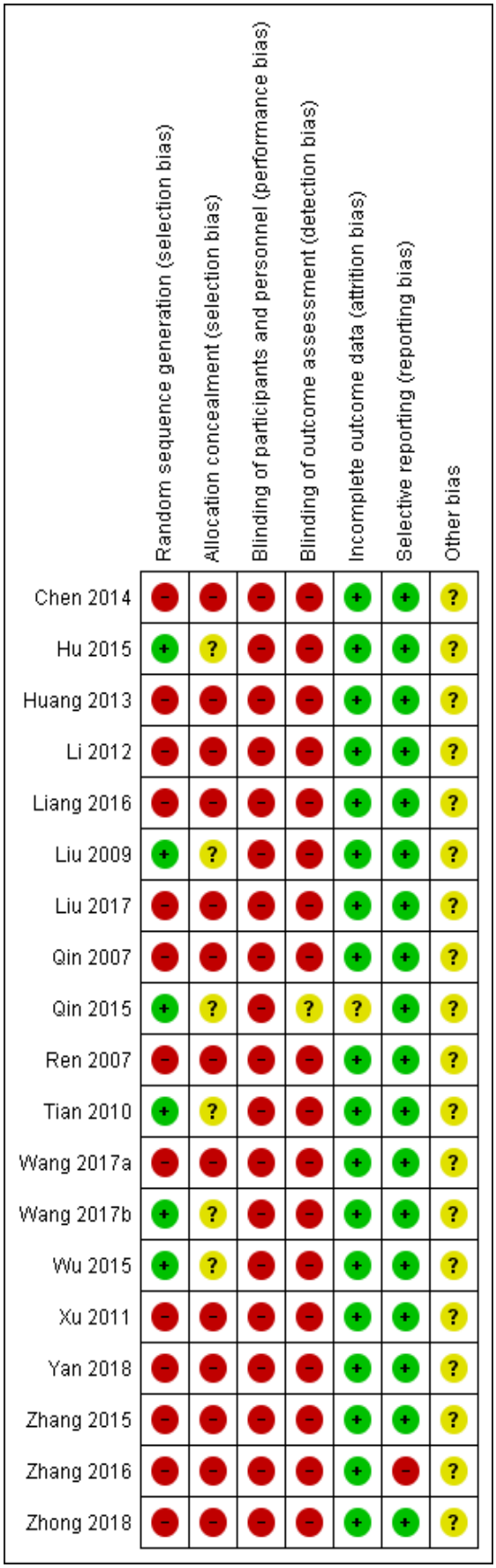


Figure 4.3. Risk of bias ratings for each of the 19 included studies.

4.3.3 Risk of bias assessment

The selected studies presented an overall high risk of bias (Figure 5.2). More particularly, no study presented an appropriate method of allocation concealment, and no study used a double-blind design. This is of particular concern as the outcomes used in the studies were subjective and assessed by either the participant (e.g., sleep quality) or the clinician (e.g., clinical severity), neither of them being blinded to allocation. The overall risk of bias for incomplete outcome is low. However, it may be due to a lack of report of attrition, as most of the studies (n=18, 90%) did not report any attrition (Figure 4.3), which is unlikely in clinical trials on insomnia [370].

4.3.4 Effectiveness and safety outcomes

4.3.4.1 ZRAS compared to placebo

One study compared ZRAS to placebo. In that study, ZRAS was found to improve PSQI-measured sleep quality better than placebo (-0.90 [-1.56, -0.24; 95% CI], p=0.007, 1, 60). The number of adverse events was not assessed in that particular study.

4.3.4.2 ZRAS compared to BzRAs

Fourteen studies compared ZRAS to a BzRAs drug. One of the studies [362], which had an unusually low standard deviation [371-373], was removed from the meta-analysis for the PSQI-measured sleep quality. Compared to BzRAs, ZRAS had a similar effect on sleep quality measured with the PSQI (0.17 [-0.29, 0.64; 95% CI], p=0.46, 7, 642) (Figure 5.4). Including the outlying study into the analysis, the meta-analysis still showed no significant difference between ZRAS and BzRAs in PSQI score (-0.18 [-1.38, 1.01; 95% CI], p=0.76, 8, 770). A similar effect between ZRAS and BzRAs was also found for sleep quality measured with the SRSS (0.40 [-0.60, 1.40; 95% CI], p=0.44, 2, 275) and the SDRS (-1.48 [-5.01, 2.04; 95% CI], p=0.41, 2, 190), for SOL (0.80 [-5.57, 7.17; 95% CI], p=0.81, 1, 62), NAWAK (0.00 [-0.25, 0.25; 95% CI], p=1.00, 1, 62) and SE measured with PSG (2.00 [-1.21, 5.21; 95% CI], p=0.22, 1, 62), for clinical severity measured with CGI-S (0.10 [-0.35, 0.55; 95% CI], p=0.66, 1, 100) and for anxiety measured with the HARS (1.00 [-1.14, 3.14; 95% CI], p=0.36, 1, 100). Compared to BzRAs, ZRAS had a lower effect on PSG-measured TST (20.20 [0.71, 39.69; 95%

CI], *p*=0.04, 1, 62). Sub-analyses showed that both ZRAS capsule (-0.01 [-0.30, 0.29; 95% CI], *p*=0.97, 5, 462) and ZRAS granule (0.55 [-1.21, 2.31; 95% CI], *p*=0.54, 2, 180) had similar PSQI results with BzRAs. The similarity was also present when ZRAS was compared both with benzodiazepines (0.24 [-0.26, 0.74; 95% CI], *p*=0.35, 6, 522) and with Z-drugs (-0.40 [-1.44, 0.64; 95% CI], *p*=0.45, 1, 120).

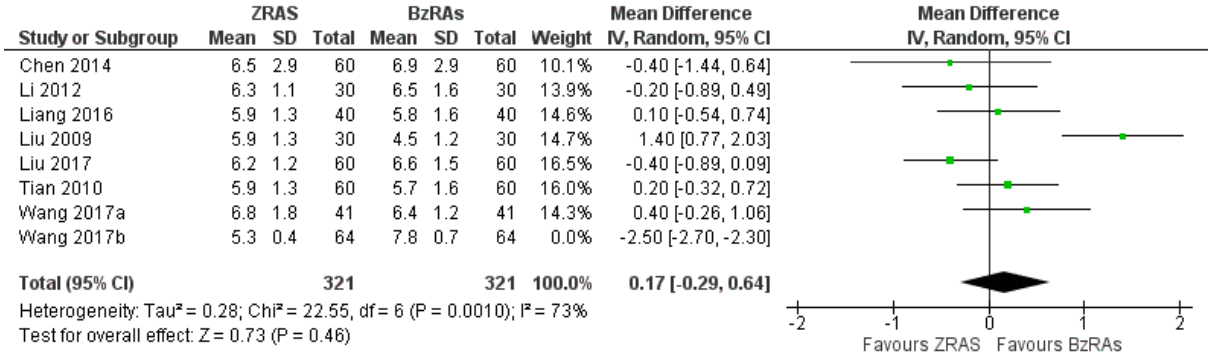


Figure 4.4. Comparison of the sleep quality measured with PSQI between the ZRAS group and the BzRAs group (n=7).

Compared to BzRAs, ZRAS provoked less adverse events (0.13 [0.10, 0.17; 95% CI], *p*<0.001, 10, 1003) (Figure 4.5). This difference was observed for both ZRAS capsule (0.17 [0.12, 0.23; 95% CI], *p*<0.001, 9, 883) and ZRAS granule (0.13 [0.03, 0.52; 95% CI], *p*=0.004, 1, 120), and for ZRAS compared with both benzodiazepines (0.15 [0.10, 0.23; 95% CI], *p*<0.001, 7, 605) and Z-drugs (0.19 [0.11, 0.34; 95% CI], *p*<0.001, 3, 398). The adverse events observed in the ZRAS group are fatigue (n=21), somnolence (n=3), acid reflux (n=2), lip numbness (n=2), and dizziness (n=1).

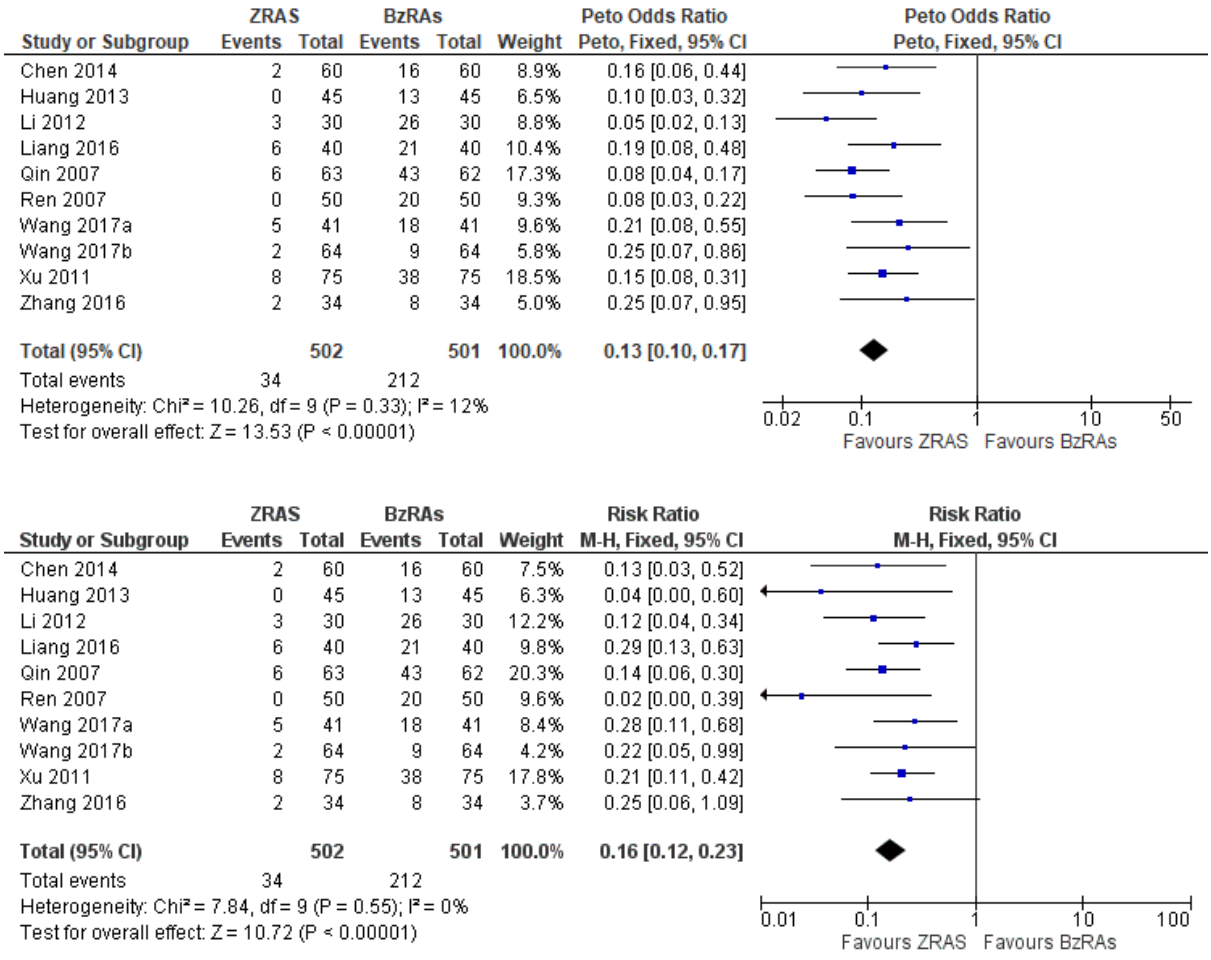


Figure 4.5. Comparison of the number of adverse events between the ZRAS group and the BzRAs group (n=10).

4.3.4.3 The combination of ZRAS and BzRAs compared to BzRAs alone

Three studies compared a combination of ZRAS and BzRAs to BzRAs alone. Compared to BzRAs alone, the combination showed a better efficacy in terms of PSQI-measured sleep quality (-3.14 [-3.46, -2.83; 95% CI], p<0.001, 3, 259), TST measured by PSG (0.50 [0.36, 0.64; 95% CI], p<0.001, 1, 70), a similar efficacy in terms of SOL measured by PSG (-1.70 [-3.48, 0.08; 95% CI], p=0.06, 1, 70) and NAWAK measured by PSG (-0.10 [-0.50, 0.30; 95% CI], p=0.62, 1, 70), and less adverse events (0.28 [0.14, 0.55; 95% CI], p<0.001, 2, 163).

4.3.4.4 The combination of ZRAS and TAU compared to TAU alone

Two studies compared a combination of ZRAS and TAU to TAU alone. Compared to TAU alone, the combination showed a better efficacy in terms of PSQI-measured sleep quality (-6.90 [-8.31, -5.49],

p<0.001, 1, 60), participant-reported TST (4.17 [-1.12, 9.47], 0.12, 2, 126), participant-reported SOL (-28.32 [-30.53, -26.10], p<0.001, 2, 126), participant-reported SE (15.20 [10.10, 20.30], p<0.001, 1, 60), and a similar number of adverse events (7.00 [0.38, 129.93], p=0.19, 1, 60).

4.4. Discussion

4.4.1 Effectiveness of ZRAS for insomnia

ZRAS was found to improve the PSQI score about 1 point more than placebo. The improvements in terms of sleep quality, objective sleep parameters and anxiety levels were not significantly different between ZRAS and BzRAs. ZRAS was also found to improve sleep significantly when used in combination with BzRAs (3-point reduction in PSQI score and 30 min increase of objective TST) or with conventional treatment for comorbidities (7-point reduction in PSQI score and 4h increase of subjective TST). The findings in terms of effectiveness of ZRAS compared to BzRAs were similar when ZRAS capsule and ZRAS granule were analysed separately and when benzodiazepines and Z-drugs were analysed separately.

4.4.2 Safety of ZRAS for insomnia

The absolute safety profile is unknown because no clinical trial assessed the safety of ZRAS compared to placebo. ZRAS was found to provoke adverse events when added to amlodipine, but the difference was not significant. ZRAS showed a significantly better safety profile than BzRAs and was even able to reduce the number of adverse events when used in combination with BzRAS, although the reason for this reduction is unknown. The adverse reactions that can be provoked by BzRAs include morning sedation, anterograde amnesia, anxiety, falls, undesired sleep behavior and somatic symptoms [140, 374]. The findings in terms of safety of ZRAS compared to BzRAs were similar when ZRAS capsule and ZRAS granule were analysed separately and when benzodiazepines and Z-drugs were analysed separately. As the method of assessing the adverse events was not reported in the included studies, the above findings should be taken cautiously.

4.4.3 Limitations of the findings

These findings have to be considered carefully as the overall risk of bias of the studies included in this systematic review was high. Not a single study used appropriate methods of blinding, which is particularly of concern as the outcomes were mainly subjective and participant- or clinician-assessed. Even objective outcomes such as PSG-measured sleep parameters cannot be fully trusted as it is unclear whether the technicians who interpreted the measures were blinded or not to the allocation. The effect of ZRAS on subjective sleep parameters measured with a sleep diary was not assessed. This is a significant weakness as impairment of subjective sleep quality is an important feature of insomnia [80, 143, 375, 376], and the sleep diary is one of the main assessment tools for insomnia [134, 148, 311]. Additionally, measures of psychological well-being, fatigue, and quality of life were not reported, even though this is recommended in insomnia trials [134, 311].

4.4.4 Relationship with related studies

Previous systematic reviews assessing the effectiveness and safety of CHM for insomnia reported similar results, i.e. CHM better than placebo and similar to BzRAs but with less adverse events [278, 316, 377]. The results are also congruent with another systematic review assessing the evidence for CHM formulas that contain Suan zao ren, the main ingredient of ZRAS [378]. A narrative review published in Chinese [379] also found ZRAS effective for insomnia, however, that review included other formulas than the one composed of Suan zao ren, Dan shen and Wu wei zi. Attention has to be paid to this point as many studies excluded in the full-text screening of the present review had very similar names to ZRAS, such as Fu Fang Zao Ren An Shen capsule [380, 381], Zao Ren An Shen decoction [382, 383] and Zao Ren An Shen Pian [384], but different ingredients. ZRAS has also been found effective for other psychiatric diseases [385-387], and has a particular potential with comorbid vascular and mental disorders [388-390], as its components have curative effects on the vascular and the central nervous systems [329, 333, 391-394]. The methodological flaws of the clinical trials assessing CHM for insomnia have already been pointed out [279, 316], and it seems to be a global issue for the Chinese medicine trials [395-398].

4.4.5 Therapeutic approach

CHM is holistic in nature and tends not to focus on the disease but the person as a whole [399]. Treatments are individualised according to the pattern (i.e., global physiological state reflected by the signs and symptoms) of the patient, which is determined by the clinician [400-402]. The use of ZRAS, which is a standardized treatment using sedative herbs taken only before bedtime, reflects a symptomatic approach that is different from traditional CHM approach. However, one of the studies included in this review focused on participants with a specific pattern, i.e. 'blood deficiency' [353]. The influence of the pattern on ZRAS effectiveness and safety is unclear. As several studies showed that ZRAS as a standardized treatment of insomnia is less effective than individualised CHM treatments [403, 404], trained Chinese medicine clinician might prefer an individualised approach. ZRAS might still be a useful option for clinician who are unable to conduct pattern diagnosis.

4.4.6 Implications for future research

The findings of this review, although indicative of the potential equivalent effectiveness of ZRAS to BzRAs, because of the high risk of bias in the studies, cannot be considered strong enough to recommend the use of ZRAS in the treatment of insomnia at this time. Future studies need to comply with clinical research guidelines, such as appropriate methods of randomization and blinding [405-407], and various outcomes measures [124, 311]. There is also a need to assess the safety of ZRAS compared to placebo and to CBT-I, which is now recommended as a first-line treatment for insomnia [153]. Future clinical trials should assess the influence of the pattern on treatment effectiveness and safety.

4.4.7 Strengths and limitations of the review

To the knowledge of the author, this is the first systematic review assessing the effectiveness and safety of ZRAS. With an extensive search in the English and Chinese literature, this review might reflect the current state of the knowledge on ZRAS for insomnia appropriately. However, some important databases such as Allied and Complementary Medicine database and Chinese Biomedical Literature database were not searched because of an absence of access and articles written in other languages than English and Chinese were not included, which limit the scope of the search.

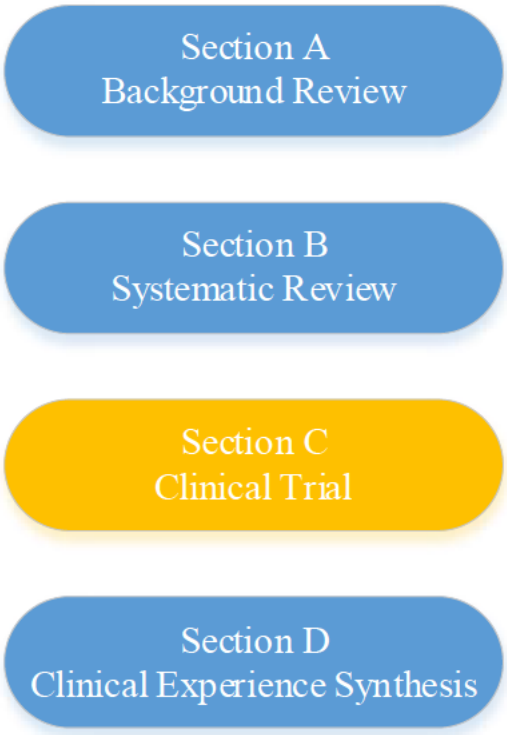
4.4.8 Conclusion

The studies included in this systematic review favor ZRAS against BzRAs and placebo. However, the poor methodology of the studies prevents a clear conclusion from these findings. Clinical trials with higher quality designs are required in order to support ZRAS as a treatment for insomnia.

Section C

ZRAS capsule for insomnia:

A randomised, double-blind, placebo-controlled trial



This section presents a clinical trial in which ZRAS capsule was tested on human volunteers suffering from insomnia against a placebo.

The objective of the trial was to test the efficacy and safety of ZRAS capsule as a treatment of insomnia disorder.

The section is divided in three chapters, i.e. Chapter 5 which presents the context, the objective and the methods of the study, Chapter 6 which presents the results of the clinical trial and Chapter 7 which discusses the results of the study and places them in the context of the broader literature.

Chapter 5. Background and methods

This chapter has been published in the journal *Medicine* as a clinical trial protocol [408].

5.1. Background

CHM is one of the most common treatments for insomnia in Chinese populations [12, 13] and its use is increasing in Western countries [275]. Recent systematic reviews of RCTs suggest that CHM is relatively safe and can effectively improve sleep quality and sleep parameters [278, 316]. However, the need of evidence for individual formulas was highlighted.

ZRAS is a CHM formula composed of three herbs, i.e. Suan zao ren (Ziziphi Spinosae Semen), Wu wei zi (Schisandrae Chinensis Fructus) and Dan shen (Salviae Miltiorrhizae Radix et Rhizoma), which have all sedative effects and low toxicity [327-331, 409-411]. This formula, manufactured in the forms of capsule, granule and solution, is indicated for insomnia [289]. Clinical trials on ZRAS have showed a better effect than placebo and a similar or better effect than BzRAs [307, 346-351, 353, 355, 358-360, 362, 412]. Adverse events were also less reported by participant taking ZRAS compared to BzRAs [306, 307, 346, 349-353, 358, 359, 362]. However, none of these studies used appropriate methods of randomization and blinding. There is a need for high-quality RCTs.

5.1.5. Objective

The objective of this study is to assess the efficacy and the safety of Zao Ren An Shen capsule compared to placebo for chronic insomnia. As ZRAS is proposed as an alternative treatment and not a first-line treatment, we will use placebo as a comparator with a superiority framework. The primary outcomes are insomnia severity measured with the ISI for efficacy and the number of adverse events (AEs) for safety. The primary endpoint is post-treatment (week 4). We hypothesize that ZRAS capsule will show a better efficacy than and a similar safety to placebo. Secondary outcomes include objective and subjective sleep parameters, fatigue levels, psychological status, quality of life, adherence, and acceptability. The secondary endpoints are mid-treatment (week 2) and follow-up (week 8).

5.2. Methods

5.2.1. Study design

This study is a randomized, double-blind, placebo-controlled design with a 1:1 allocation ratio and parallel groups. After one week of single-blinded placebo run-in, the participants were randomized to the experimental group or the control group and took Zao Ren An Shen (ZRAS) capsule or a placebo, for four weeks. Outcomes were assessed at pre-treatment, mid-treatment, post-treatment and at a 1-month follow-up. The study was registered in the Australia New-Zealand Clinical Trial Registry (Registration number ACTRN12619000140156).

5.2.2. Settings

The three visits of the trial were conducted at four campuses of Western Sydney University, i.e., Parramatta City campus, Bankstown Campus, Westmead campus and Campbelltown campus around Sydney, Australia.

5.2.3. Participants

5.2.3.1. Recruitment strategy

Participants were recruited through advertisement and referrals from the 15th of February 2019 to the 29th November 2019. Ads were put in social media (e.g., Facebook, Instagram and Wechat) and poster and flyers in public places (e.g., Universities, libraries), pharmacies and healthcare practices. Pharmacists around the trial sites were contacted for potential referrals.

5.2.3.2. Screening procedures

The potential participants were contacted by phone for a pre-screening assessment before the first visit. During the first visit, a medical interview including the Mini International Neuropsychiatric Interview and the sleep disorders section of the Structured Clinical Interview for the DSM-5 was conducted by the principal investigator (YB), who is a Chinese medicine practitioner trained in mental disorder diagnosis. Between the first and the second visit, the participant underwent blood tests including full blood count, liver function test, and electrolytes-urea-creatinine at Laverty Pathology, if needed, and an oximetry assessment at home using the WristOx (Nonin) when sleep apnea was

suspected. A General practitioner involved in the trial (NA) crosschecked the medical eligibility of the participant. Enrolment was confirmed during the third visit, after a re-assessment of insomnia severity.

5.2.3.3. Eligibility criteria

The eligibility criteria, based on the diagnosis criteria for insomnia disorder (307.42) from the DSM-5 [73], were as following:

Inclusion criteria

1. 18 years old or older.
2. Complaint of difficulty initiating, frequent awakenings or early morning awakenings occurring at least three times per week for at least three months despite adequate opportunity to sleep, and resulting in distress or impaired daytime functioning.
3. ISI score ≥ 10. This cut-off score has a sensitivity of 86.1% and a specificity of 87.7% [413].
4. Willing to abstain from any other treatment for insomnia, including pharmaceutical treatment, CAM, and psychotherapy, during the baseline and intervention periods.
5. Willing to use birth control methods and to not donate sperm during the baseline and intervention periods, or sterile.
6. Ability to understand and speak English.

Exclusion criteria

1. Imminent need of psychiatric (e.g., suicide risk) or medical care (e.g., stroke).
2. Abnormal blood tests, including full blood count, liver function test, and electrolytes-urea-creatinine, within the last six months, if not approved by a general practitioner.
3. No evidence that substance use (e.g., caffeine or a medication), coexisting medical conditions or mental disorders, including sleep-wake disorder, do not adequately explain the predominant complaint of insomnia.
4. Use of any other treatment for insomnia less than 14 days prior to randomization.

5. Any psychotic disorder or bipolar disorder if not appropriately treated or stable for less than two years.
6. Alcohol or drug addiction.
7. Other mental disorders such as major depressive disorder or generalized anxiety disorder, if the disorder is untreated or treated for less than one month.
8. Cognitive impairment preventing the participant to understand the trial instructions, complete questionnaires or provide informed consent.
9. Allergy history to any of the ingredient of the ZRAS capsule or the placebo (Table 3).
10. Taking a Warfarin-type anticoagulant [414, 415], quetiapine, clozapine, or olanzapine [416].
11. Women being pregnant or breast-feeding.
12. Considered not suitable for the trial by the investigator.

5.2.4. Randomization and blinding

A randomization sequence without stratification was generated using computer-generated random numbers by a NICM Heath Research institute researcher not directly affiliated with this study to ensure blinding. The sequence generated was used to identify the investigational product. The participants were randomized during the second visit of the trial. Both the investigator and the participants were blinded at recruitment and during the intervention. The codes were broken in case of emergency, such as a serious adverse event that requires knowledge of the treatment being taken in order to manage a participant's condition.

5.2.5. Interventions

The investigational product is ZRAS capsule, a CHM product composed of Suan zao ren (*Ziziphus jujuba* Mill. var. *spinosa*, 417mg/capsule), Wu wei zi (*Schisandra chinensis* (Turcz.) Baill., 70mg/capsule), and Dan shen (*Salvia miltiorrhiza* Bge., 167mg/capsule). The above dosage was based on the Chinese Pharmacopeia [289]. The placebo, composed of microcrystalline cellulose, calcium hydrogen phosphate dehydrate, carob pod powder, silicon dioxide and magnesium stearate, matches the active in terms of appearance and taste. The participants were asked to take 3 capsules of placebo (2.16g in total) orally once a day one hour before bedtime for one week. After randomization, the

participants were asked to take 3 capsules of ZRAS (2.28g in total) or placebo (2.16g in total) orally once a day one hour before bedtime for four weeks. Both ZRAS capsule and the placebo were provided by Global Therapeutics, Pty, Ltd. The participants were asked to refrain from taking any other treatment for insomnia during the week preceding and the five weeks following the first visit, except for rescue medication.

5.2.6. Assessments

5.2.6.1. Primary outcomes

5.2.6.1.1. Insomnia severity

Insomnia severity was measured with the Insomnia Severity Index (ISI). The ISI [150] is a brief 7-item scale used to assess perceived insomnia severity and consequences in accordance with the diagnostic criteria for insomnia of the DSM, 4th edition, and the ICSD. Unlike the Pittsburgh Sleep Quality Index, another questionnaire commonly used for insomnia assessment, the ISI is specific to insomnia disorder. The ISI has good psychometric properties [150] and can be used to detect insomnia cases and evaluate treatment response [413]. The range of the scale is 0-28 points and the score is positively associated with insomnia severity. A total score of 0-7 represents ‘no clinically significant insomnia’, a score of 8-14 represents ‘subthreshold insomnia’, a score of 15-21 represents ‘clinical insomnia (moderate severity)’ and a score of 22-28 represents ‘clinical insomnia (severe)’.

5.2.6.1.2. Adverse events

The participants were encouraged to report any AE at any time during the intervention or follow-up period. The participants will be asked at every time point if they have experienced adverse reactions during the last intervention or follow-up period. A description of the AE along with the seriousness, severity, relationship with the investigational product and expectedness of the AE in the AE form. The number of adverse events was used as the primary outcome for safety. Serious adverse events were reported to the Western Sydney University Human Research Ethics Committee and the Therapeutics Goods Administration. All significant safety issues and suspected unexpected serious adverse reactions were reported within 72 hours to the trial site (Western Sydney University).

5.2.6.2. Secondary outcomes

5.2.6.2.1. Questionnaires-measured outcomes

The Depression Anxiety Stress Scale 21-item [417] is a self-report questionnaire composed of 21 items assessing the levels of depression, anxiety, and stress of the subject. The Assessment of Quality of Life [418] questionnaire is a self-report instrument used to assess health-related quality of life. This study will use the 4-dimension version of the questionnaire, which measures independence, relationships, mental status, and senses. The Fatigue Severity Scale [419] is a 7-point Likert scale that measures different aspects of fatigue. All the questionnaires used in this study have acceptable psychometric properties [418, 420, 421].

5.2.6.2.2. Sleep parameters

Sleep parameters, including TST, sleep onset latency, number of awakenings, wake after sleep onset duration, and SE, will be recorded with the Consensus Sleep Diary (CSD) and an actigraph. The CSD is a self-report table in which the participant reports his sleep-related behaviours, including time and duration [148]. The CSD has been validated in an insomnia disorder population. An actigraph is a device, usually wrist-worn, capable of measuring gross motor activity. Sleep parameters can be calculated by a software using the 24-hour gross motor activity measured by the actigraph. In this study, we will use the readiband (Fatigue Science, Canada), which has been validated against polysomnography [422]. The sleep parameters were assessed during the one-week placebo run-in, the one-week intervention period, and for the last week of the four-week follow-up. The sleep parameters were averaged on one week if at least four days of data are available.

5.2.6.2.3. Acceptability and tolerability

Acceptability was assessed by the adherence to the treatment assessed by the capsule count. Adherence rate was calculated as the number of used capsules divided by the number of capsules the participant was supposed to use. Tolerability was assessed with the completion rate, i.e. the number of participants who completed the intervention divided by the number of participants allocated to the group.

5.2.6.2.5. Chinese medicine pattern diagnosis

A Chinese Medicine pattern diagnosis was determined on the basis of a self-report questionnaire and an examination of the complexion, the pulse and the tongue by the principal investigator (YB). The items of the questionnaire and the examination are based on a widely recognised CM manual [423]. Each positive symptoms or sign counts for 1 point and the participant is diagnosed with the pattern that has the highest score, or the pattern determined by the principal investigator in case of equal score. The CM pattern diagnosis was used as an efficacy outcome and a predictor variable for efficacy outcomes.

5.2.7. Clinical significance

A decrease of 7 points in the ISI score was found to be an indicator of moderate improvement for insomnia disorder [413]. Therefore, a decrease of 7 points or more in the ISI score at post-treatment compared to pre-treatment was considered clinically significant.

5.2.8. Data collection and management

Electronic data were collected with Research Electronic Data Capture (REDCap) database. REDCap surveys utilize a secure connection to the server for data collection which does not record IP addresses of participants. The questionnaires were completed by the participant on REDCap via an iPad during the three face-to-face visits and by the investigator during the mid-treatment and follow-up phone interviews according to the participant's oral answers. A secured link to the database for the CSD were sent every day via email to the participant. Paper forms for the sleep diary were offered as an option for those who prefer them. For the follow-up, these were supplied along with reply paid envelopes. Electronic data was stored in REDCap for the duration of the trial and paper data was stored in a locked cabinet at the trial site. Personal information was kept in REDCap and an excel file protected with a password before and during the trial, and in a masterlist stored in a shared drive with restricted access after the trial. The final trial dataset is accessible only to the investigators. In order to avoid missing data, the importance of complete data collection was emphasized at enrolment and participants who withdraw from the study were asked to complete the data collection, if willing. The research team monitored data on an ongoing basis.

5.2.9. Statistical analysis

Continuous data were analysed with linear mixed effects model, the data being corrected for baseline characteristics; mean, standard deviation, effect size, 95% CI and *p*-value were reported. Dichotomous data were analysed with Chi-square and counts, percentages, and *p*-value were reported. We analysed the final value of the outcomes with a significance level of α=0.05. Both an intention-to-treat analysis and a per-protocol analysis were conducted, the intention-to-treat analysis being of primary interest as it reflects better the effectiveness of the investigational product. We also analyzed the effect of the CM pattern score at baseline on the ISI score at the end of treatment with an ordinal regression analysis.. The statistical analysis was performed with SPSS 25 (IBM).

5.2.10. Sample size

In a validation study of the ISI, in which 145 insomnia patients from a sleep disorder clinic were evaluated, the mean ISI score was 19.7 points and the standard deviation 4.1 points [150]. A difference of 7 points between baseline and post-treatment is considered as clinically significant [413]. As placebo would give a decrease of approximately 4 points [424], the difference between the two groups at post-treatment has to be of 0.73 standard deviations. Using a 0.05 significance level, 90% power and allowing for 10% dropout rate, a sample size of 90 participants, 45 in each group, was required.

5.2.11. Ethics and dissemination

Informed consent was obtained by the principal investigator (YB) from all the participants during the first visit of the trial. The participants were withdrawn from the study in case a serious AE or the worsening of the condition justifies the withdrawal, and the participant were allowed to withdraw at any time for any reason. The trial was conducted in accordance with the World Medical Association Declaration of Helsinki and the National Statement on Ethical Conduct in Human Research. Ethic approval has been obtained from the Human Research Ethic Committee (HREC) of Western Sydney University (ethics approval number H12990). Any protocol revision was implemented after HREC approval only. The trial results and the allocation were disseminated to the participant after the end of the trial and the trial result were reported in a peer-reviewed journal.

5.2.12. Trial monitoring

This trial, which is part of YB doctoral thesis project, was monitored by XZ, AB and CT, the supervisors of YB. Monthly meetings were held to discuss trial progression and monitor data collection. NA monitored the trial in terms of AEs management. A meeting was called at any time by any member of the research team in the event of participant risk concerns in the trial. Based on this information, the research team would have stopped the trial if it became possible that risk might outweigh benefit for the participants as a group. Based on existing safety information of the investigational products, this scenario was regarded as highly unlikely.

Chapter 6: Results

6.1. General results

A total of 85 participants completed the placebo run-in and were randomly allocated to the placebo group (N=47) and the active group (N=38). Three participants withdrawn in the placebo group due to lack of efficacy. These three participants all accepted to complete the assessments of the study. One participant in the placebo group and two participants in the active group did not complete the follow-up assessment. Their data were completed using the "last observation carried forward" method. Due to technical issues, sleep parameters measured with actigraphy were missing for two participants. These outcomes were considered missing-at-random.

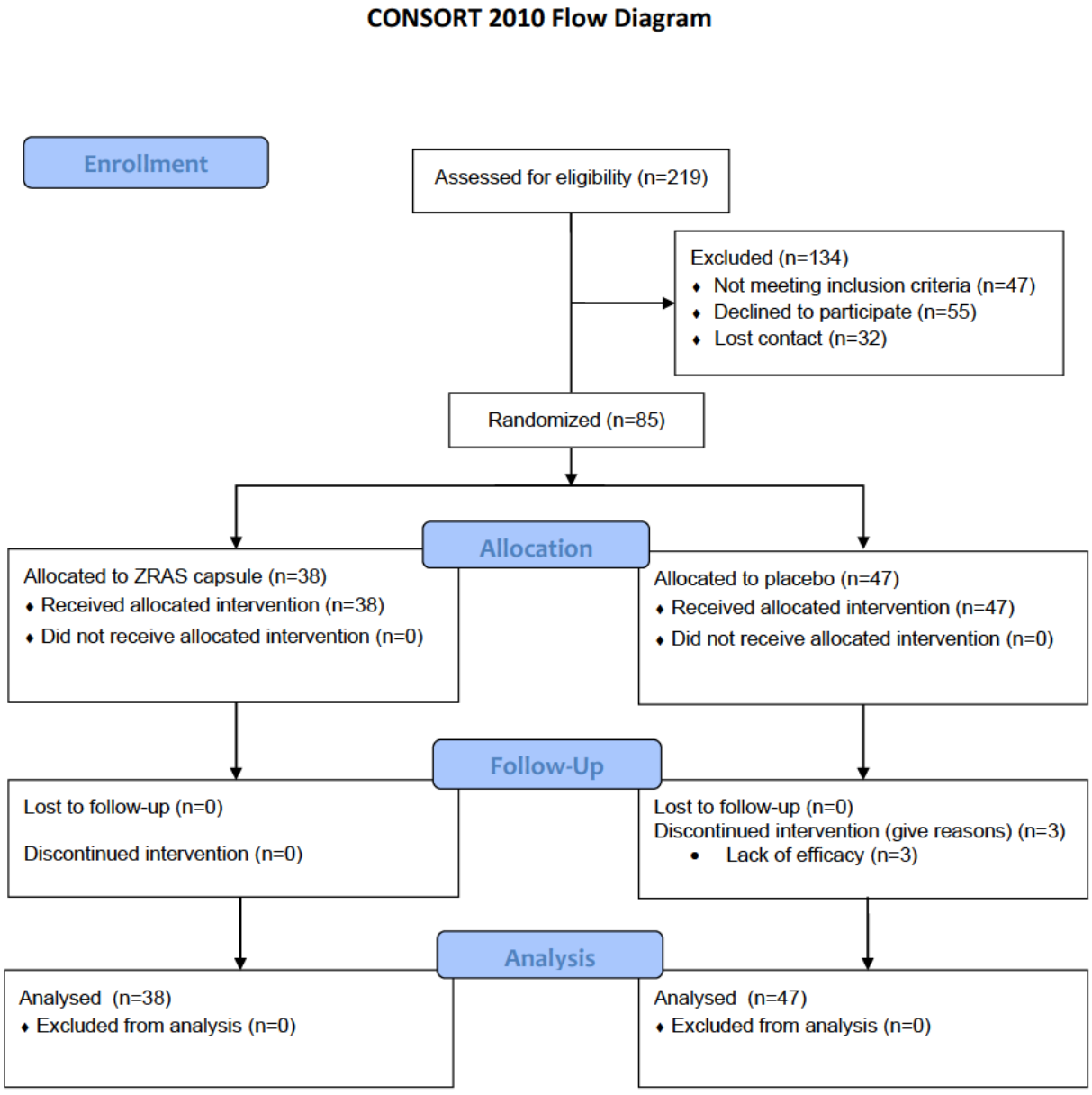


Figure 6.1. Participant flowchart.

The sociodemographic and baseline outcomes of the two group are presented in Table 6.1. The differences between the active and the placebo group were not statistically significant (P >0.05 for all).

	Placebo (N=47)	Active (N=38)	P value
Age (years old)	50 (16)	52 (13)	0.463
Females	30 (64%)	29 (76%)	0.214
Education (years)	14.5 (3.2)	15.5 (3.7)	0.189
Professional status			0.152
Student	9 (19%)	2 (5%)	
Working	26 (55%)	23 (61%)	
Not working	12 (26%)	13 (34%)	
Marital status			0.929
Single	14 (30%)	10 (26%)	
Married	23 (49%)	20 (52%)	
Previously married	10 (21%)	8 (21%)	
Household income			0.749
<50,000 AUD/year	14 (31%)	9 (24%)	
50,000-100,000 AUD/year	10 (29%)	9 (24%)	
>100,000 AUD/year	21 (60%)	20 (53%)	
BMI (kg/m^2)	26.9 (6.2)	27.5 (8.1)	0.706
Physical disorder	36 (76%)	27 (71%)	0.562
Mental disorder	4 (9%)	8 (21%)	0.099
Sleep disorder	13 (28%)	8 (21%)	0.483
Medication	30 (65%)	21 (55%)	0.352
English as language spoken at home	42 (89%)	36 (95%)	0.370
Smoker	2 (6.1%)	2 (7.7%)	1.000
Caffeine consumption (mg per day)	133.5 (97.0)	127.5 (14.7)	0.771
Alcohol consumption			0.186
Not drinking	20 (43%)	10 (26%)	
<7 standard drinks per week	17 (36%)	21 (55%)	
≥7 standard drinks per week	10 (21%)	7 (18%)	
ISI score	14.7 (3.6)	14.7 (5.1)	0.927
DASS score	14.2 (13.9)	14.9 (12.2)	0.824
FSS score	16.9 (3.2)	16.8 (2.2)	0.838
AQoL score	32.7 (11.8)	32.6 (12.1)	0.966

Table 6.1. Sociodemographic characteristics and baseline outcomes of the active and placebo group

6.2. Efficacy outcomes

The efficacy outcomes measured with questionnaires (i.e., insomnia severity, psychological status, fatigue level and quality of life) are presented in Table 7.2 and Table 7.3. In the placebo group, significant within-group differences were observed in insomnia severity, psychological status, fatigue levels and quality of life at mid-treatment and post-treatment compared to baseline ($P < 0.05$ for all), except for quality of life at post-treatment compared to baseline ($P > 0.05$). A significant difference ($P < 0.05$) was also observed for psychological status at follow-up compare to post-treatment, but not for the other outcomes ($P > 0.05$ for all). In the active group, significant within-group differences were observed in insomnia severity and psychological status at mid-treatment and post-treatment compared to baseline ($P < 0.05$ for all), but not for fatigue levels and quality of life ($P > 0.05$ for all). No difference was observed between follow-up and post-treatment outcomes for the active group ($P > 0.05$ for all). For all the outcomes measured with questionnaires, between-group differences were not statistically significant ($P > 0.05$ for all) at every time-point and the overall time by group effects were not statistically significant ($P > 0.05$ for all).

Subjective sleep parameters measured with the sleep diary are presented in Table 7.4 and Table 7.5. In the placebo group, significant within-group differences were observed only in subjective SE at mid-treatment and in subjective SOL, SE and TST at post-treatment compared to baseline ($P < 0.05$ for all). In the active group, significant within-group differences were observed only in subjective SE and subjective TST at mid-treatment and in subjective SOL, SE and TST at post-treatment compared to baseline ($P < 0.05$ for all). Subjective SOL was significantly shorter ($P = 0.023$) in the active group compared to the placebo group at post-treatment. However, this difference was significant only in the intention-to-treat analysis and the overall time by group effect for subjective SOL was also not significant. For all the other subjective sleep parameters, between-group differences were not statistically significant ($P > 0.05$ for all) at every time-point and the overall time by group effects were not statistically significant ($P > 0.05$ for all).

Objective sleep parameters measured with the actigraph are presented in Table 7.6 and Table 7.7. For the placebo group, significant within-group differences were observed only in objective WAS at mid-

treatment and in objective TST at post-treatment compared to baseline ($P < 0.05$ for all). In the active group, within-group differences were observed only in objective WAS at mid-treatment compared to baseline ($P < 0.05$). For all the objective sleep parameters, between-group differences were not statistically significant ($P > 0.05$ for all) at every time-point and the overall time by group effects were not statistically significant ($P > 0.05$ for all).

	Mean values (SE)		Between-group differences			Group by time interaction	
	Active (N = 38)	Placebo (N = 47)	Mean (95% CI)	T-test	P value	F-test	P value
ISI							
Baseline	14.7 (0.8)	14.7 (0.5)	0.1 (-1.8, 2.0)	T(83) = 0.092	0.927		
Week 2	12.3 (0.8)	12.7 (0.8)	0.4 (-1.9, 2.7)	T(80) = 0.341	0.734	F(2,246) = 0.074	0.929
Week 4	11.6 (0.9)	12.3 (0.9)	0.7 (-1.8, 3.1)	T(83) = 0.568	0.572		
Week 8	11.8 (0.8)	12.2 (0.7)	0.4 (-1.8, 2.6)	T(79) = 0.340	0.735		
DASS							
Baseline	14.9 (2.0)	14.2 (1.2)	-0.6 (-6.4, 5.1)	T(83) = -0.224	0.824		
Week 2	5.2 (0.6)	5.3 (1.0)	0.1 (-2.3, 2.5)	T(80) = 0.057	0.955	F(2,246) = 0.041	0.960
Week 4	5.8 (0.8)	5.9 (1.0)	0.0 (-2.5, 2.5)	T(83) = 0.024	0.981		
Week 8	4.8 (0.7)	5.1 (1.1)	0.3 (-2.4, 3.1)	T(76) = 0.248	0.805		
FSS							
Baseline	32.6 (2.0)	32.7 (1.7)	0.1 (-5.1, 5.3)	T(83) = 0.043	0.966		
Week 2	33.4 (1.8)	29.6 (1.8)	-3.8 (2.5, -8.9)	T(79) = -1.501	0.137	F(2,245) = 0.838	0.434
Week 4	33.1 (2.0)	28.9 (1.8)	-4.3 (-9.7, 1.2)	T(83) = -1.560	0.123		
Week 8	31.0 (2.3)	30.1 (2.1)	-0.3 (-7.1, 5.4)	T(74) = -0.276	0.783		
AQoL							
Baseline	16.8 (0.4)	16.9 (0.5)	0.1 (-1.1, 1.3)	T(83) = 0.205	0.838		
Week 2	16.3 (0.4)	16.4 (0.5)	0.1 (-1.2, 1.3)	T(79) = 0.099	0.921	F(2,245) = 0.052	0.949
Week 4	16.3 (0.4)	16.7 (0.5)	0.4 (-1.0, 1.7)	T(83) = 0.511	0.611		
Week 8	16.1 (0.5)	16.6 (0.5)	0.6 (-0.7, 2.0)	T(75) = 0.930	0.355		

Table 6.2. Intention-to-treat analysis of questionnaire outcomes. The results are presented as estimated marginal means (with associated standard errors), independent T-tests and F-tests.

	Mean values (SE)		Between-group differences			Group by time interaction	
	Active (N = 38)	Placebo (N = 44)	Mean (95% CI)	T-test	P value	F-test	P value
ISI							
Baseline	14.7 (0.8)	14.3 (0.5)	0.1 (-1.8, 2.0)	T(80) = -0.416	0.678		
Week 2	12.3 (0.8)	12.2 (0.8)	0.4 (-1.9, 2.7)	T(77) = -0.093	0.926	F(2,237) = 0.068	0.935
Week 4	11.6 (0.9)	11.8 (0.9)	0.7 (-1.8, 3.1)	T(80) = 0.153	0.879		
Week 8	11.8 (0.8)	11.8 (0.7)	0.4 (-1.8, 2.6)	T(76) = -0.014	0.989		
DASS							
Baseline	14.9 (2.0)	13.1 (2.1)	-1.7 (-7.5, 4.0)	T(80) = -0.601	0.549		
Week 2	5.2 (0.6)	5.1 (1.0)	-0.1 (-2.5, 2.3)	T(77) = -0.082	0.935	F(2,237) = 0.226	0.798
Week 4	5.8 (0.8)	5.7 (1.0)	-0.1 (-2.8, 2.5)	T(80) = -0.086	0.932		
Week 8	4.8 (0.7)	5.0 (1.2)	0.2 (-2.6, 3.1)	T(73) = 0.160	0.873		
FSS							
Baseline	32.6 (2.0)	32.5 (1.8)	-0.2 (-5.5, 5.2)	T(80) = -0.058	0.954		
Week 2	33.4 (1.8)	29.6 (2.0)	-3.8 (-9.0, 1.5)	T(76) = -1.422	0.159	F(2,236) = 0.637	0.530
Week 4	33.1 (2.0)	29.1 (1.9)	-4.0 (-9.5, 1.6)	T(80) = -1.431	0.156		
Week 8	31.0 (2.3)	30.1 (2.2)	-0.8 (-7.3, 5.6)	T(71) = --0.259	0.796		
AQoL							
Baseline	16.8 (0.4)	16.9 (0.5)	0.1 (-1.2, 1.3)	T(80) = 0.155	0.878		
Week 2	16.3 (0.4)	16.4 (0.5)	0.1 (-1.2, 1.4)	T(76) = 0.141	0.888	F(2,236) = 0.048	0.953
Week 4	16.3 (0.4)	16.7 (0.5)	0.3 (-1.0, 1.7)	T(80) = 0.496	0.621		
Week 8	16.1 (0.5)	16.6 (0.5)	0.7 (-0.7, 2.1)	T(72) = 0.965	0.338		

Table 6.3. Per-protocol analysis of questionnaire outcomes. The results are presented as estimated marginal means (with associated standard errors), independent T-tests and F-tests.

	Mean values (SE)		Between-group differences			Group by time interaction	
	Active (N = 38)	Placebo (N = 47)	Mean (95% CI)	T-test	P value	F-test	P value
SOL, min							
Baseline	41.3 (4.5)	48.4 (6.0)	7.1 (-8.4, 22.5)	T(83) = 0.908	0.366		
Week 2	34.1 (3.2)	38.0 (5.1)	3.9 (-8.5, 16.3)	T(79) = 0.625	0.534	F(2,242) = 0.407	0.666
Week 4	25.5 (2.6)	37.7 (4.3)	12.2 (1.7, 22.7)	T(80) = 2.312	0.023		
Week 8	27.9 (4.2)	32.5 (4.3)	4.6 (-7.4, 16.6)	T(72) = 0.765	0.447		
WASO, min							
Baseline	56.1 (6.2)	48.6 (6.1)	-7.5 (-24.9, 9.9)	T(83) = -0.854	0.395		
Week 2	48.7 (6.4)	45.2 (5.6)	-3.5 (-20.4, 13.4)	T(73) = -0.411	0.682	F(2,232) = 0.112	0.894
Week 4	45.3 (6.1)	43.3 (5.4)	-2.1 (-18.2, 14.1)	T(76) = -0.257	0.798		
Week 8	47.3 (7.3)	45.5 (6.2)	-1.8 (-20.8, 17.2)	T(66) = -0.190	0.850		
SE, %							
Baseline	67.5 (2.2)	65.8 (2.7)	-1.7 (-9.0, 5.6)	T(83) = -0.460	0.647		
Week 2	72.6 (1.7)	72.9 (2.2)	0.3 (-5.4, 5.9)	T(79) = 0.094	0.926	F(2,242) = 0.226	0.798
Week 4	74.0 (2.1)	72.1 (2.4)	-1.9 (-8.3, 4.5)	T(80) = -0.588	0.558		
Week 8	74.2 (1.9)	74.0 (2.5)	-0.1 (-6.5, 6.2)	T(72) = -0.045	0.964		
TST, min							
Baseline	370.3 (13.2)	342.6 (14.1)	-27.7 (-66.9, 11.4)	T(83) = -1.408	0.163		
Week 2	391.7 (9.7)	374.3 (13.2)	-17.5 (-50.8, 15.9)	T(79) = -1.042	0.301	F(2,242) = 0.105	0.901
Week 4	394.2 (12.0)	376.8 (14.0)	-17.4 (-55.0, 20.2)	T(80) = -0.919	0.361		
Week 8	394.8 (10.9)	387.8 (13.7)	-7.0 (-42.5, 28.4)	T(72) = -0.395	0.694		

Table 6.4. Intention-to-treat analysis of subjective sleep parameters. The results are presented as estimated marginal means (with associated standard errors), independent T-tests and F-tests.

	Mean values (SE)		Between-group differences			Group by time interaction	
	Active (N = 38)	Placebo (N = 44)	Mean (95% CI)	T-test	P value	F-test	P value
SOL, min							
Baseline	41.3 (4.5)	42.4 (5.3)	1.2 (-12.8, 15.2)	T(80) = 0.165	0.870		
Week 2	34.1 (3.2)	34.4 (4.3)	0.35 (-10.4, 11.1)	T(77) = 0.066	0.948	F(2,234) = 0.762	0.468
Week 4	25.5 (2.6)	35.3 (4.3)	9.8 (-0.6, 20.2)	T(77) = 1.879	0.064		
Week 8	27.9 (4.2)	32.3 (4.5)	4.4 (-7.9, 16.7)	T(70) = 0.720	0.474		
WASO, min							
Baseline	56.1 (6.2)	45.3 (6.0)	-10.8 (-27.9, 6.2)	T(80) = -1.261	0.211		
Week 2	48.7 (6.4)	43.0 (5.5)	-5.7 (-22.5, 11.2)	T(71) = -0.668	0.506	F(2,224) = 0.164	0.849
Week 4	45.3 (6.1)	40.8 (5.5)	-4.5 (-20.8, 11.8)	T(73) = -0.554	0.581		
Week 8	47.3 (7.3)	45.4 (6.5)	-1.9 (-21.4, 17.7)	T(64) = -0.190	0.850		
SE, %							
Baseline	67.5 (2.2)	66.9 (2.8)	-0.6 (-8.0, 6.8)	T(80) = -0.153	0.879		
Week 2	72.6 (1.7)	73.9 (2.2)	1.3 (-4.2, 6.8)	T(71) = 0.470	0.639	F(2,234) = 0.242	0.785
Week 4	74.0 (2.1)	72.8 (2.5)	-1.2 (-7.7, 5.3)	T(83) = -0.352	0.726		
Week 8	74.2 (1.9)	74.2 (2.6)	0.1 (-6.4, 6.5)	T(64) = -0.016	0.988		
TST, min							
Baseline	370.3 (13.2)	345.5 (14.8)	-24.8 (-64.7, 15.2)	T(80) = -1.233	0.221		
Week 2	391.7 (9.7)	377.5 (13.4)	-14.3 (-47.6, 19.1)	T(77) = -0.851	0.398	F(2,234) = 0.086	0.918
Week 4	394.2 (12.0)	377.3 (14.7)	-16.9 (-55.3, 21.5)	T(87) = -0.877	0.383		
Week 8	394.8 (10.9)	387.0 (14.3)	-7.8 (-43.9, 28.3)	T(70) = -0.433	0.666		

Table 6.5. Per-protocol analysis of subjective sleep parameters. The results are presented as estimated marginal means (with associated standard errors), independent T-tests and F-tests.

	Mean values (SE)		Between-group differences			Group by time interaction	
	Active (N = 35)	Placebo (N = 46)	Mean (95% CI)	T-test	P value	F-test	P value
SOL, min							
Baseline	24.4 (3.1)	18.3 (1.5)	-6.1 (-12.5, 0.2)	T(79) = -1.927	0.058		
Week 2	22.0 (2.9)	20.6 (1.6)	-1.4 (-7.6, 4.8)	T(77) = -0.447	0.656	F(2,232) = 0.617	0.540
Week 4	22.7 (2.5)	18.5 (1.6)	-4.2, (-9.7, 1.3)	T(76) = -1.512	0.135		
Week 8	20.1 (1.8)	22.4 (2.1)	2.3 (-3.5, 8.1)	T(70) = 0.798	0.427		
WASO, min							
Baseline	46.7 (4.3)	53.3 (4.7)	6.6 (-6.3, 19.4)	T(79) = 1.015	0.313		
Week 2	48.8 (4.7)	53.2 (5.0)	4.4 (-9.5, 18.4)	T(77) = 0.635	0.527	F(2,232) = 0.316	0.729
Week 4	50.3 (4.6)	49.5 (4.7)	-0.9 (-14.6, 12.8)	T(76) = -0.126	0.900		
Week 8	47.1 (4.2)	55.5 (5.8)	8.4 (-6.7, 23.6)	T(70) = 1.110	0.271		
SE, %							
Baseline	83.4 (1.1)	83.3 (0.9)	-0.2 (-2.9, 2.5)	T(79) = -0.132	0.895		
Week 2	83.8 (1.1)	82.9 (1.0)	-0.8 (-3.9, 2.2)	T(77) = -0.537	0.593	F(2,232) = 0.272	0.762
Week 4	82.7 (1.2)	83.4 (1.0)	0.7 (-2.4, 3.9)	T(76) = 0.459	0.648		
Week 8	84.2 (1.1)	81.8 (1.3)	-2.3 (-5.8, 1.1)	T(70) = -1.341	0.184		
TST, min							
Baseline	434.9 (12.3)	426.3 (12.3)	-8.5 (-38.0, 20.9)	T(79) = -0.576	0.566		
Week 2	435.2 (11.0)	419.1 (8.5)	-16.2 (-43.4, 11.1)	T(77) = -1.182	0.241	F(2,232) = 0.071	0.931
Week 4	421.0 (13.5)	408.6 (7.8)	-12.4 (-41.6, 16.7)	T(76) = -0.849	0.398		
Week 8	422.5 (13.4)	405.0 (7.2)	-17.5 (-46.0, 11.0)	T(70) = -1.225	0.225		

Table 6.6. Intention-to-treat analysis of objective sleep parameters. The results are presented as estimated marginal means (with associated standard errors), independent T-tests and F-tests.

	Mean values (SE)		Between-group differences			Group by time interaction	
	Active (N = 35)	Placebo (N = 43)	Mean (95% CI)	T-test	P value	F-test	P value
SOL, min							
Baseline	24.4 (3.1)	17.6 (1.2)	-6.9 (-13.1, -0.7)	T(76) = -2.205	0.030		
Week 2	22.0 (2.9)	20.4 (1.6)	-1.6 (-7.9, 4.7)	T(74) = -0.511	0.611	F(2,223) = 0.754	0.472
Week 4	22.7 (2.5)	18.2 (1.6)	-4.5 (-10.2, 1.1)	T(73) = -1.605	0.113		
Week 8	20.1 (1.8)	21.7 (2.1)	1.6 (-4.0, 7.2)	T(68) = 0.558	0.579		
WASO, min							
Baseline	46.7 (4.3)	49.6 (4.2)	2.9 (-9.3, 15.0)	T(76) = 0.473	0.638		
Week 2	48.8 (4.7)	49.3 (4.7)	0.5 (-12.8, 13.9)	T(74) = 0.078	0.938	F(2,223) = 0.418	0.659
Week 4	50.3 (4.6)	45.2 (4.2)	-5.2 (-17.7, 7.4)	T(73) = -0.819	0.415		
Week 8	47.1 (4.2)	50.3 (4.7)	3.2 (-9.7, 16.1)	T(68) = 0.496	0.621		
SE, %							
Baseline	83.4 (1.1)	84.3 (0.7)	-0.8 (-1.5, 3.2)	T(76) = 0.709	0.480		
Week 2	83.8 (1.1)	83.9 (0.9)	0.11 (-2.7, 3.0)	T(74) = 0.077	0.939	F(2,223) = 0.272	0.762
Week 4	82.7 (1.2)	84.2 (1.0)	1.6 (-1.5, 4.6)	T(73) = 1.023	0.310		
Week 8	84.2 (1.1)	83.0 (1.0)	-1.2 (-4.1, 1.8)	T(68) = -0.785	0.435		
TST, min							
Baseline	434.9 (12.3)	434.8 (7.8)	-0.0 (-28.1, 28.1)	T(76) = -0.002	0.998		
Week 2	435.2 (11.0)	425.9 (7.9)	-9.3 (-35.8, 17.1)	T(74) = -0.706	0.482	F(2,223) = 0.132	0.876
Week 4	421.0 (13.5)	412.8 (8.0)	-8.2 (-37.8, 21.3)	T(73) = -0.555	0.581		
Week 8	422.5 (13.4)	410.0 (6.7)	-12.5 (-40.5, 15.6)	T(68) = -0.888	0.378		

Table 6.7. Per-protocol analysis of objective sleep parameters. The results are presented as estimated marginal means (with associated standard errors), independent T-tests and F-tests.

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6.3. Adverse events

The adverse events reported in the placebo and active groups are reported in Table 6.4. The number of adverse events and severe adverse events was not different between the two groups. No serious adverse event was observed during the trial. In the active group, five adverse events were considered "probably" or "definitely" related with the treatment, including dry mouth (N=2), frequent awakenings at night (N=1), skin rash on the face (N=1) and urgency for urination (N=1).

	Active (N=38)	Placebo (N=47)	χ^2 value	P value
Severe adverse events	1 (3%)	1 (2%)		1.000
Total adverse events	10 (26%)	16 (34%)	0.591	0.442

Table 6.8. Number of participants who experienced adverse events during the intervention period.

6.4. Clinical significance

The number of participants who achieved a clinically significant change during the intervention was not statistically different (χ^2=1.206, P=0.368) between the placebo group (19%) and the active group (11%).

6.5. Acceptability and tolerability

The average adherence rate was higher (t=-2.793, P=0.006) in the active group (96.8%) than the placebo group (84.1%). The number of completers in the active group (100%) and in the placebo group (94%) was not statistically significantly different (χ^2=2.514, P=0.250).

6.6. Pattern diagnosis

The results of the between-group analysis of Chinese medicine patterns of the participants at post-treatment are reported in Table 7.9. No statistical difference was observed between the active and placebo groups ($P > 0.05$ for all). The influence of each pattern scores on the post-treatment ISI score was not statistically significant ($0.241 < P < 0.608$). There was no significant influence on sleep diary measured SOL ($P > 0.121$ for all), the only outcome in which statistical difference was achieved between the active and placebo groups.

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	Ordinal regression analysis	
	χ^2 value	P value
Liver fire	0.676	0.411
Phlegm-heat	0.060	0.806
Heart-spleen deficiency	0.663	0.415
Non-interaction between heart and kidney	0.777	0.378
Gallbladder and heart qi deficiency	1.326	0.250

Table 6.9. Results of the ordinal regression analysis for the Chinese medicine patterns scores at post-treatment.

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Chapter 7: Discussion and conclusion

7.1. Main findings

In this study we found no difference in insomnia severity between the group taking ZRAS capsule and the group taking a placebo at post-treatment. However, the subjective SOL was significantly shorter in the group taking ZRAS capsule. The difference was significant only in the intention-to-treat analysis with independent t-test. There was no statistically difference at any time point for the other outcomes.

7.2. Explanations of the findings

ZRAS capsule performed better than a placebo in terms of reducing SOL but not in reducing insomnia severity. There might be five explanations. The first is that there was not enough power to detect a difference in insomnia severity. Indeed, the improvements tended to be larger in the active group for most outcomes. The sample size was not based on the expected effect of ZRAS capsule and may have been underestimated. The second is that the duration of the treatment was not long enough. Chinese herbal medicine is known for its slow efficacy and long treatment phases are usually needed. The third is that the dosage may not have been high enough. In section D, we will see that clinician use on average seven herbs for the treatment of insomnia and the average recommended dose for *suanzaoren* is 27g of raw herb per day. ZRAS capsule contains three herbs and only 6g (raw herb equivalent) of *suanzaoren*, the main ingredient of the product. The fourth explanation is that the sedative effect of ZRAS capsule is excessively short. This would explain the improvement in subjective SOL and the absence of improvement in subjective WASO. The fifth explanation is the possibility of false positive results, as 64 independent t-test were conducted in this study.

7.3. Comparison with existing evidence

A systematic review of the evidence for ZRAS products is reported in section B. None of the studies that assessed the efficacy and safety of ZRAS for insomnia used a double-blind randomised design. The only study in which ZRAS was compared to placebo showed positive results in terms of sleep quality. ZRAS was found to be as effective as BzRA drugs. However, in our study the difference between ZRAS capsule and placebo was not significant. These discrepancies might be attributed to bias due to the absence of blinding. From a safety perspective, the studies included in the systematic

review reported that 7% of the participants experienced adverse events, much lower than the 26% of participants reporting adverse events in our study. This difference might be attributed to differences in adverse events assessment.

7.4. Strength and limitations

To our best knowledge, this is the first randomised trial using a double-blind design to assess the efficacy and safety of ZRAS for insomnia. The study provided a comprehensive overview of the acceptability, safety and efficacy profile of ZRAS capsule, including objective sleep parameters. The low drop-out and missing data rates allow the results to be representative. Our results contribute to a better understanding of the potential of ZRAS as an alternative treatment for insomnia.

The main limitation of this study was the imbalance in terms of sample size between the active and placebo groups. This imbalance could be attributed to an imbalance in drop-out rate during the placebo run-in. Due to the implementation of remote procedures after the beginning of the COVID pandemic, the drug bottles of drop-out participants, which were already in the hand of participants and for which we could not control the quality of the product, could not be re-used. It is unlikely that this imbalance affected the outcomes as the two group were balanced in terms of socio-demographic and pathological characteristics. However, this imbalance did limit the power of the statistical analysis. Future studies should consider the possibility of being unable to conduct face-to-face visits and plan drug distribution accordingly. Another limitation of the study is the difference in weight between the active (2.28g) and the placebo (2.16g). It is unlikely that participant could have ‘guessed’ the allocation based on the weight difference, however future studies should avoid differences in weight between the active and the placebo.

7.5. Implications for clinical practice

As the effects on the various sleep outcome were not large, ZRAS capsule should not be used instead of recommended treatments (which include pharmaceutical drugs and CBT-I). However, ZRAS was found generally safe and effective for subjective SOL and TST. As such, ZRAS capsule can be considered as an alternative for patients experiencing subjective difficulty falling asleep and subjective lack of sleep and who refuse or do not have access to recommended treatments.

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7.6. Implications for research

There was no statistically significant difference in the primary outcomes of the study. Nonetheless, the subjective SOL was significantly better at post-treatment in the active group. As the discrepancies between different outcomes could be due to limited sample size, excessively short treatment duration and excessively low dose, future studies should evaluate the efficacy of ZRAS capsule with an increased sample size, longer treatment duration and higher dose. A dose-response study should be conducted before conducting any further randomised-controlled trial.

7.7. Conclusion

In our study, we found that ZRAS capsule is overall safe and acceptable, yet not able to improve insomnia severity more than placebo. ZRAS may more effective in reducing subjective SOL. Larger studies with higher doses and/or longer treatment duration are needed to explain these mixed results.

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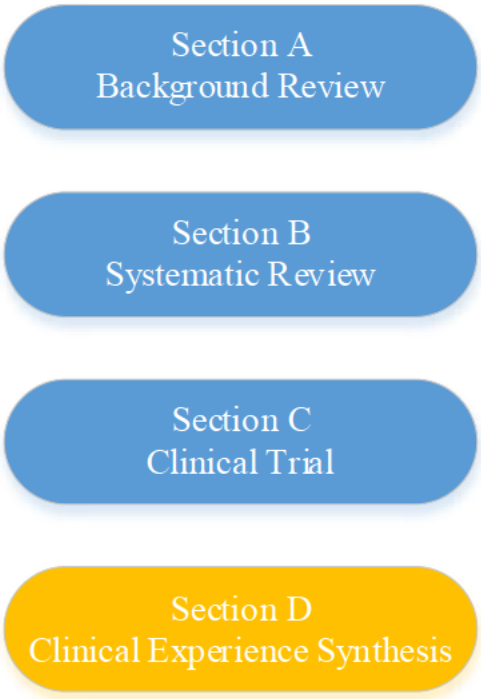
Section D

Chinese Medicine for Insomnia:

A Clinical Experience Synthesis



This section presents a qualitative study of published clinical experience reports from clinicians who described their treatment of insomnia disorder with Chinese medicine.

The objective of this study was to provide guidance for clinicians and answers the question "HOW should Chinese medicine be used for insomnia". It shows the mainstream understanding of the treatment of insomnia with Chinese medicine as well as alternative approaches. We present key clinical issues such as the adaptation of treatments, treatment modalities and clinical pathways.

This study is not a replacement of existing guidelines which are based on expert consensus or experimental evidence from clinical trial. Rather, it clarifies, develops and presents a hierarchy of the current knowledge and practices.

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Chapter 8: Introduction and methods

8.1 Introduction

Chinese medicine is a traditional medicine developed through the interactions between ancient Chinese philosophy and clinical practice. Chinese medicine includes various therapies such as Chinese herbal medicine (CHM), acupuncture, moxibustion (i.e., dried mugwort burning) and food therapy [251]. The treatment can target a certain disease (the disease approach) or a pattern (the pattern approach). A pattern is a global state of the patient's mind and body that is determined through the analysis of signs and symptoms. As Chinese medicine tends to have a holistic approach without a separation of the mind and the body, it would seem particularly suitable for the treatment of diseases, like insomnia, that have both biological and psychological factors.

Recent systematic reviews of randomised controlled trials (RCTs) with standardised CM treatments for insomnia suggested that CHM and acupuncture are relatively safe and can effectively improve sleep quality and sleep parameters (e.g., sleep latency, total sleep time) in insomnia patients [259, 278, 316, 425]. However, as individualised treatments are preferred by Chinese medicine practitioners, the usefulness of these systematic reviews in guiding the decision-making process in the clinical practice is disputed [9]. Several guidelines and textbooks guide the individualised treatment options for insomnia [6, 7, 423, 426, 427]. However, the basis of their recommendation is unclear, and it is possible that these guidelines merely reflect the opinion of the authors. As Chinese medicine clinicians recognise the importance of clinical practice guidelines [428], there is a need to develop an evidence-base for decision making on the treatment of insomnia in CHM. This evidence base will inform practice guidelines and offer greater confidence in CHM clinical decision making.

Clinical experience is a fundamental part of the decision-making process in evidence-based medicine [429]. In Chinese medicine, the role of clinical experience is even more important and is highly valued by clinicians [430-432]. Many published articles describing the clinical experience of CM clinicians (often older and famous specialists) are available in the literature [433]. These articles, which we will call clinical experience reports (CER), provide clear guidance on the use of CHM treatment on a pattern basis. However, individual CERs may reflect the author's preferences and must

be synthesized in order to reflect collective experience. There is a need to develop a methodology to systematically collect and report clinical experience from a large pool of clinicians.

The purpose of this study is to generate an understanding of CM clinicians' clinical experiences in their treatment of insomnia with Chinese medicine. By synthesising the content present in published CERs about Chinese medicine for insomnia, this study aims to answer the question: "How should Chinese medicine be used to treat insomnia?".

8.2. Methods

8.2.1. Study design

This study is a clinical experience synthesis (CES), i.e., a systematic collection and qualitative analysis of CERs. A qualitative synthesis is a systematic interpretation of study findings through a series of expert judgments to represent the overall meaning of the collected work [434]. The methodology of the CES has been developed during this study. The approach of this study is inductive (i.e., theory driven from the data instead of hypothesis-testing) [435] and integrative (i.e., summarizes the findings without interpretation) [436] and based on an objective idealism assumption (i.e., there is a world of collectively shared understandings) [437]. The methodology for data analysis was derived from thematic and content analysis [438]. Chinese medicine is a holistic medicine based heavily on empiricism. Chinese medicine theory has evolved for thousands of year and continues to evolve through clinical practice and clinical observation. Thematic analysis allows us to explore the complexity of themes identified through clinical practice, and use the perspective of the clinicians rather that the study authors. The qualitative data was partially transformed into numerical data to reduce the biases of the authors. However, most part of the analysis was qualitative in nature and therefore potentially affected by the opinion and beliefs of the authors.

8.2.2. Study authors

This study was conducted by a field expert (YB) and a non-field expert (MJ) in order to allow in-depth analysis and prevent bias at the same time. Yoann Birling is a Chinese medicine practitioner specialized in the treatment of mental disorder. His clinical focus is primarily on Chinese herbs and

secondarily on acupuncture. He views insomnia as a bio-psychological disease in which psychological maintaining factors are essential. As a Chinese medicine clinician, he prefers using liver-draining and phlegm-transforming methods (such as the formula Wen Dan Tang) and blood-nurturing and fire-clearing methods (such as the formula Huang Lian E Jiao Tang) for the treatment of insomnia. Mingxian Jia is a Chinese medicine pharmacology expert with experience in clinical research and conducting systematic reviews. She views insomnia as a neurological disorder caused by biological and psychological factors. She has no experience or opinion about the treatment of insomnia with Chinese medicine. Xiaoshu Zhu (XZ) is an academic with experience in practicing and teaching Chinese medicine for 40 years.

8.2.3. Search

Five international databases, i.e. EMBASE, PubMed, the Cochrane library, Allied and Complementary Medicine database and PsycINFO, and four Chinese databases, i.e. Chinese National Knowledge Infrastructure, Wanfang, Chinese Biomedical Literature and Chong Qing VIP (CQVIP) were searched from their inception until November 2019. The searched terms used were ("Chinese medicine" OR "Chinese herbal medicine" OR "acupuncture" OR "massage" OR "food therapy") AND ("clinical experience" OR "treatment") AND ("sleep disturbance" OR "sleep disorder" OR "insomnia"). The databases were all searched with keywords both in English and Chinese in the full text (when possible) and the searches were adapted to each database (see Annexe 1). The search was conducted by one author (YB) only. The review did not include a manual search of clinical experience present in books as this type of search could be influenced by the authors knowledge and preferences.

8.2.4. Screening and categorisation

After combining the results of the searches in Endnote, the duplicates were removed. The reports were then screened by the two review authors (YB and MJ) with a two-step process, first using the title and abstract and then using the full text [343]. Disagreements were resolved by discussion, and by the senior Chinese medicine academic (XZ) if consensus could not be reached. The articles included in the review were categorised directly after the screening.

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8.2.4.1. Selection criteria

The articles were systematically reviewed and screened according to the following criteria, in the order in which they are presented here. The article was included in the review only if all the criteria were met.

A. Full text in Chinese or English available

The full text of the article has to be accessible by the reviewer. If the article is presented in the form of an abstract (e.g., for a conference), it was excluded. If the full text is not in Chinese or English, it was excluded.

B. Not a duplicate

If the article had already been published, it will be considered as a duplicate and therefore excluded. If the content is similar to the content of another article written by the same or a different author, but the presentation is different, it will not be considered as a duplicate. If the content and the presentation of the section on the treatment of insomnia with Chinese medicine are identical or quasi-identical to another article already published, no matter if the author is the same or different, the article was considered as a duplicate.

C. Clinical experience report (CER)

To our knowledge, there is no published definition of a CER and its characteristics. Therefore, a definition of CERs and criteria to distinguish CER from other similar type of documents was developed by the two review authors. Articles selected during the title/abstract screening were analysed by the authors independently, who shared their views about CER characteristics (e.g., structure, writing style, content) and differences with similar documents until consensus was reached. After clear distinction criteria (see Annexe 2) were designed, these criteria were used to screen again all the articles from the beginning.

In this study a CER was defined as an article that described the clinical experience of a clinician. The article could include theoretical analysis and reviews of the literature as long as the main point of the

article (as described in the title, abstract or introduction) was to describe clinical experience. It could also include clinical trial reports and case reports if used to illustrate a particular point of experience or if the experience was drawn from these clinical trials/cases. The focus on the clinician's experience differentiated CERs from theoretical discussions, case reports, clinical trials, literature reviews, literature analyses, guidelines, consensus and educational material (see Annexe 2).

D. Include treatment

The article did not focus only on the aetiology, pathology, prognostic or comorbidities of the disease but instead described treatment or prevention methods of insomnia. The treatment approach had to be described as part of the overall experience and not only in a specific clinical case. Articles were included even if the specific formula was not described, as long as at least one treatment method was stated (e.g. draining the liver and clearing the heat). If the treatment section did not include specific recommendation but only vague suggestion such as "consider the period of the year" or "take account of the specificity of the individual", the article was not included. The form of administration such as "paste" or "manufactured product" was considered as a description of the treatment but articles that listed types of treatment such as "acupuncture", "diet therapy" without any further description were not accepted. A treatment approach such as "treating from the perspective of the liver", "regulating the spleen and the stomach" without further description was not accepted either. A list of formulas without the corresponding syndromes was also not accepted.

E. Focus on insomnia

The article focused on insomnia as defined by recognised diagnosis standards [72, 73], i.e. a difficulty to induce or maintain sleep. A loose definition of insomnia was accepted, as international diagnosis standards with stringent criteria in terms of duration, frequency and impact may not be widely used by clinicians. Articles focusing on nonrestorative sleep or dream disorders alone were not included. Articles focusing on some categories of insomnia such as psychophysiological, chronic or primary insomnia were included. A condition called "sleep disorder" with a description that corresponded mostly to insomnia was included even if it included symptoms such as "turning around in the bed",

"crying at night" or "having frequent dreams" - as long as it did not include other sleep disorders such as sleep apnoea or circadian rhythm disorders.

F. Include Chinese medicine therapies

The article included at least one Chinese medicine related treatment or prevention methods, including Chinese herbal medicine (regardless of the mode of administration), acupuncture and related techniques (cupping, bleeding, moxibustion, Guasha), Tuina (i.e., Chinese massage), Chinese medicine psychotherapy (any type of psychotherapy used on the basis of Chinese medicine principles), Chinese medicine food therapy, Qigong and Tai Chi. Integrative treatments and nursing methods including at least one of the above treatments was accepted. Chinese medicine techniques such as acupuncture were not accepted if applied under the principles of ethnic medicines (e.g., Mongolian medicine) or non-Chinese medicines (e.g., Korean medicine, "dry needling").

G. Qualitative approach

The experience must come from the clinician directly or results from the observation of the author. Conclusions drawn from quantitative analysis (e.g., through the analysis of patient data with a software) were not accepted.

H. Clinician as an author

If the clinician was not an author, there must be evidence that he/she reviewed the manuscript (and therefore acknowledges the content).

8.2.4.2. Categorisation

In order to combine the data from CER of the same categories, the articles were categorised according to the following variables.

A. Precision

Two degrees of precision:

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1. No precision: only treatment principle or method; the name of the basic formula was given, but there were not enough details to know all the ingredients/acupuncture points (e.g., modified formula); the ingredients/acupuncture points of the formula were stated, but not all of them ("etc.").

2. Enough precision: all the ingredients/acupuncture points were known; the formula is famous enough for its ingredients to be found in a formula textbook; the formula is "modified" but the ingredients were described in the following text.

The degree of precision concerns only the basic formula, not the modification. If there is a choice (X or Y) in terms of formula or ingredient, the degree of precision was considered as "no precision". If the treatment recommended was a group of formula (e.g., "Gui-Zhi-Tang-type 桂枝汤类"), the article was labelled as having "no precision". The degree of precision of the article was the highest degree of precision reached by any treatment (e.g., for any pattern) described in the article for a particular treatment (e.g., herbs, acupuncture).

B. Population

If there is any specificity that is not related to the pattern (e.g., age, gender, comorbidity, severity, duration, etc.), the population is considered "specific". If the population was described as general, if there was no detail on the population or if the specificity concerns the pattern, the population was considered "general". The general population of insomniac can be described as people who experience "insomnia" as a symptom, "insomnia disorder", "primary insomnia" or "chronic insomnia", since the terms above are acceptable definition of insomnia. A sub-category such as "sleep initiation insomnia", "long-term insomnia", etc. is considered as "specific". If part of the article concerns a specific population and another part of the article concerns a general population, the population was considered "both". If several specific populations were included (e.g., insomniac with liver diseases and insomnia with cardiovascular diseases), the population was considered as "specific".

C. Diagnostic approach

If the treatment was based on the pattern (e.g., Xiao Yao San for Liver Stagnation pattern), the treatment type was considered as “pattern differentiation”. If the treatment was based on the disease (i.e., insomnia), without distinction of pattern, the treatment type was considered as “disease differentiation”. If the two approaches were combined (e.g., single formula for insomnia with modification according to the pattern), the treatment type was considered as “both”. The modification of the formula according to symptoms was not taken into account. If the treatment did not fall in any of the above category, it was classified as “other”.

D. Type of treatment

The articles were categorised according to the type of treatment they proposed, i.e. “herbal medicine”, “acupuncture”, “massage” and “others”. The presence of each modality was assessed independently of the others as one article could include several treatment modalities. The “herbal medicine” category included any modality of oral treatment (e.g., decoction, infusion, capsule, granule), manufactured herbal products, herbal foot bath and herbal pillows. The “acupuncture” category included all approaches of needle acupuncture (e.g., body acupuncture, ear acupuncture, scalp acupuncture, abdominal acupuncture) moxibustion, cupping, Guasha, fire needles and bleeding techniques. The “massage” category included all kinds of manual techniques within the scope of Chinese medicine.

8.2.5. Data collection

The articles in which the treatment had “enough precision” were classified according to the population, diagnostic approach and treatment type. The groups including at least 20 formulae (i.e., herbal formula, set of point or set of techniques) were selected for numerical analysis. If the pattern approach was in minority (i.e., including less than 25% of the articles), the data was combined with the disease approach and each formula was considered as a pattern-modification formula.

Data from the articles were collected independently by YB and MJ using an excel spreadsheet. Every row was associated with one formula, either the main formula (in both the disease approach and the pattern approach) or the pattern-based modification (in the disease approach). Only the data associated with formulae with “enough precision” (see 9.2.4.2. Categorisation) were collected. These

data included the article ID (assigned before the full-text screening), the type of treatment, the type of population, the diagnostic approach of the article, the name of the clinician, the diagnostic approach of the formula, the name of the pattern (for pattern approach or pattern-based modification) or the mechanism (for the main formula of the disease approach), the pathological mechanism (including causes, intermediary patterns and final patterns), the signs and symptoms associated with the pattern, the characteristics of the population of the pattern, the name of the formula (if mentioned by the author), the herbs and acupuncture points constituting the formula (including doses of individual herbs), the preparation methods of herbal treatment (e.g., timing and mode of administration) or the technique used for acupuncture treatment (e.g., insertion and manipulation techniques), the analysis of the formula by the author, the modification (excluding the pattern-based modification of the disease approach, which is considered as its own formula; collected regardless of the degree of precision) and notes from the author (i.e., tips and recommendations).

For the herbs included in the formula, the herb was collected in the herbs column if "usually added 常加入", collected in the modification column if "added when [the symptoms are] severe 重者加，甚者加", but not collected if "sometimes added 时加", "can be added 可加入" or "added according to the circumstances 酌加". If the ingredients of the formula were not described but the name of the formula was well known, the ingredients were added in the "herbs or acupuncture points" column according to a textbook of CHM formula [439], without the dose or the preparation method (e.g., raw or stir-fried).

8.2.6. Data processing and reporting

8.2.6.1. Preliminary data processing

The names of the herbs were standardised according to the Chinese medicine Pharmacopeia [289] (e.g., "shanzhi 山栀" changed to "zhizi 栀子"). Names combining two herbs were separated into the names of the two individual herbs (e.g., "sheng longmu 生龙牡" changed to "sheng longgu, sheng muli 生龙骨，生牡蛎"). To our knowledge, there is no existing standard for the standardisation of

the names of signs and symptoms (SSs) in Chinese medicine. Therefore, we designed a standard for the sake of this Clinical Experience Synthesis (CES) (See Annexe 3). This standard includes methods of separating compound SSs (e.g., pain-distension in the thorax-abdomen 胸腹胀痛) and standardisation of highly-similar terms. The similarity of the SSs was assessed according to clinical significance rather than semantic meaning. The standard was drafted by YB and then reviewed and corrected by a group of eight Chinese medicine clinicians and scholars, first individually and then collectively. In case of disagreement, XZ made the final decision.

The excel functions ISNUMBER and SEARCH were used to identify the presence of herbs or acupuncture points in the "herbs or acupuncture points" column and the presence of SSs in the "signs and symptoms" column. The FALSE or TRUE code was then converted to a 0 or 1 code. The number of herbs, acupuncture points or SSs of each formula were counted manually and then compared to the total of herbs, acupuncture points and SSs identified with the functions. The system was adjusted until the two numbers were identical for each formula. The herbs, acupuncture points and SSs identified in the two reviewers' datasets were then compared and the datasets adjusted until they were identical.

8.2.6.2. Formulae classification

For the herbal treatments according to pattern differentiation in both the pattern approach and the pattern-based modification of the disease approach, formulae were clustered according to their composition with a k-means cluster analysis. To our knowledge this is the first time k-means cluster analysis is used to cluster formulas. The reason for choosing the herbs and not the SSs for the cluster analysis is that a preliminary test showed a better distinction between pattern for the clustering according to herbs. This may be because of the higher variety and/or the more subjective interpretation of the meaning of SSs by the clinicians compared to individual herbs. The formulae were not categorised by pattern names as patterns representing the same pathological entity (i.e., similar SSs and herbs) may be labelled differently. The cluster analysis was used to find groups of similar formulae that are used to treat a specific pattern of insomnia. Both formulas with and without a formula name were included in the cluster analysis.

Participant Initials				Participant ID			

The patterns resulting from the cluster analysis were labelled according to the pattern names of the cluster, the decision of the name being reviewed by XZ. The number of formulae present in each pattern and the most commonly cited, when applicable, were also reported.

8.2.6.3. General reporting guidelines

When possible, different values of the same numerical data (e.g., individual herb dose, duration of the treatment) were combined and the mean, maximum and minimum were reported. If the numerical value is a range in the original report, the minimum and maximum of the range were used for the calculation of the pooled minimum and maximum and the middle of the range was used for the calculation of the pooled average. Two parameters, the sensitivity (i.e., the ratio of the number of formulae including the herb or SS on the total number of formulae in the group) and the specificity (i.e., the ratio of the number of formulae including the herb or SS in this cluster on the total number of formulae including the herb or SS) were reported when possible. For non-numerical data (e.g., herb preparation method), the number of reports in which the information was stated was reported in bracket.

For each pattern, the SSs with the highest sensitivity (i.e., the most frequently cited) were reported. High-specificity SSs, defined as SSs both with a 100% specificity level and cited at least two times, were reported as well. High-sensitivity SSs are more widely acknowledged as indicators of the pattern and may be more frequently encountered in clinic while high-specificity SSs may have a stronger role in differentiating one pattern from another.

The number of high-sensitivity SSs and core herbs reported was set as the average number of SSs (for the formulae for which SSs were reported) and herbs for the pattern. The SSs and core herbs were reported in order of main parameter (i.e., sensitivity or specificity) and secondary parameter if the main parameter is identical between two SSs. In case the sensitivity level of the last SS or core herb is identical to other SSs or herbs, these SSs or herbs were reported as well, regardless of the average number of SSs or herbs in the cluster.

Participant Initials				Participant ID			

8.2.6.4. General reporting for the pattern approach of herbal treatment

The pathogenesis of the different patterns used in the treatment of insomnia with herbal medicine and acupuncture was synthesised as a flowchart using the content of the pathological mechanism column. Squares were used to represent the causes of diseases (e.g., emotions, overstrain), rounds were used to represent intermediary and final patterns (e.g., Liver Stagnation) and arrows were used to represent causal relationships. Systems (causes, patterns and their causal relationships) were combined when at both sides of at least one relationship were identical or highly similar. The number of times each cause or pattern was cited was recorded, with a limit of one time per formula. The type of transformation from one pattern to another was recorded when applicable. Two patterns that shared similarities (common characteristics, causes or consequences) but were not similar enough to be combined were linked with dashes. The similarity of the elements (causes and patterns) was assessed by YB and reviewed by XZ. In order to improve the readability of the flowchart, the elements with a low citation score were removed from the flowchart until the flowchart was considered readable by XZ.

For the formula names, the terms “supplemented 加味” and “modified 加减，化裁” were removed from the names as they could reduce the weight of the formula. When the formula was composed of two formulae, the name was changed to “X and Y” (e.g., An Shen Ding Zhi Wan and Suan Zao Ren Tang). Word clouds of the formula names used in the pattern approach were designed using wordart [440]. The size and colour of each word (i.e., formula) was set according to the number of times it was cited and the pattern to which it belonged. The formula names were only reported for herbal treatments as acupuncture formulae usually did not have names. There were two goals for the formulae word cloud, the first is to give an overview of the most commonly used formulae for each pattern; the second to allow the reader to know which formulae were removed from the report by pattern.

Participant Initials				Participant ID			

8.2.6.5. Pattern-specific reporting for the pattern approach of herbal treatment

In addition to the SSs and herbs associated with a specific pattern, the populations and characteristics associated with the pattern, modification methods and notes from the author were also reported for each pattern.

The populations (e.g., older adults, women) and characteristics of the disease (e.g., persistent insomnia, acute onset) associated with the pattern were reported if cited at least two times.

The modification methods were first classified manually according to the global direction (e.g., spirit-calming, purging, heat-clearing) of the modification. As formulae are usually modified according to secondary SSs and/or pattern, the information regarding the SSs, the pattern and the herbs added or removed were divided into three columns. A component of the modification was defined as a sign or symptom (e.g., headache or red tongue), an aspect of the pattern (e.g., liver or qi deficiency), or a herb that was added or removed. Component of the modification were reported if the component was cited at least two times in the group. The group itself was reported only if at least one of the clinical indications (i.e., SSs or pattern) and one associated modification achieved the two-citation threshold.

Notes from the CER author on the formulae included in the pattern were also reported either directly, with quotation marks, or indirectly. These notes covered areas that were relevant to clinical practice (e.g., specificities of the population, lifestyle recommendations) but not included in the other parts of the report.

8.2.6.6. Analysis and reporting for the disease approach of herbal treatment

The basic formulae used in herbal treatment with a disease approach were analysed by YB in order to define categories. These categories were reviewed by XZ in order to strengthen the validity and credibility of the analysis. Quantitative criteria were developed to classify the formulae. These criteria were adjusted to optimise the distinction between different categories of formulae. The formulae which did not fit into any criteria were classified in a “other” category. The core herbs of each

category were reported with their sensibility level, except for the "other" category, for which only formulae were reported with the number of citations.

For the pattern-based modification, the herbal formulae were clustered according to their ingredients with a k-means cluster analysis. The outliers were eliminated by two ways, i.e. removing the clusters with an excessively low number of cases and removing cases with an excessively high distance to the centre of the cluster it belonged to. The number of clusters and the thresholds for eliminating outliers were pre-determined by preliminary analyses testing different possibilities, then the "best" classification was selected by XZ. The patterns resulting from the cluster analysis were labelled according to the pattern names of the cluster, the decision of the name being reviewed by XZ.

8.2.6.7. Analysis for the spirit-calming herbs

The formulae were grouped according to content of tonic herbs (i.e., herbs in the category "*qi* tonic", "*blood* tonic", "*yang* tonic" or "*yin* tonic". The correlation between the percentage of tonic herbs and different types of spirit-calming herbs (heart-nurturing herbs, heavy-sedative herbs, typical spirit-calming and all spirit-calming) was tested with a Pearson correlation test. The impact of the percentage of tonic herbs or the pattern on the percentage of different types of spirit-calming herbs was tested with One-Way ANOVA tests.

8.2.6.8. Analysis and reporting for specific populations

For specific populations (e.g., older adults), the difference in terms of frequency of use of herbs and herb categories were calculated as following:

$$n_s/ N_s - n_g/ N_g$$

with

n_s=number of citations of the herb or herb category in the specific population

N_s=total number of herbs used in the specific population

n_g=number of citations of the herb or herb category in the general population

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N_g=total number of herbs used in the general population

This mode of calculation was used to avoid the representation of rarely used herb (for which a difference due to random factor such as preferences is more likely to be significant). Only differences equal or superior in absolute value to 0.5 for herbs and 1.0 for herbs categories were reported. In order to allow an easier reading, the differences were reported in terms of percent of increase or decrease compared to the general population, as calculated according to the following formula:

$$(n_s/ N_s - n_g/ N_g) / n_g/ N_g \times 100$$

8.2.7. Quantitative analyses and quantitative data reporting

Several quantitative analyses methods and data reporting methods were used across the study. The main rationale for using these methods is to strengthen the validity and reliability of the findings. These methods including cluster analysis, decision tree, radar plots and word clouds.

The rationale for the cluster analysis is to use a relatively objective method to classify Chinese medicine patterns in a model that can be used relatively easily by clinicians. The k-mean cluster analysis was conducted with SPSS 25 (IBM). The number of clusters was pre-determined by a visual observation of the results of the analysis depending on the number of clusters. For the pattern approach of the herbal treatment of insomnia, the pre-determined number of patterns were seven, eight, nine and ten clusters. For the pattern-based modification on the basis of the disease approach, the pre-determined number of patterns were six, seven and eight.

In order to obtain clusters representing the patterns that are widely accepted, the outliers were eliminated by two ways, i.e. removing the clusters with an excessively low number of cases and removing cases with an excessively high distance to the centre of the cluster it belongs to. The number of clusters and the thresholds for eliminating outliers were pre-determined by preliminary analyses testing different possibilities. Different options were retained according to the following principles, i.e., each cluster represented a syndrome that could be identified according to Chinese medicine theory (e.g., liver stagnation), each cluster was different from the others, most of the formulae correspond to the pattern represented by the cluster it belonged to. The cluster analysis was

repeated after removing the outliers (removing firstly the small clusters and secondly the distant cases) until no outlier could be removed anymore. For the pattern approach, the pre-determined distance to the cluster at which outliers were removed were 2.8, 2.9, 3.0 and 3.1, the pre-determined threshold to remove small clusters was six or less cases. For the pattern-based modification on the basis of the disease approach, the pre-determined distance to the cluster at which outliers were removed were 2.0, 2.2, 2.4 and no limit. In both cases, the different classifications with the pre-determined parameters were reviewed by the senior clinician (XZ) and the "best" classification (according to the above principles) was selected.

In order to facilitate pattern differentiation, a decision tree was created with the Chi-squared automatic interaction detection growing method using "cluster" as the dependent variable and all the SSs as independent variables. The maximum tree depth was set at 20 levels and the minimum number of cases at 20 for parent node and 12 for child node. The most represented pattern for each branch were reported, with the percentage of cases belonging to that pattern. Branches that lead to the same decision (i.e., most represented pattern) were combined. The role of the decision tree is to provide an easy tool for pattern differentiation. It may not reflect the complexity of the pattern differentiation process. The decision tree was created with SPSS 25 (IBM).

"Pattern signatures" of each pattern were also created using excel (version Microsoft 365). These "pattern signatures" are radar plots of the ratio of each herb category (e.g., heat-clearing) used in the pattern. This ratio was calculated as the number of herbs from one specific category to the total number of herbs used in the formula of this pattern. For a better readability, only categories covering at least 5% of the total herb count for at least one pattern are reported. As herbs categories represent the direction of therapeutic effect of the treatment, these "pattern signatures" allow the reader to have a better understanding of the similarities and differences between patterns. A general "pattern signature" combining the herbs from all the patterns was also created as a reference.

Word clouds reporting the formulas, SSs and herbs in the pattern-based approach of Chinese herbal medicine and the acupuncture points were created using the wordart website [440]. The words were

allocated colors (where relevant), which represented the pattern the information belonged to, shade grades, which represented the specificity of the information, and sizes, which represented the citation number of the information. Theses words clouds were used to help the reader to visualise the information and grasp the essential quickly. For example, SSs with a high specificity or a high sensitivity, which are clinically more important, appeared dark or big, both of which making it more important to the eye than other SSs.

8.2.8. Thematic analysis

The original articles were imported to NVivo and analysed using a thematic analysis process. The first step was data familiarization, then initial codes were generated using open-coding, after which themes were conceptualised, defined and named, and finally reported [441]. As the primary question is "how to treat insomnia with Chinese medicine?", sections reviewing the literature and theoretical discussions about the nature of sleep, insomnia and etiological factors were not coded. Coding guidelines, which were built before the coding and modified during the coding are reported in Table 8.1. The analysis of the data was primarily descriptive (reporting the data from the CERs, similar to content analysis) but sometimes interpretative (creating theories from the data) (Table 9.1). The coding was conducted by YB and reviewed by MJ.

Themes and codes	Code description	Analysis
1. Treatment according to the three factors		
1.1. According to the person		
1.1.1. Age	Specificities of age groups (children, older adults) and treatment protocols (except if specific to older adults or perimenopause)	Des
1.1.2. Sex	Specificities of both sex and treatment protocols	Des
1.1.3. Constitution	Treatment according to constitution: principles and protocols	Des
1.1.4. Personality	Treatment according to personality: principles and protocols	Des
1.1.5. Comorbidities		Int
1.1.5.1. Principles	Relationship between insomnia, comorbidity and pattern, and treatment principles	
1.1.5.2. Treatment	Treatment protocols of comorbid insomnia	Des
1.2. According to the time	Rationale and protocol for modification according to the season or climate	Des

Participant Initials				Participant ID			

1.3. According to geography	Rationale and protocol for modification according to the geography, including climatic and cultural characteristics	Des
2. Treatment of insomnia subtypes		
2.1. Acute/persistent	Specificities of acute or persistent insomnia and treatment protocols for acute insomnia	Des
2.2. Complaint	Specificities and treatment protocols for insomnia according to the complaint	Des
3. General principles of treatment		
3.1. General recommendations	General recommendations regarding diagnosis and treatment	Des
3.2. Recommendations specific to pattern	Recommendations and information about a specific pattern (if not included in the previous analysis)	Des
3.3. Relation between disease and pattern differentiation	Relationship between the treatment according to the pattern and according to the disease	Des-Int
3.4. Treatment pathway	Stages of treatment or actions when treatment is not effective	Des
4. Herbal medicine		
4.1. Spirit-calming herbs		
4.1.1. Principles	Principles of use of spirit-calming herbs	Des
4.1.2. Types	Types of spirit-calming herbs and indications	Des
4.1.3. Atypical	Description of herbs that are usually not considered spirit-calming	Des
4.1.4. Pharmacology	Use of pharmacology studies as a reference	Des-Int
4.2. Herbs combinations		
4.2.1. Principles	Principles of combining pairs or trios of herbs	Int
4.2.2. Combinations	Description of pairs and trios of herbs	Des
4.3. Preparation and intake methods	Description of preparation and intake methods	Des
4.4. Treatment regimen	Number of doses and treatment duration	Des
4.5. Special patterns		
4.5.1. Non-interaction between heart and kidney	Principles, aetiological pathways, signs and symptoms and treatment protocols	Des-Int
4.5.2. Stomach disharmony	Principles, aetiological pathways, signs and symptoms and treatment protocols	Des-Int
4.5.3. Deregulation between protective and nutritive	Principles, aetiological pathways, signs and symptoms and treatment protocols	Des-Int
4.5.4. Yang and qi deficiency	Principles, aetiological pathways, signs and symptoms and treatment protocols	Des-Int
4.6. Additional herbal treatments		
4.6.1. Herbal footbath	Protocol for herbal footbath	Des

Participant Initials				Participant ID			

4.6.2. Infusion	Protocol for infusion	Des
4.6.3. Herbal pillow	Protocol for herbal pillow	Des
4.6.4. Manufactured products	Rationale and protocol for manufactured product	Des
4.6.5. Herbal paste	Rationale for use and treatment protocol	Des
4.6.6. Injections	Rationale for use and treatment protocol	Des
5. Acupuncture and massage		
5.1. Techniques	Acupuncture techniques	Des
5.2. Special approaches	Non-mainstream treatment approaches	Des
5.3. Treatment regimen	Number of sessions and duration of the therapeutic course	Des
5.4. Point selection rationale	Rationale for point selection and related points	Des
5.5. Massage	Treatment protocols	Des
5.6. Scalp acupuncture	Treatment protocols	Des
5.7. Ear acupuncture	Treatment protocols	Des
5.8. Hand and foot acupuncture	Treatment protocols	Des
5.9. Cupping and Guasha	Treatment protocols	Des
5.10. Bloodletting	Treatment protocols	Des
5.11. Moxibustion	Treatment protocols	Des
5.12. Plaster	Treatment protocols	Des
5.13. Buried wire	Treatment protocols	Des
5.14. Plum flower acupuncture	Treatment protocols	Des
6. Additional treatments		
6.1. Psychotherapy	Categories and treatment protocol	Des
6.2. Qigong	Treatment protocol	Des
6.3. Music therapy	Treatment protocol	Des
7. Self-treatment		
7.2. Lifestyle recommendations	Recommendations	Des
7.3. Sleep hygiene	Recommendations	Des
7.4. Food therapy	General and specific recommendations	Des
7.5. Exercise	Recommendations	Des
7.6. Acupressure	Recommendations	Des
8. Combination with other therapies		
8.1. Principles	Principles of combining Chinese medicine with other treatments	Des
8.2. Application	Treatment protocols	Des

Table 8.1. Codes description and type of analysis

Participant Initials			

Participant ID			

8.2.9. Rigor

The rigor of this systematic review, which is qualitative in nature, was enhanced by disclosing the authors' background and perspective about the topic, describing the analysis process in detail (including the decision-making process), using quotes from the source, using analyst triangulation, and with an audit conducted by the main supervisor (XZ).

Participant Initials				Participant ID			

Chapter 9. Results

The content of this chapter was presented as a workshop organised by Chinese Medicine Education the 18th April at the Sydney Institute of Traditional Chinese Medicine. It will be published as a book by the publishing house Singing Dragon.

Section	Page	Content
9.1. Generalities		Reports flowchart and overview of the diagnostic and therapeutic process for insomnia
9.2. Pattern approach		Typical and atypical patterns of insomnia with associated signs and symptoms and individual herbs.
9.3. Disease approach		Treatment protocols based on the disease.
9.4. Treatment according to the three factors		Modification of the treatment according to the patient, the location and the climate.
9.5. Treatment according to disease characteristics		Diagnostic considerations related with the type of insomnia.
9.6. Spirit-calming herbs		Clinical use of spirit-calming herbs.
9.7. General considerations		General considerations regarding the use of herbs for insomnia.
9.8. Preparation, intake methods and treatment regimen		Preparation, intake methods and treatment regimen.
9.9. Other herbal treatments		Herbal treatment modalities except decoctions and granules.
9.10. Psychological interventions		Psychological aspects of a Chinese medicine consultation for insomnia
9.11. Recommendations and self-treatment		Recommendations to insomnia patients and self-treatment protocols.
9.12. Integrative Chinese medicine		Integration of Chinese herbal medicine with Western medicine and psychotherapy.

Table 9.1. Overview of the results of the clinical experience synthesis

9.1. Generalities

9.1.1. Included studies

Participant Initials				Participant ID			

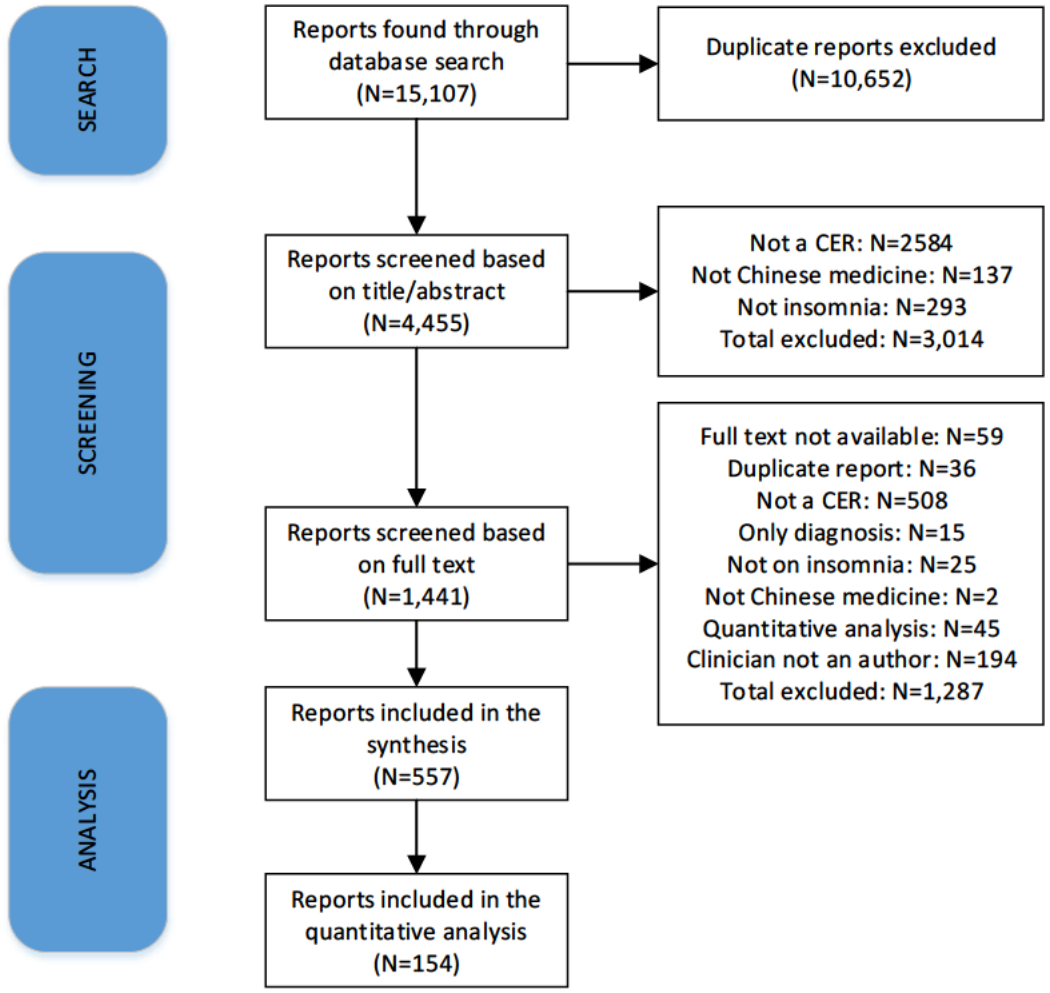

Figure 9.1. Clinical Experience Report (CER) flow chart

9.1.2. General considerations in the treatment of insomnia

The two main models used by the clinicians are the pattern-differentiation model and the disease-differentiation model. In the former, the diagnosis is based on patterns of signs and symptoms and a specific treatment is given for each pattern. In the latter, one single formula is used in every case of insomnia. In both cases, the treatment can be modified according to specific signs and symptoms and other considerations such as the age, comorbidities, and constitution of the patient.

The pattern-differentiation model is preferred by clinicians who use herbal medicine (58%) whereas the disease-differentiation model is preferred by clinicians who use acupuncture (80%) and massage (80%). Most clinicians use either one model or another, however the two models can be used simultaneously. For example, one clinician uses a disease approach with herbs that regulate the *yinyang* and calm the spirit when there is not enough evidence for pattern differentiation. Another

clinician uses generally a disease approach but changes to a pattern-specific treatment in case of blood stasis or food stagnation. The modification of the main formula in the disease approach according to the pattern is common and sometimes a disease-based treatment is added to the pattern-based formula. In the latter case, the purpose of the added disease-based treatment is generally to calm the spirit and sometimes to improve *qi* circulation.

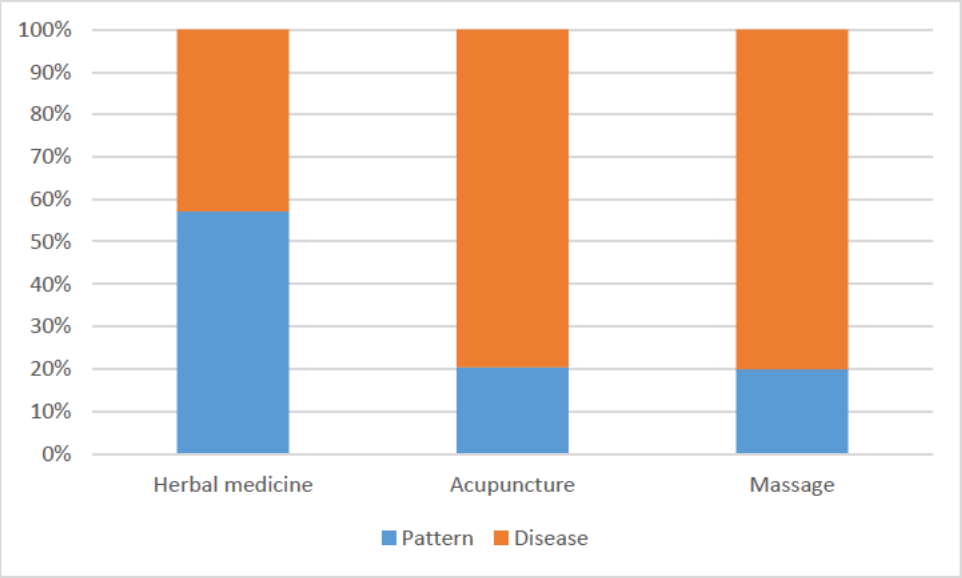

Figure 9.2. Percentages of therapeutic models used according to the treatment modality

Some clinicians propose a stepped-care approach. This means that different therapeutic approaches can be used depending on the severity of the condition. In one 4-step model, cognitive-behavioural therapy is proposed as the first step, then non-pharmacological Chinese medicine methods such as acupuncture and massage are used as the second step, Chinese herbal medicine is used as the third step, and finally Western medicine used as the fourth step (1). Another clinician proposes a therapeutic course composed of acupuncture needling first, then moxibustion, fire needles or bloodletting according to the condition of the patient, and ear acupuncture or buried needle at the end of the treatment (1).

In case of absence of treatment response, three approaches can be used in addition to a re-assessment followed by an appropriate treatment. These approaches are used regardless of the signs and symptoms of the patient. The first approach is the treatment of blood stasis with Xue Fu Zhu Yu Tang

(4). The second approach is the treatment of yang deficiency with warm-tonifying herbs such as *huangqi*, *yinyanghuo*, *guizhi*, *fuzi* and *ganjiang* and oppressing-immersing herbs such as *wuweizi*, *cishi*, *longgu*, *muli* or *guijia* (3). This approach is used especially when *yin*-nurturing and spirit-calming methods are ineffective (2) and can be used only when there is no significant sign of *yang*-heat (1). The third approach is the treatment of phlegm with Wen Dan Tang (1).

9.1.3. Chinese medicine diagnostic model of insomnia

The two basic diagnostic approaches in Chinese medicine are the pattern approach and the disease approach.

In the pattern approach, the diagnosis is based mainly on the signs and symptoms (SSs) of the patient. The seven typical patterns and five atypical patterns of insomnia can be observed across various conditions, yet the SSs and associated treatments of these patterns is influenced by the disease diagnosis (i.e., insomnia). The cause of the disease (e.g., excessive emotions), the sociodemographic characteristics of the patient (e.g., gender, age), the constitution of the patient (e.g., *yin* deficiency constitution), the personality of the patient (e.g., introverted), the comorbidities of the patient (e.g, hypercholesterolemia) and the location (e.g., humid location or large city with high stress levels) are also taken into account to identify the pattern diagnosis.

The primary disease diagnosis (i.e, insomnia) provides a framework to understand insomnia patients. The core feature of insomnia is a disturbed *shen* (i.e. spirit) and its primary pathological mechanism is liver qi stagnation. The secondary pathological mechanisms of insomnia are liver/heart fire, blood-yin deficiency and phlegm. The secondary disease diagnosis (i.e., comorbidities) provide important information to understand the context of the disease. It can provide an explanation for insomnia (in which case the treatment should target the comorbidity), provide guidance to understand the pattern (i.e. pathological mechanism) and can suggest a complex treatment plan that addresses both insomnia and the comorbidity.

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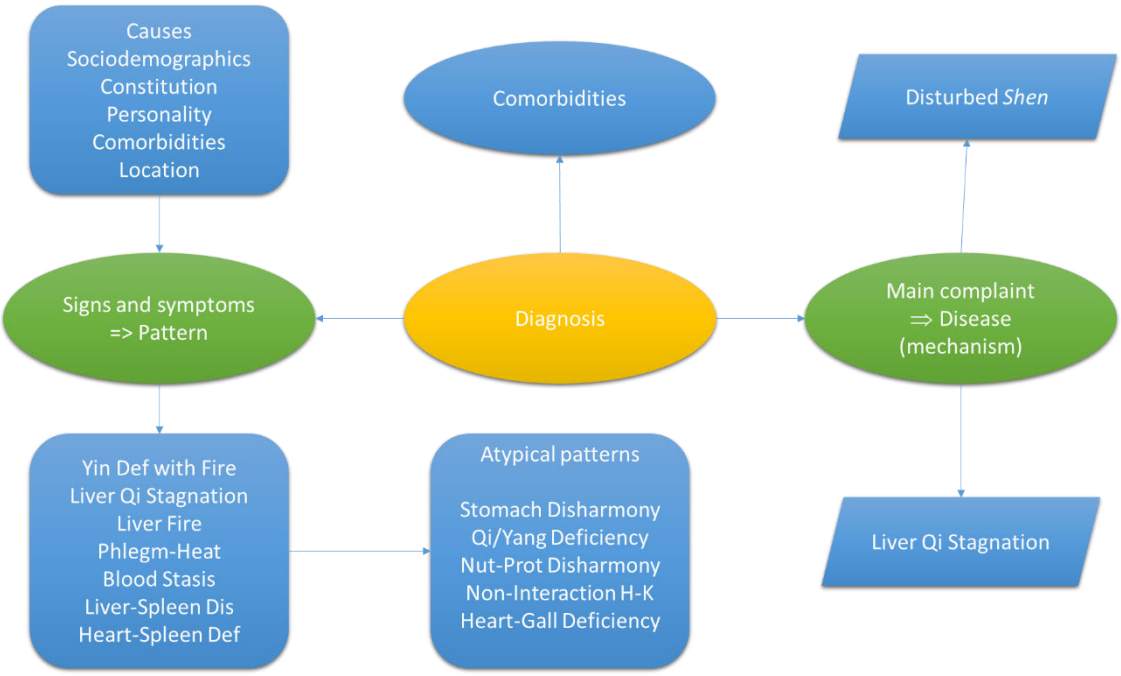

Figure 9.3. Main diagnostic approaches in the treatment of insomnia with Chinese medicine

9.1.4. Chinese medicine treatment model of insomnia

The three basic treatment modalities for the treatment of insomnia with Chinese medicine are Chinese herbal medicine, acupuncture and massage.

For acupuncture and massage, the points (zones) and techniques are mainly selected on the basis of the disease. The treatment aims at regulating *yinyang* (excess of *yang* and lack of *yin* are one of the core mechanism of insomnia), regulating qi movements (liver *qi* stagnation is the primary mechanism of insomnia) and regulate brain-spirit (the brain-spirit controls sleep). The treatment can also be based on or adapted according to the pattern of the patient.

The clinical reasoning for CHM is more complex. The treatment is generally based on the pattern diagnosis, which includes seven typical patterns and five atypical patterns. The treatment is then modified according to secondary patterns and symptoms. Some clinicians prefer a disease-based treatment which targets can target the core feature of insomnia (i.e., disturbed *shen*), the primary mechanism of insomnia (i.e., liver *qi* stagnation), the global mechanism of insomnia with either a narrow approach (i.e., Suan Zao Ren Tang) or a large approach (big and varied formulas), or be based on the clinician's individual understanding of insomnia's pathology. The main formula can then be

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modified according to the pattern of the patient. In both the pattern and the disease approach, the clinician should consider the season, the geographic location, the constitution of the patient, the comorbidities of the patient, the demographic characteristics of the patient, and the protection of the spleen-stomach and the yin, and modify the formula accordingly. Beside the formula itself, the clinician should also choose a modality (i.e., decoction, paste, infusion) and preparation and intake methods that are appropriate for the patient.

Besides the "core" treatment with herbs, acupuncture and/or massage, the clinician should give pattern-based and disease-based recommendations to the patient and can provide self-treatment methods. The psychological aspect of the consultation and various psychological interventions have to be considered as well. Finally, the clinician should consider the need of integrating the Chinese medicine treatment with Western medicine and psychotherapy.

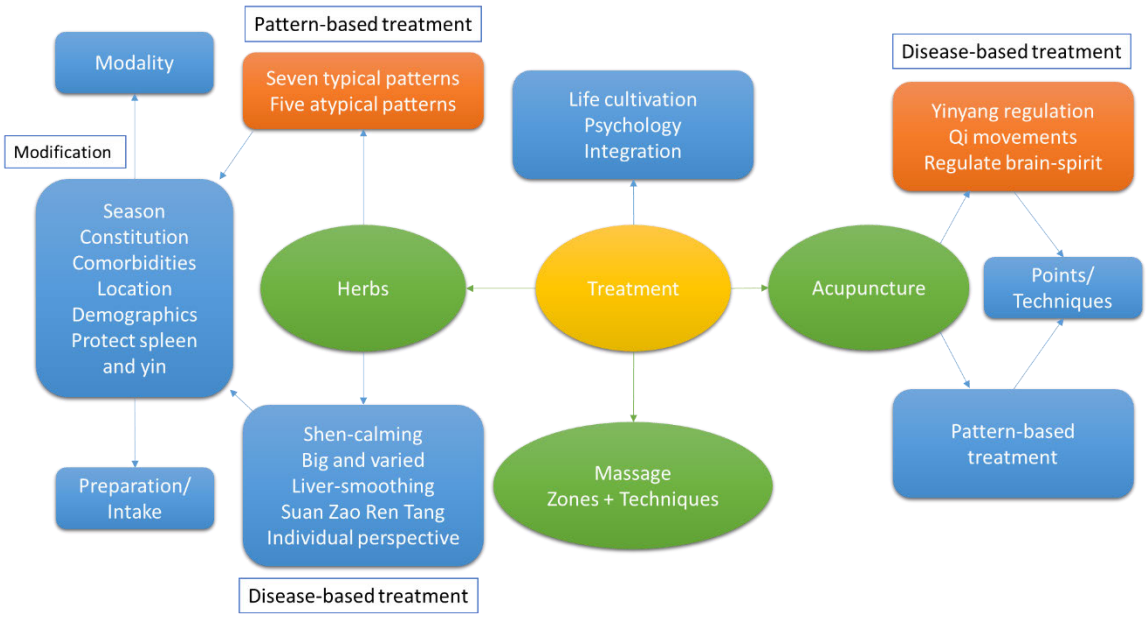

Figure 9.4. Important considerations in the clinical reasoning for the treatment of insomnia with Chinese medicine

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9.2. Pattern approach

9.2.1. Overview

For the synthesis of the causes and mechanisms leading to insomnia according to the clinicians, removing the causes and mechanisms cited less than six times allowed for a relatively clear flowchart (Figure 9.3). Height different mechanisms were finally maintained, including blood stasis, liver stagnation, phlegm-heat, liver blood deficiency, liver fire, spleen deficiency, heart-spleen deficiency, kidney *yin* deficiency and heart fire. The primary causes of insomnia were synthesised as emotions, excessive thinking, excessive diet, alcohol intake, constitution, overstrain, severe or long-term diseases, aging and excessive sexual life. The most extensively cited cause is “emotions”, with 122 citations, and the most extensively cited mechanism is “liver stagnation”, with 114 citations. Some causes were proposed to induce different patterns, for example emotions causing either liver stagnation, liver blood deficiency, liver fire or heart fire. Complex relationships between causes and mechanisms or between two mechanisms were identified. Liver stagnation is the mechanism with the most consequences, i.e. blood stasis, phlegm-heat, liver blood deficiency, liver fire and spleen deficiency. Kidney yin deficiency is the mechanism with the most primary causes, i.e. constitution, severe or long-term disease, aging, excessive sexual life and overstrain. Phlegm-heat and liver blood deficiency are the mechanisms with the most secondary causes (i.e. mechanism as a cause), including liver stagnation, liver fire and spleen deficiency for both.

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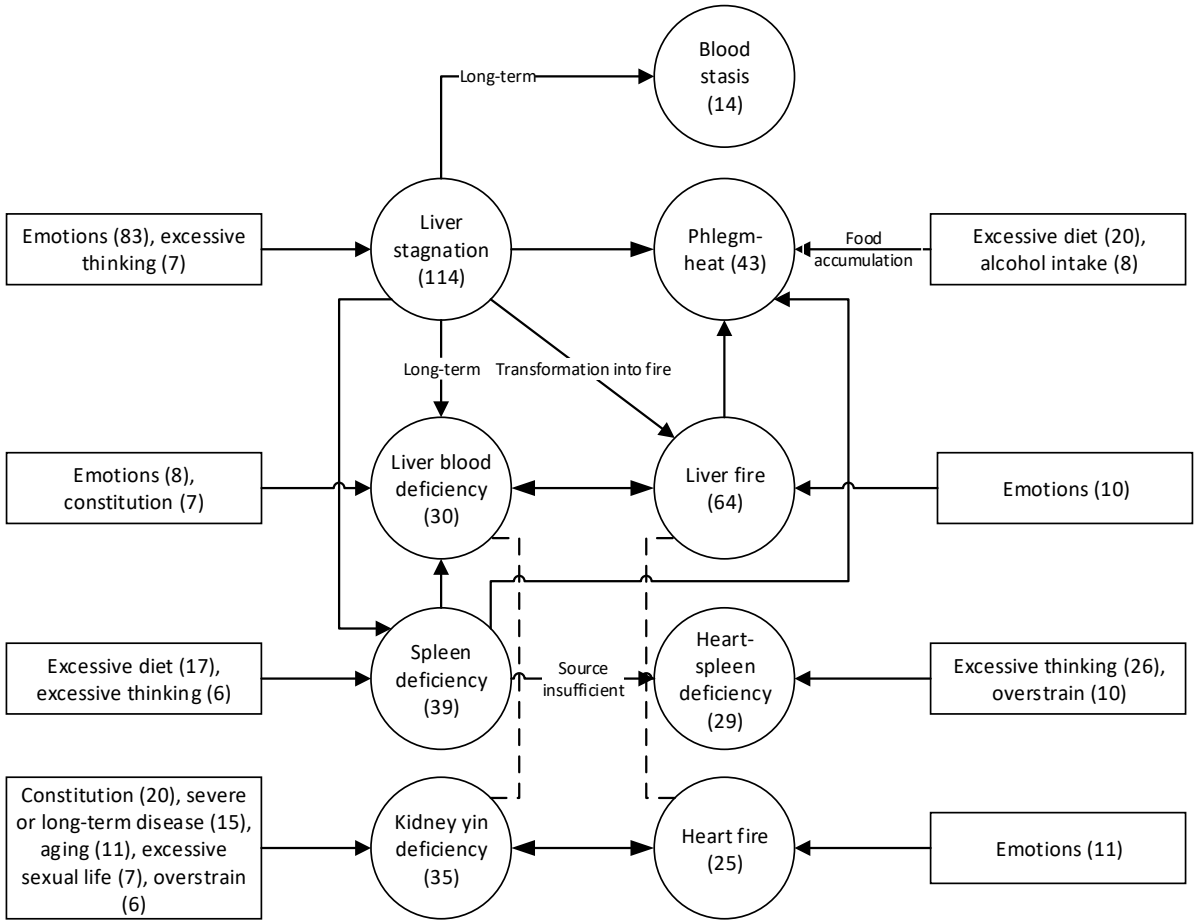

Figure 9.5. Flowchart of the causes and mechanisms leading to insomnia described by the authors in the context of Chinese herbal medicine treatment with a pattern approach. Causes are presented in rectangles and mechanisms are presented in squares. Arrows show a causality relationship and dot lines show a proximity between two mechanisms. The text inlaid on the arrow represent additional descriptions of the causality relationship by the author. Causes have been placed on both side of the flowchart to allow a better readability of the chart.

For the clustering of formulae, the cluster analysis was conducted for seven clusters with a limit distance to the cluster mean of 2.8 and a minimum of seven cases for each cluster. Among the initial 498 formulae, 388 were finally clustered into seven clusters. These clusters were identified as seven patterns and labelled as “Yin Deficiency with Effulgent Fire”, “Liver-Spleen Disharmony”, “Phlegm-Heat”, “Heart and Spleen Deficiency”, “Liver Fire”, “Liver Stagnation” and “Blood Stasis” (Table 9.1). The difference between this categorisation and the other categorisations that were pre-selected is the number of clusters related to “Yin Deficiency with Effulgent Fire”, ranging from one to four (labelled “Non-Communication Between Heart and Kidney”, “Heart Blood Deficiency”, “Liver Blood Deficiency” and “Kidney Deficiency”) depending on the number of clusters set for the analysis, and

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the formulae included in the "Liver-Spleen Disharmony" pattern, which included Huang Lian E Jiao Tang and Zhu Sha An Shen Wan in some categorisations.

Cluster ID	Label	Abbreviation	Most common formula	Number of formulas
1	"Yin Deficiency with Effulgent Fire"	Yin-Def-Fire	Suan Zao Ren Tang	122
2	"Liver-Spleen Disharmony"	L-S Dis	Chai Hu Jia Long Gu Mu Li Tang	45
3	"Phlegm-Heat"	Phlegm-Heat	Wen Dan Tang	75
4	"Heart and Spleen Deficiency"	H-S Def	Gui Pi Tang	45
5	"Liver Fire"	Liver Fire	Long Dan Xie Gan Tang	20
6	"Liver Stagnation"	Liver Stag	Dan Zhi Xiao Yao San	55
7	"Blood Stasis"	Blood Stasis	Xue Fu Zhu Yu Tang	26

Table 9.2. Seven patterns identified through cluster analysis

Among the 438 formulae for which the name of the formula was expressed by the author, 189 different formulae were cited (Figure 9.4). The most commonly cited formulae were Gui Pi Tang (30), Suan Zao Ren Tang (22), Wen Dan Tang (21), Xue Fu Zhu Yu Tang (21), Huang Lian Wen Dan Tang (20), Huang Lian E Jiao Tang (19), Dan Zhi Xiao Yao San (18), Long Dan Xie Gan Tang (16), Chai Hu Shu Gan San (13) and Chai Hu Jia Long Gu Mu Li Tang (10). The ten most cited formulae accounted for 43% of all the formulae.

Participant Initials				Participant ID			

Figure 9.6. Word cloud of the formulae names expressed by the authors. The size of the words is determined by the number of reports that cited the formula. The colour was determined by the pattern the formula belongs to. Blue = Yin-Def-Fire, purple = L-S Dis, orange = Phlegm-Heat, yellow = H-S Def, red = Liver Fire, green = Liver Stag, brown = Blood Stasis. Formulae that were removed during the cluster analysis are shown in black.

The pattern signature of the different patterns and of the 388 formulae included in the cluster analysis (labelled as “general”) are represented on Figure 9.5. The herb categories purging, wind-dampness removing, dampness-transforming, food-transforming, blood-stopping, orifice-opening, *yang*-tonifying, and collecting and consolidating herbs were not included in the plot as they did not achieve at least 5% ratio in any pattern.

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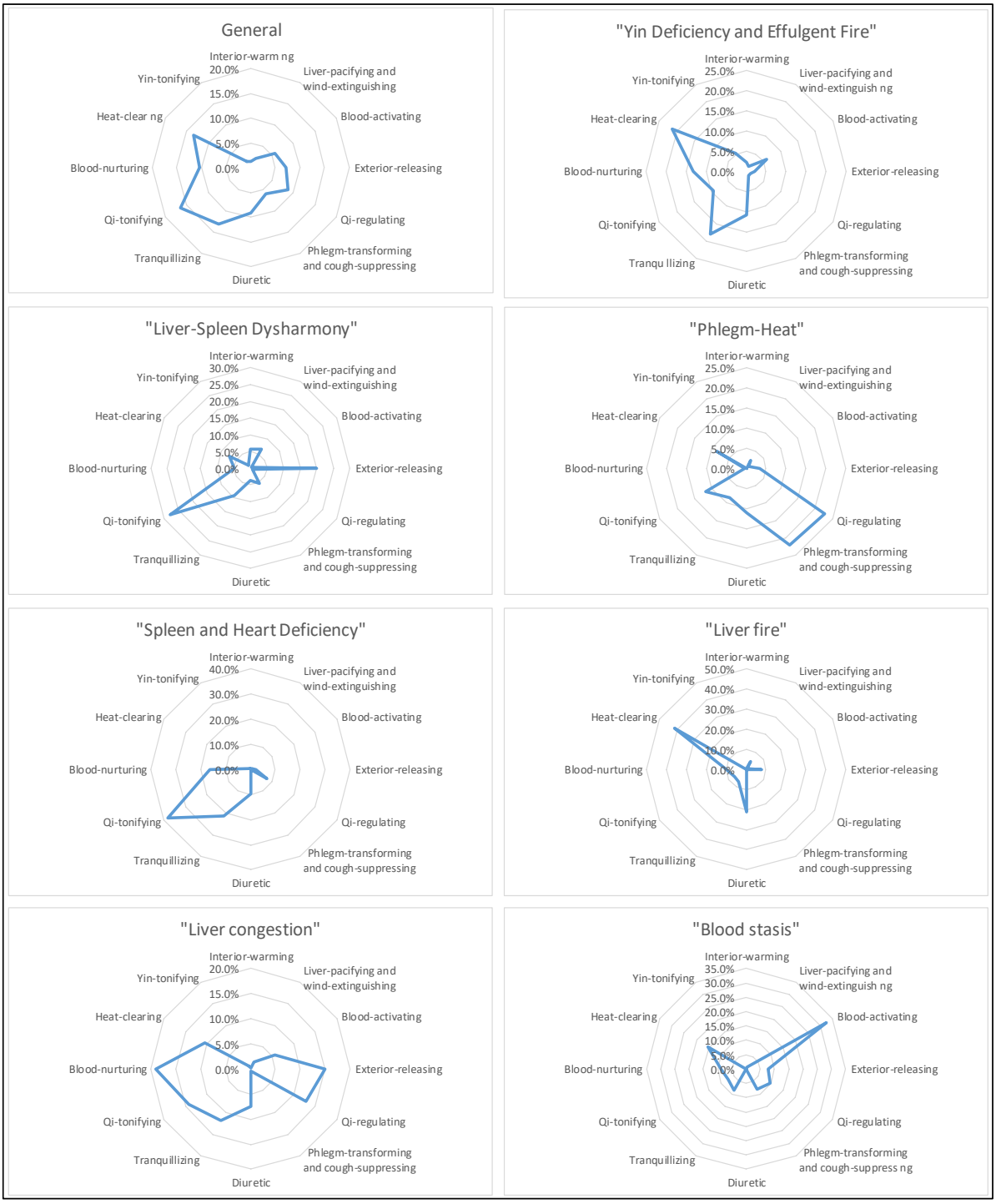

Figure 9.7. Radar plot of the ratio of each herb category in every pattern and in the formulae included in general.

The key signs and symptoms allowing for pattern differentiation are presented in figure X. The model has a risk of 0.446 (±0.25). It was able to predict the patterns with an overall correct prediction rate of 55.4%. The correct prediction rate is 82.0% for “Yin Deficiency with Effulgent Fire”, 0.0% for

"Liver-Spleen Disharmony", 57.3% for "Phlegm-Heat", 46.7% for "Spleen and Heart Deficiency", 65.0% for "Liver Fire", 38.2% for "Liver Stagnation" and 65.4% for "Blood Stasis". This decision tree is based on 304 patterns for which at least one sign or symptom was described.

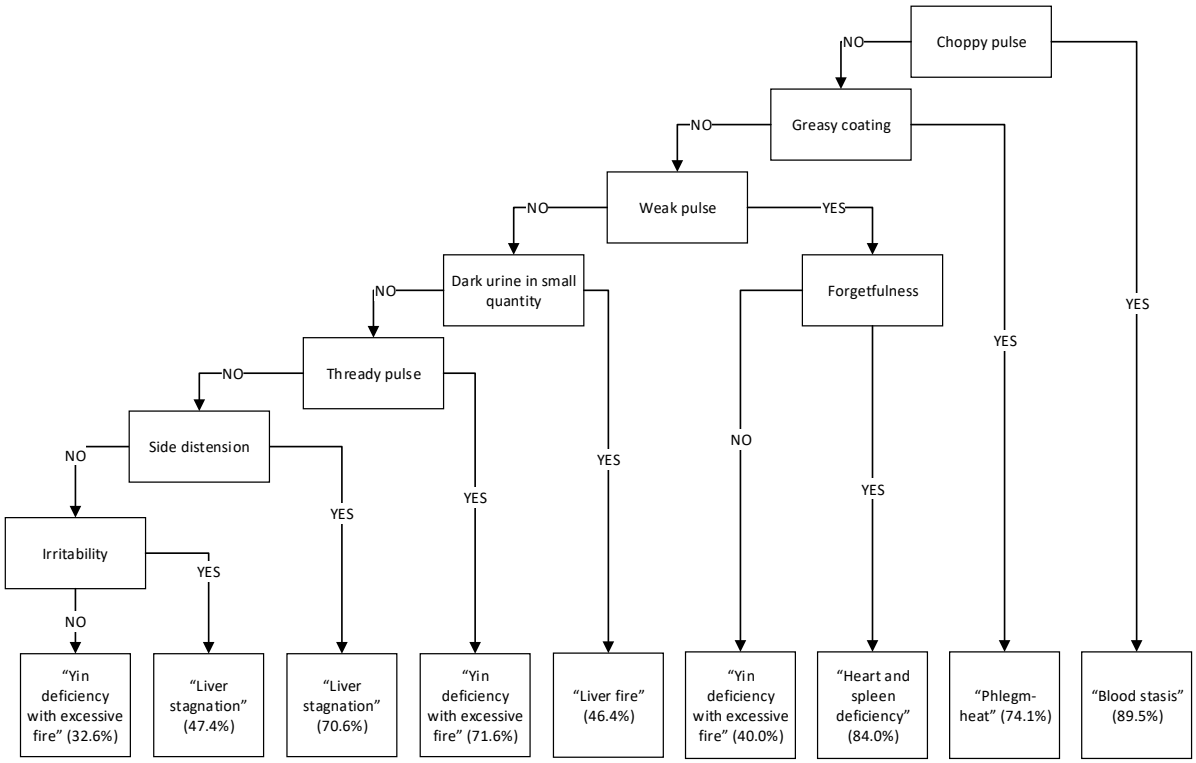

Figure 9.8. Decision tree of the signs and symptoms allowing for differentiation of patterns. The percentage of cases belonging to the pattern are shown in brackets.

Besides the seven patterns described above, we identified four "atypical" patterns through thematic analysis. These atypical patterns cannot be identified with the formula composition as they do not represent one single direction but rather a higher conceptual level. Therefore, the formulae of one atypical pattern can be separated in several "typical" patterns. The four atypical patterns are "Non-Interaction between Heart and Kidney", "Qi and Yang Deficiency", "Stomach Disharmony" and "Disharmony between Nutritive and Protective".

9.2.2. Yin Deficiency with Effulgent Fire

This pattern is commonly observed in older adults (4), white collar workers (2). This pattern is also associated with persistent insomnia (2).

Participant Initials				Participant ID			

The SSs indicating Yin-Def-Fire are represented in Figure 9.7. In this cluster, for the formulae for which associated SSs were reported, the average number of SSs is ten. The ten SSs with the highest sensitivity are agitation (63%, 40%), fine pulse (59%, 51%), palpitations (39%, 42%), red tongue (36%, 35%), wiry pulse (35%, 30%), rapid pulse (33%, 33%), pale tongue (32%, 36%), frequent dreams (31%, 27%), dry mouth (25%, 48%) and fatigue (25%, 31%). Five SSs had a 100% specificity level and were cited at least two times, respectively hot flushes (6%, 100%), blurred vision (4%, 100%), pale nails (3%, 100%), faint pulse (2%, 100%) and dull nails (2%, 100%).

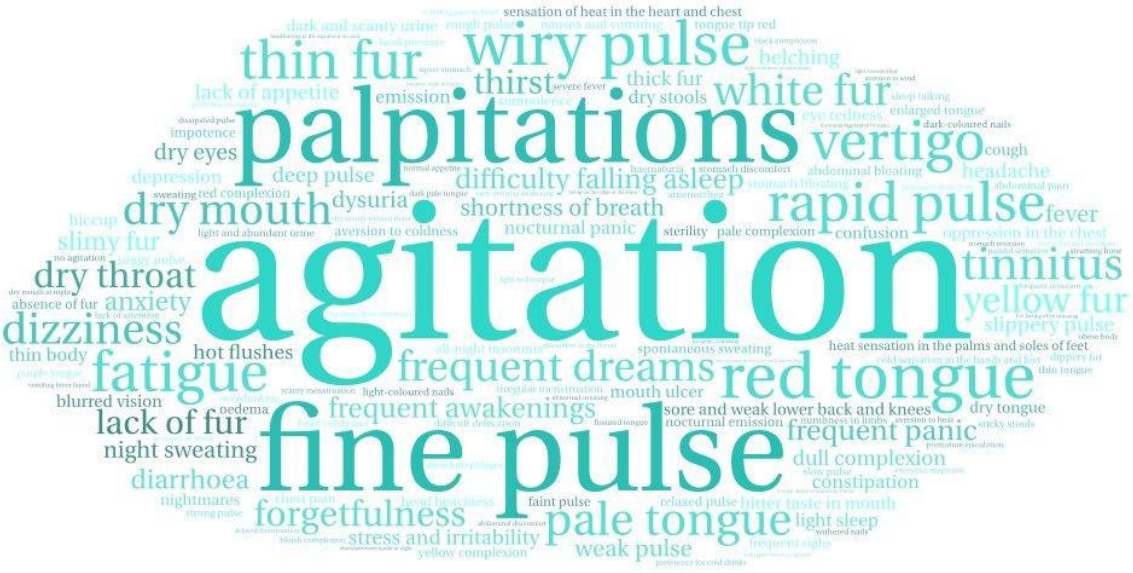

Figure 9.9. Signs and symptoms associated with the Yin-Def-Fire pattern. The font is darker for SSs with a high specificity level and bigger for SSs with a high sensitivity level.

The herbs used for Yin-Def-Fire are represented in Figure 9.8. The formulae of this cluster include on average seven herbs. The seven herbs with the highest sensitivity are reported in the Table 9.2.

Participant Initials			

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Figure 9.10. Herbs used for the Yin-Def-Fire pattern. The font is darker for herbs with a high specificity level and bigger for herbs with a high sensitivity level.

9.2.3. Liver-Spleen Disharmony

The populations associated with this pattern are women (2), young people (2). L-S Dis is also associated with psychological (3) and physical (2) comorbidities, and acute-onset insomnia (2).

The SSs indicating L-S Dis are shown in Figure 9.9. In this cluster, for the formulae for which associated SSs were reported, the average number of SSs is twelve. These twelve SSs are agitation (40%, 8%), fine pulse (37%, 10%), pale tongue (33%, 11%), wiry pulse (33%, 9%), lack of appetite (33%, 11%), yellow fur (30%, 11%), fatigue (30%, 11%), red tongue (27%, 8%), rapid pulse (27%, 8%), frequent dreams (27%, 7%), constipation (23%, 19%) and depression (23%, 18%).Five SSs had a 100% specificity level and were cited at least two times, respectively preference for hot drinks (13%, 100%), delirious speech (13%, 100%), deficient pulse (10%, 100%), mania (10%, 100%) and throat pain (7%, 100%).

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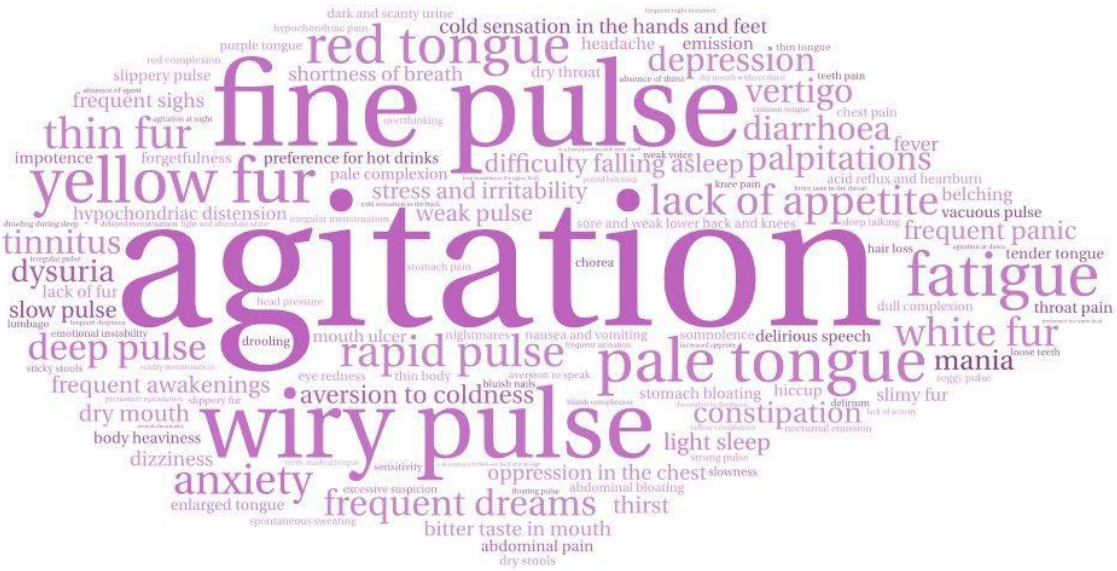

Figure 9.11. Signs and symptoms associated with the L-S Dis pattern. The font is darker for SSs with a high specificity level and bigger for SSs with a high sensitivity level.

The herbs used by the clinician for L-S Dis are shown in Figure 9.10. The formulae of this cluster include on average eight herbs. The eight herbs with the highest sensitivity are reported in the Table 9.5. One herb, i.e. *chaihu*, had the same sensitivity level as *banxia* (40%), but a lower specificity (18%) and was therefore not included in the table.

Figure 9.12. Herbs used for the L-S Dis pattern. The font is darker for herbs with a high specificity level and bigger for herbs with a high sensitivity level.

Participant Initials				Participant ID			

9.2.4. Phlegm-Heat

The populations associated with Phlegm-Heat are obese people (3) and older adults (2). Common comorbidities are hyperlipidaemia (2), hyperviscosity syndrome (2) and depression (3).

The SSs indicating Phlegm-Heat are shown in Figure 9.11. In this cluster, for the formulae for which associated SSs were reported, the average number of SSs is twelve. The most commonly reported signs are slimy fur (74%, 74%), slippery pulse (69%, 65%), oppression in the chest (64%, 42%), agitation (62%, 23%), yellow fur (55%, 39%), nausea and vomiting (52%, 77%), rapid pulse (52%, 30%), red tongue (50%, 28%), bitter taste in mouth (48%, 41%), head heaviness (38%, 88%), belching (36%, 58%) and abundant phlegm (33%, 95%). Only two SSs have both a 100% specificity level and cited at least for two formulae. These SSs are aversion to food (9%, 100%) and sticky sensation in mouth (9%, 100%).

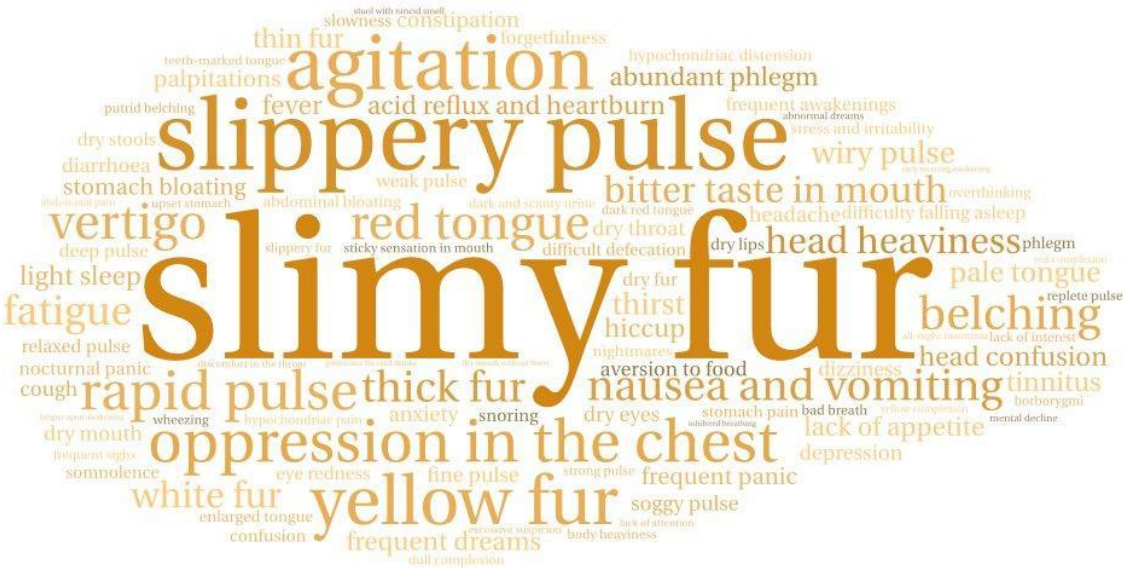

Figure 9.13. Signs and symptoms associated with the Phlegm-Heat pattern. The font is darker for SSs with a high specificity level and bigger for SSs with a high sensitivity level.

The herbs used for Phlegm-Heat are shown in Figure 9.12. The formulae of this cluster include on average nine herbs. The nine herbs with the highest sensitivity are reported in the Table 9.7.

Participant Initials			

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Figure 9.14. Herbs used for the Phlegm-Heat pattern. The font is darker for herbs with a high specificity level and bigger for herbs with a high sensitivity level.

9.2.5. Heart-Spleen Deficiency

H-S Def is commonly seen in women (2), older adults (2), patients with a weak constitution (2) and thoughtful people (2).

The SSs indicating H-S Def are shown in Figure 9.13. In this cluster, for the formulae for which associated SSs were reported, the average number of SSs is twelve. The twelve most commonly reported SSs are fatigue (94%, 42%), palpitations (92%, 36%), pale tongue (83%, 34%), fine pulse (81%, 25%), weak pulse (75%, 60%), forgetfulness (72%, 49%), lack of appetite (72%, 29%), frequent dreams (69%, 22%), thin fur (64%, 36%), dull complexion (61%, 51%), frequent awakenings (56%, 34%) and white fur (47%, 27%). Stomach bloating after eating (6%, 100%) was the only symptom with both a 100% specificity level and cited least two times.

Participant Initials			

Participant ID			

Figure 9.15. Signs and symptoms associated with the H-S Def pattern. The font is darker for SSs with a high specificity level and bigger for SSs with a high sensitivity level.

The formulae of this cluster include on average eleven herbs. The eleven herbs with the highest sensitivity are reported in the Table 9.9.

Figure 9.16. Herbs used for the H-S Def pattern. The font is darker for herbs with a high specificity level and bigger for herbs with a high sensitivity level.

9.2.6. Liver Fire

No associated population or characteristic of the "Liver Fire" pattern has been able to reach the threshold of two citations.

The SSs indicating Liver Fire are shown in Figure 9.15. In this cluster, for the formulae for which associated SSs were reported, the average number of SSs is thirteen. The thirteen SSs with the highest sensitivity are bitter taste in mouth (82%, 20%), dark and scanty urine (77%, 42%), stress and irritability (77%, 21%), rapid pulse (77%, 13%), eye redness (71%, 38%), yellow fur (71%, 15%), red tongue (65%, 11%), wiry pulse (65%, 10%), agitation (65%, 7%), constipation (47%, 22%), dry mouth (47%, 15%), frequent dreams (47%, 7%), all-night insomnia (41%, 25%). Two SSs had the same sensitivity level as the thirteenth symptom but a lower specificity level, i.e., tinnitus (41%, 20%) and dizziness (41%, 18%). No SS had both a 100% specificity level and was cited two times at least.

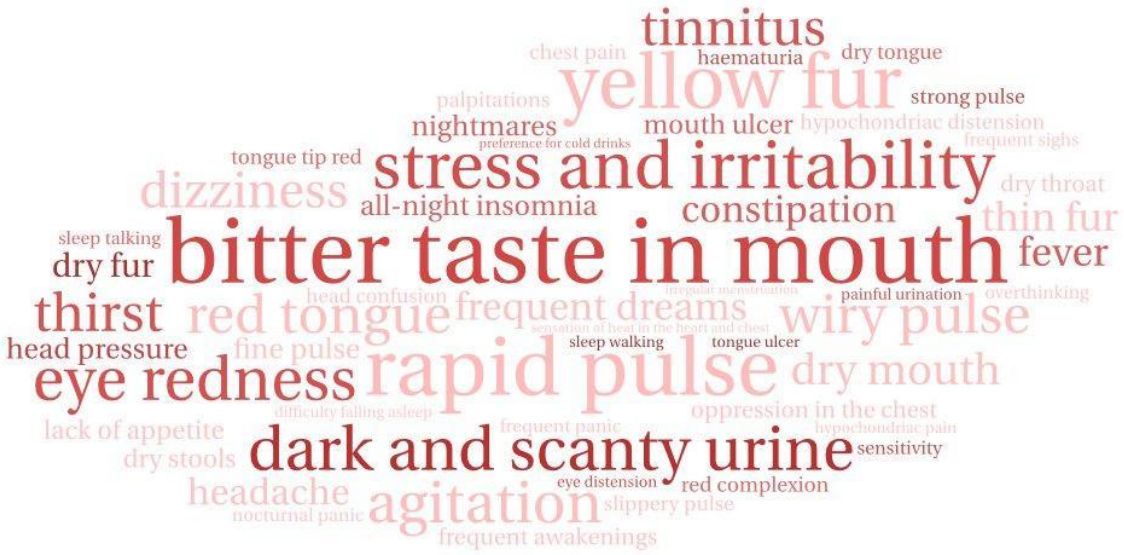

Figure 9.17. Signs and symptoms associated with the Liver Fire pattern. The font is darker for SSs with a high specificity level and bigger for SSs with a high sensitivity level.

The herbs used for Liver Fire are shown in Figure 9.16. The formulae of this cluster include on average ten herbs. The ten herbs with the highest sensitivity are reported in the Table 9.11.

Participant Initials				Participant ID			

Figure 9.18. Herbs used for the Liver Fire pattern. The font is darker for herbs with a high specificity level and bigger for herbs with a high sensitivity level.

9.2.7. Liver Stagnation

The populations associated with Liver Stag are young people (3), females (3), middle-aged people (2), white collar (2). This pattern is also associated with depression (2).

The SSs indicating Liver Stag are shown in Figure 9.17. In this cluster, for the formulae for which associated SSs were reported, the average number of SSs is thirteen. The thirteen SSs with the highest sensitivity are wiry pulse (77%, 28%), stress and irritability (56%, 38%), hypochondriac distension (51%, 52%), lack of appetite (51%, 25%), oppression in the chest (46%, 23%), agitation (46%, 13%), frequent dreams (42%, 16%), hypochondriac pain (40%, 59%), depression (40%, 45%), yellow fur (40%, 21%), red tongue (40%, 17%), bitter taste in mouth (33%, 20%) and frequent sighs (30%, 54%). Three SSs had a sensitivity level equal to the thirteenth symptom with a lower specificity level, i.e., dry mouth (30%, 25%), difficulty falling asleep (30%, 19%) and rapid pulse (30%, 13%). Nine SSs qualified as high-specificity SSs, i.e., speaking less (9%, 100%), pain in the body (7%, 100%), electric sensation (7%, 100%), oppressive pain in the back, chest and abdomen (7%, 100%), running pain in the back, chest and abdomen (7%, 100%), stabbing pain in the back, chest and abdomen (7%,

100%), emotion-triggered symptoms (7%, 100%), distension and pain in the breast (5%, 100%) and hypochondriac running pain (5%, 100%).

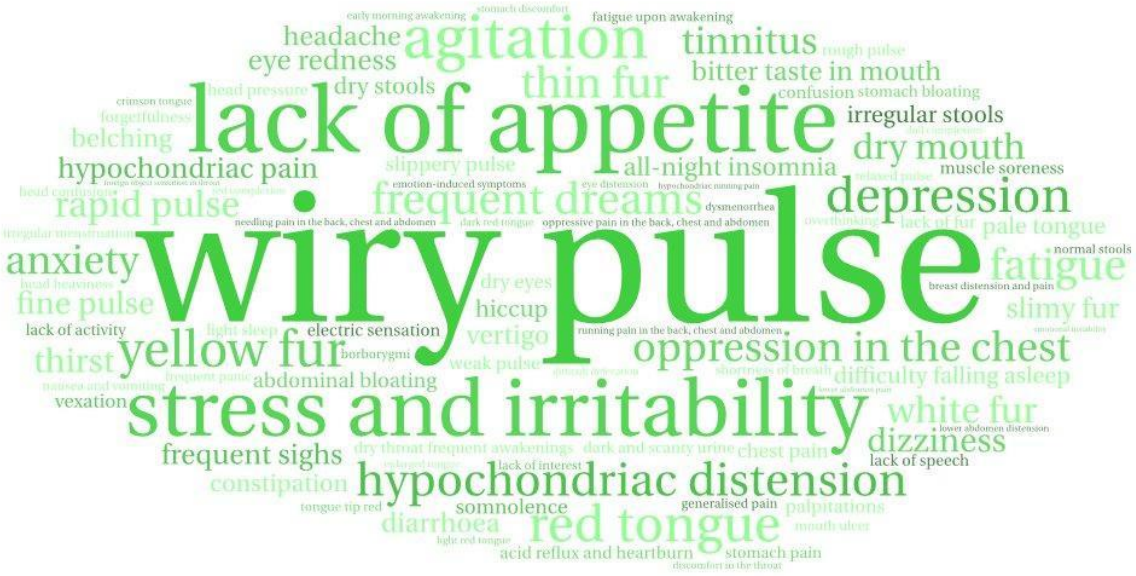

Figure 9.19. Signs and symptoms associated with the Liver Stag pattern. The font is darker for SSs with a high specificity level and bigger for SSs with a high sensitivity level.

The herbs used to treat Liver Stag are shown in Figure 9.18. The formulae of this cluster include on average nine herbs. The nine herbs with the highest sensitivity are reported in the Table 9.13.

Figure 9.20. Herbs used for the Liver Stag pattern. The font is darker for herbs with a high specificity level and bigger for herbs with a high sensitivity level.

9.2.8. Blood Stasis

Blood Stasis pattern is associated with long-term insomnia (4) and treatment-resistant insomnia (4).

The SSs indicating Blood Stasis pattern are shown in Figure 9.19. In this cluster, for the formulae for which associated SSs were reported, the average number of SSs is eleven. The eleven SSs with the highest sensitivity are rough pulse (81%, 90%), purple tongue (71%, 83%), wiry pulse (62%, 11%), agitation (62%, 8%), petechiae on the tongue (48%, 91%), headaches (38%, 35%), oppression in the chest (38%, 9%), frequent dreams (38%, 7%), difficulty falling asleep (33%, 10%), chest pain (29%, 50%) and irregular period (29%, 46%). Two SSs, i.e. hypochondriac pain (29%, 21%) and hypochondriac distension (29%, 14%), had a sensitivity level equal to the last symptom but a lower specificity level. Seven SSs qualified for high-specificity SSs, i.e. tight pulse (10%, 100%), stabbing pain in chest (10%, 100%), hypochondriac stabbing pain (10%, 100%), absence of sleepiness (10%, 100%), suffering (10%, 100%), purple lips (10%, 100%) and cracked skin (10%, 100%).

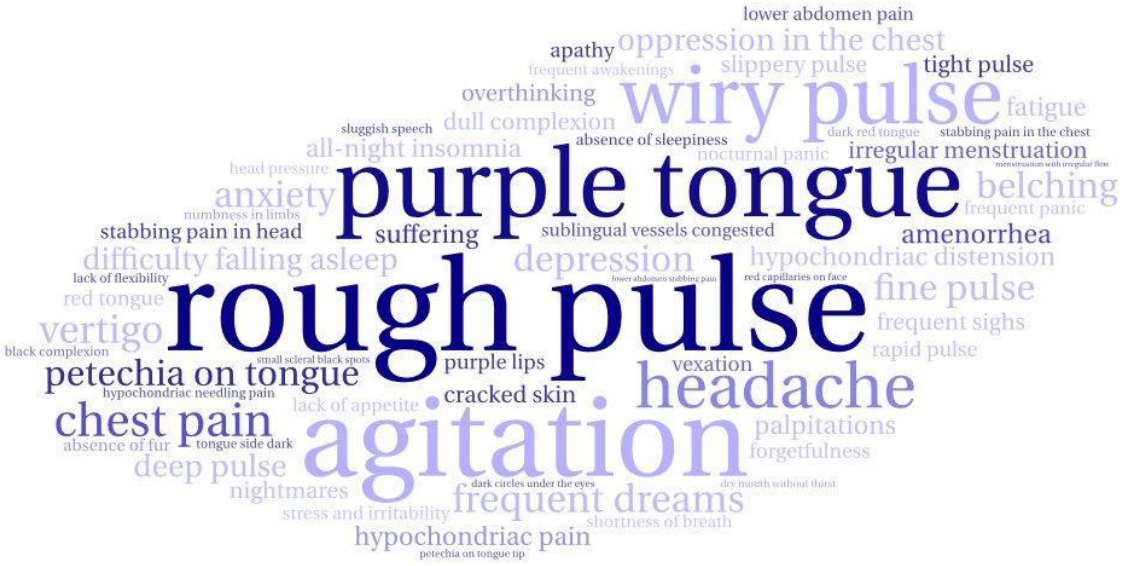

Figure 9.21. Signs and symptoms associated with the Blood Stasis pattern. The font is darker for SSs with a high specificity level and bigger for SSs with a high sensitivity level.

Participant Initials				Participant ID			

The formulae of this cluster include on average twelve herbs. The twelve herbs with the highest sensitivity are reported in the Table 9.15.

Figure 9.22. Herbs used for the Blood Stasis pattern. The font is darker for herbs with a high specificity level and bigger for herbs with a high sensitivity level.

9.2.9. Non-Interaction between Heart and Kidney

Chinese medicine focuses on the balance of different energies in the body. The heart is located in the upper burner, at the top of the body, and is associated with the element (or movement) fire. The kidney is located in the lower burner, at the bottom of the body, and is associated with the element (or movement) water. In order to keep a balance within the body, the water of the kidney has to go upward and connect with the heart, keeping its fire controlled; the fire of the heart has to go downward and connect with the kidney, keeping it warm. The absence of interaction between heart and kidney causes imbalance in the body and can provoke medical conditions such as insomnia.

Four different types of situations (or patterns) of Non-Interaction between Heart and Kidney have been found (Table 9.3). The Kidney Yin Deficiency and Heart Fire Excess are relative to each other and appear most of the time simultaneously, therefore treatment should combine both aspects by using a combination of Huang Lian E Jiao Tang and Jiao Tai Wan for example.

Pattern	Mechanism	Formulae

Participant Initials				Participant ID			

Kidney Yin Deficiency	The *yin*-essence of the kidney is exhausted because of aging, chronic illnesses, etc., and cannot interact with the heart	Huang Lian E Jiao Tang, Tian Wang Bu Xin Dan, Liu Wei Di Huang Wan, Zuo Gui Wan
Heart Fire Excess	Excessive emotions create fire in the heart, preventing its yang to connect with the kidney	Jiao Tai Wan
Kidney Yang Deficiency	Kidney *yang* is too weak to steam the kidney *yin* upward to the heart	Qian Yang Dan, Er Xian Tang, Shen Qi Wan
Pathogen in the Middle Burner	The interaction between heart and kidney is blocked by excess pathogen in the middle burner such dampness, phlegm and food, in relation with spleen deficiency	Ban Xia Xie Xin Tang, Er Chen Tang, Wen Dan Tang

Table 9.3. Non-Interaction between Heart and Kidney patterns, pathological mechanism and related formulae.

9.2.10. Qi and Yang Deficiency

Generally speaking, warm-tonifying herbs are not recommended for insomnia. However, they can be used in case of *qi* or *yang* deficiency. There are two different situations. In the first situation, warm-tonifying herbs are added to another formula, such as adding *renshen* in case of deficiency pattern (1), using 3 to 6g (and up to 9g maximum) of *fuzi* in case of kidney *yang* deficiency, or adding 30g of *zhi huangqi* in case of persistent insomnia or older adult insomnia. In the second situation, a pattern of *qi* or *yang* deficiency is diagnosed and a treatment given accordingly. The pattern can be diagnosed on the basis of the SSs or on the absence of response to the treatment (3). *Qi* and *yang* deficiency is associated with older adults (12), persistent insomnia (5) and treatment-resistant insomnia (3).

According to the clinicians, the main causes of *qi* and *yang* deficiency are exhaustion (from study, work, etc.) (12); catching cold (10), usually because of living and working in an environment with air-conditioning or because not wearing enough clothes; aging (9); deficient constitution (9); cold drinks and food (9) such as cold beer, cold soft drinks, ice cream, raw food and fruits; deregulated diet (eating too much fat and sugar, irregular meals) harming the spleen (9); use of medication of cold nature (6) such as heat-clearing herbs, antibiotics and steroids; stress and emotions (6); staying up late at night (6); consumption from chronic illnesses (5); treatment mistake (2) such as excessive sweating; excessive sexual life (2); surgeries and chemotherapy (1); lack of physical activity (1) and abundant sweating (1).

There are different mechanisms by which *qi* and *yang* deficiency can provoke insomnia, which is somehow counterintuitive. They can be divided into two groups, spleen deficiency and *yang*

Participant Initials				Participant ID			

deficiency. When the transportation and transformation function of the spleen is impaired, phlegm, dampness, food and fire stagnate, they can disturb the heart-spirit or prevent interaction between heart and kidney. The impaired spleen cannot create *qi* and blood, which impacts the nutrition of heart-spirit. Spleen deficiency can also provoke yin fire or an inability of the earth to hide the fire, both disturbing the heart-spirit. Finally, as the spleen controls the thinking, spleen deficiency can provoke overthinking and cognitive distortions which are intertwined with depression and anxiety, provoking insomnia. As for *yang* deficiency, the *yang* can be unable to nurture the heart-spirit, partially because the heart *yang* cannot push the blood to nurture the brain or heart-spirit. When kidney *yang* is deficient, it cannot steam the kidney *yin* to the heart, which becomes excessive and disturbs the heart-spirit. The deficient *yang* can also be unable to self-contain, float on the top and exterior and being unable to go back to the *yin*. *Yang* deficiency can create excessive *yin* which pushes the deficient *yang* upward and outward or prevents the *yang* to return to the *yin*.

In total, *qi* and *yang* deficiency patterns were reported in 55 CERs, including 67 different patterns and associated formulae. Due to the atypical nature of qi and yang deficiency patterns, we presented the formulas instead of the individual herbs (Figure 9.21). The patterns reported were clustered into six different categories, Heart Yang Deficiency (6), Spleen Yang (or Qi) Deficiency (15), Kidney Yang Deficiency (including “Heart and Kidney Yang Deficiency” and “Spleen and Kidney Yang Deficiency”) (39), Liver Coldness or Liver Qi Deficiency (3), Lung Qi Deficiency (1) and Cold-Dampness (1). The formulae associated with these patterns are shown in Figure 9.21. The characteristics of *yang* deficiency in general and of the main pattern categories are shown in Table 9.21.

Participant Initials			

Participant ID			

Figure 9.23. Word cloud of the formulae used for *qi* and *yang* deficiency patterns. The size of the words is proportional to the number of citations. The colour of the words depends on the type of pattern. Black = Kidney Yang Deficiency, orange = Spleen Yang Deficiency, green = Liver Cold, blue = cold-dampness.

Pattern	Specificity	Herb combinations	Specific SSs
General Yang Deficiency	Lack of warmth and energy	Warm herbs such as *guizhi*, *ganjiang* or *fuzi*, sweet herbs such as *dangshen* and *gancao*, and spirit-calming herbs such as *suanzaoren* and *yuanzhi*	Fatigue, aversion to cold, cold hands and feet, pale tongue with white coating and weak pulse
Heart Yang Deficiency	Heart yang floating on the exterior	Warm-tonifying herbs such as *guizhi* and *gancao* and collecting herbs such as *longgu* and *muli*	Palpitations, sweating and stuffy chest with light pain
Spleen Yang Deficiency	Stagnation of phlegm, liquid retention, water and dampness	Sweet-tonifying herbs such as *dangshen*, *baizhu* and *huangqi*, dampness-transforming herbs such as *chenpi*, *banxia* and *sharen*, and water-draining herbs such as *fuling* and *zexie*	Yellow complexion, lack of appetite, abdominal distension, nausea, loose stools and diarrhoea, large tongue with teeth marks and slimy fur
Kidney Yang Deficiency	Deficiency *yang* floating on the top	Warm-tonifying herbs such as *tusizi*, *yinyanghuo*, *bajitian* and *duzhong*, rich-tonifying herbs such as *shudi*, *guijia*, *gouqizi* and *huangjing*, pungent-hot herbs such as *fuzi*, *rougui* and *ganjiang*, and collecting herbs such as *longgu*, *muli*, *baishao* and *wuweizi*	Signs of fire on the top such as agitation, headaches, vertigo, tinnitus, red complexion, dry mouth and throat, mouth ulcers, sore throat, teeth ache and gum bleeding; kidney deficiency signs such as dark complexion, coldness and pain in the lower back and knees, infertility, erectile disorder, irregular period, frequent urination, oedema and diarrhoea

Participant Initials				Participant ID			

Table 9.4. Specificities, herbs combination and specific SSs of *yang* deficiency in general and different pattern categories.

9.2.11. Stomach Disharmony

The concept of "Stomach Disharmony" comes from the classic Huangdi Neijing which stated that "the sleep is disturbed in case of stomach disharmony". The meaning of stomach disharmony is vague, as it can refer either to a symptom of stomach discomfort or a pathological mechanism. It can also refer to an acute or a chronic condition. In the case of referring to a symptom, a "stomach distention and pressure with pain (…) is accompanied by insomnia, principally a difficulty to fall asleep". However, Stomach Disharmony can also refer to a pathological mechanism only, as stomach bloating or pain is absent from certain patterns of Stomach Disharmony such as Wen Dan Tang pattern or Gui Pi Tang pattern. Most of the cases, it is impossible to differentiate the two as stomach discomfort is present as part of the SSs related to the pathological mechanism of Stomach Disharmony. Stomach Disharmony is sometimes associated to an acute condition of "Food Damage", a concept similar to indigestion in which excessive food intake or food intake just before bedtime leads to stomach bloating, nausea, acid reflux and eructation. It can also be associated with chronic digestive conditions such as "chronic gastritis, gastric ulcer, duodenitis or gastroptosis". Finally, Stomach Disharmony is associated with children (3) and older adults (2), which have a weaker digestive system.

Stomach Disharmony as a pattern is complex and multifaceted. The core of the pattern is either food stagnation or phlegm(-heat), the former leading to the latter. The limit between food stagnation is often unclear and the treatment sometimes similar. Additional mechanisms such as spleen-stomach *qi* stagnation, spleen *(yang)qi* deficiency, liver *qi* stagnation and stomach *yin* deficiency are unmeshed with the core mechanisms, therefore the treatment is never focused on one specific mechanism.

There are several explanations about how Stomach Disharmony can provoke insomnia. Firstly, the sensation of stomach discomfort is an "impulse sent by the digestive tube that excites the reticular system in the brain stem, which in turns excites the brain cortex". A more common explanation for

chronic conditions is that the excessive pathogen (e.g., food stagnation, phlegm-heat) disturbs the spirit. The stagnation of excessive pathogen in the middle burner can also block the interaction between heart and kidney, the heart fire is excessive in the upper burner and disturbs the spirit. In this case, one clinician recommended to first treat the spleen and stomach and then to improve the interaction between the heart and the kidney. Finally, when the spleen is deficient, its function of production of *qi* and blood is impaired and the spirit cannot be nurtured, which can also lead to insomnia.

As the mechanism of Stomach Discomfort is complex and all its different components intertwined, it was impossible to categorise the formulae of Stomach Discomfort. Due to the atypical nature of the Stomach Discomfort pattern, we presented the formulas instead of the individual herbs in Figure 9.22. The two major formulae are Bao He Wan and Wen Dan Tang.

Figure 9.24. Formulae used for Stomach Disharmony

9.2.12. Disharmony between Nutritive and Protective

The theoretical background behind Disharmony between Nutritive and Protective as a pattern of insomnia is the idea that the sleep-wake cycle is related to the movements of the protective, which circulates in the yang when we are awake and in the yin when we are asleep. Another theory is that, according to the classic Huangdi Neijing “the nutritive and protective have to be regulated when the

heart is damaged". According to the clinicians, there are three different aspects of Disharmony between Nutritive and Protective, the deficiency of the nutritive and protective, a lack of movement of the nutritive and protective, and an imbalance between nutritive and protective. The first and second aspects are linked as the nutritive and protective have to be both sufficient and moving to be effective. In the third aspect, the protective is excessively strong and cannot penetrate the nutritive-*yin*.

However, this separation does not matter in terms of treatment as Gui Zhi Tang and its modified forms can be used to address these three aspects, i.e. it can tonify and move the nutritive and protective, and also bring the protective back to the nutritive-*yin*. However, the primary cause of the disharmony has to be addressed. For example, if the deficiency of the nutritive and protective is due to spleen deficiency, it has to be treated with Si Jun Zi Tang. If the lack of movement of the nutritive and protective is due to a global stagnation in the three burners, it has to be treated with Xiao Chai Hu Tang. Due to the atypical nature of the Disharmony between Nutritive and Protective pattern, we presented the formulas instead of the individual herbs in Figure 9.23.

Figure 9.25. Formulae used for Disharmony between Nutritive and Protective

The indications for Disharmony between Nutritive and Protective can be different depending on the definition of this pattern. For example, the indication for Ban Xia Xie Xin Tang is "low mood,

sadness, difficulty falling asleep, frequent sigh, fatigue, lack of appetite, deep and wiry pulse"; the indication for Gui Zhi Jia Long Gu Mu Li tang is "vertigo, hair fall, abdominal pain, sperm emission, light tongue, thin white coating, deficient or slow pulse"; and the indication for Gui Zhi Tang is "difficulty falling asleep, bad sleep quality, frequent dreams, frequent awakenings, vulnerability to catch cold, palpitations, breathlessness and sweating after effort, vertigo". According to the clinicians, Disharmony between Nutritive and Protective can be diagnosed when there is no significant imbalance between yin and yang (1) or no significant deficiency (1), and especially in case of external affection (1).

9.2.13. Heart and Gallbladder Deficiency

The Heart and Gallbladder Deficiency pattern is also called Heart Deficiency and Timidity pattern. This pattern is not typical as it represents a psychological characteristic, literally a small-gallbladder (*danxiao* 胆小), which can be translated as timidity, cowardice or lack of courage. It is also associated with an inability to make decisions (*jueduan* 决断), which is the function of the gallbladder. This pattern is associated with psychological disorders such as depression or neuroticism (1).

Heart and Gallbladder Deficiency is mainly caused by a constitutional weakness (15) manifested by a tendency to be easily frightened (6), introversion (1) and a sensitive personality (1), and a sudden panic (14) related to a trauma. Excessive emotions (1) and severe or long-term diseases (1) are alternative causes. The mechanism of this pattern is vaguer, as the direction of the pattern in terms of deficiency/excess and heat/cold is not as clear as in other patterns. The "deficiency" in the name of the pattern shows a tendency toward deficiency pattern, however both tonifying herbs and eliminating herbs are used for this pattern. Heart and Gallbladder Deficiency is associated with *qi* and blood deficiency (2), liver stagnation (2), phlegm (2), liver blood deficiency (1), *yang* deficiency (1) and spleen deficiency (1).

The SSs associated with Heart and Gallbladder Deficiency are shown in Figure 9.24. These are mainly psychological symptoms and physical symptoms related to anxiety such as breathlessness, palpitations, sweating and fatigue.

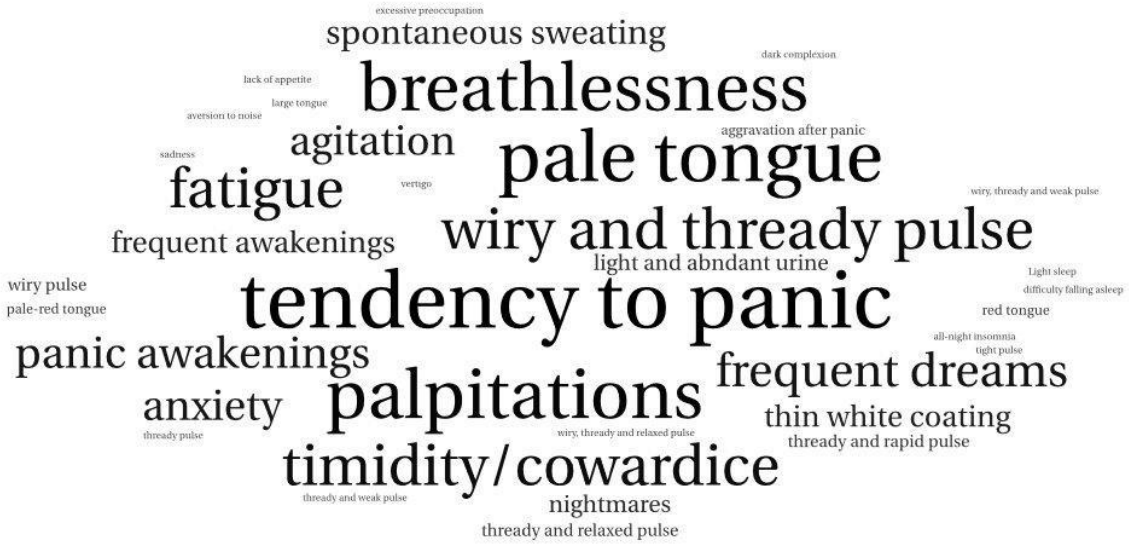

Figure 9.26. Signs and symptoms associated with Heart and Gallbladder Deficiency

The formulae used to treat Heart and Gallbladder Deficiency are mainly An Shen Ding Zhi Wan (20) and the combination of An Shen Ding Zhi Wan with Suan Zao Ren Tang (9). Chai Gui Wen Dan Ding Zhi Tang (1), the combination of Sheng Mai San and Suan Zao Ren (1), Xiao Chai Hu Tang (1), Bu Xin Zhuang Dan An Shen Tang (1), Gan Dan Liang Yi Tang (1), Wu You Tang (1), Hu Zhu San (1), Wen Dan Tang (1) and several self-designed formulae are also recommended for this pattern. The composition of the formula is mainly a mix of spirit-calming herbs (including both heart-nurturing and heavy-sedative herbs) and *qi*-tonifying such as *renshen*, *dangshen* and *gancao*. Sometimes, phlegm-transforming, blood-nurturing, heat-clearing and liver-draining herbs are added to the formula.

9.3. Disease approach

In the disease approach, a main formula is used regardless of the SSs of the patient and then modified according to the pattern. We identified 61 CERs in which the disease approach was used. The exploration of the 61 main formulae produced four different categories. These four categories have been labelled “spirit-calming”, “Suan Zao Ren Tang”, “liver-draining” and “big and diverse”. These categories included 51 (83.6%) formulae, and the remaining 10 formulae were grouped in a “miscellaneous” category.

Participant Initials				Participant ID			

The first category of disease-based formulae is composed of formulae with spirit-calming herbs such as *suanzaoren, yejiaoteng, longgu* and *muli*. The criterion for inclusion into this category was defined as 50% or more of the ingredients having a spirit-calming effect (including herbs that are not part of the spirit-calming category but have spirit-calming effects such as *fuling*). There are 27 formulae (44.3%) in this category. The average number of herbs in this category is nine. The core herbs of this category, with sensitivity level in bracket, are *suanzaoren* (83%), *gancao* (48%), *yejiaoteng* (44%), *longgu* (44%), *muli* (44%), *fushen* (39%), *baiziren* (39%), *fuling* (35%) and *yuanzhi* (35%).

The second category is composed of modification of the formula Suan Zao Ren Tang. The criteria for inclusion into this category were defined as including at least three of the ingredients of the original formula (i.e., *suanzaoren*, *chuanxiong*, *zhimu*, *fuling*, *gancao*) and having the ingredients of the original formula composing at least 50% of the whole formula. There are seven formulae (11.5%) in this category. The average number of herbs in this category is six. The core herbs of this category are *suanzaoren* (100%), *gancao* (100%), *chuanxiong* (100%), *zhimu* (100%), *fuling* (71%) and *fushen* (29%).

The third category is composed of liver-draining formula such as Xiao Chai Hu Tang and Xiao Yao San. The criteria for inclusion into this category were defined as having “liver stagnation” as the pattern name or formulae labelled as “Xiao Chai Hu Tang” or “Xiao Yao San”. There are ten formulae (16.4%) in this category. The average number of herbs in this category is nine. The core herbs of this category are *chaihu* (90%), *gancao* (80%), *banxia* (70%), *shengjiang* (60%), *huangqin* (60%), *fuling* (50%), *dangshen* (50%), *dazao* (40%) and *baizhu* (40%).

The fourth category is composed of big formulae with ingredients from different herb categories. The direction of action of the formulae in this group is not clear. The criteria for inclusion into this category were defined as having at least 13 ingredients in the formula and including ingredients from at least 8 categories. There are 15 formulae (24.6%) in this category, including four formulae that are also part of the “spirit-calming” category. The average number of herbs in this category is 17. The core herbs of this category are *suanzaoren* (80%), *gancao* (67%), *yuanzhi* (67%), *chaihu* (60%),

fuling (60%), *chuanxiong* (53%), *yejiaoteng* (53%), *baishao* (53%), *longgu* (47%), *zhizi* (40%), *dangshen* (40%), *banxia* (40%), *muli* (40%), *hehuanpi* (40%), *fushen* (33%), *changpu* (33%) and *baiziren* (33%).

The formulae that did not fit into any of the first four categories were grouped into a "miscellaneous" category. The criterion for inclusion into this category was defined as not belonging to any of the four other categories. There are ten formulae (16.4%) in this category. These formulae were respectively Xue Fu Zhu Yu Tang (1), Wen Dan Tang (1), Tiao Qi Huo Xue Tang (1), Jie Yu Yi Qi Yang Xue Tang (1), Huang Lian Wen Dan Tang (1), Ji Ben Fang (1), Dang Gui Liu Huang Tang (1), Gui Zhi Tang (1), An Mian Tang (1) and San Qing An Mian Tang (1).

9.4. Treatment according to the three factors

The treatments can be adapted to the person, to the time (season) and to the geography. This is called the "triple adaptation *(sanyin zhiyi)*" principle. The characteristics of the person that influence the clinical reasoning include the age, the sex, the constitution, the personality and the comorbidities of the person.

9.4.1. Treatment according to the person

9.4.1.1. Age of the person

In terms of age, generally speaking younger people are considered to have excess patterns (4) while older adults are considered to have deficiency patterns (4). We can identify three age categories, i.e. children, young and mature age adults, and older adults.

Children are considered to have a weak constitution as their organism is not fully developed (2). They have a weak spleen (3) which can lead to food stagnation (3) manifested by crying, panicking or teeth-grinding at night (1). For school age children, stress from study burden (2) can lead to liver stagnation (3) and liver fire (1). When treating young children, the clinician should recommend to not feed the baby at night in order to avoid milk or food stagnation (1) and not comforting the child every time he or she wakes up to avoid conditioning (1). Mild and neutral herbs should be used instead of high doses of bitter-cold herbs (1).

Participant Initials				Participant ID			

Lifestyle factors are the main causes of insomnia in young and mature age adults, including stress from work, studies and family burden (4), overthinking (2), excessive diet (3), sleep deprivation (2) and lack of exercise (1). The factors provoke liver stagnation (7) and spleen deficiency (2), which can result in fire (3) and phlegm-heat (2). The duration of the disease is relatively short for young and mature age adults (2).

Progressive consumption of vital substances due to aging is the main cause of insomnia in older adults (7). Along with spleen deficiency (2), it can cause a deficiency in the blood-essence of the liver and the kidney (10), *qi*-blood deficiency (5) and also *yang* deficiency (4). Aging can also cause blood stasis (4), in relation with arteriosclerosis (2). In addition to aging, emotions are also an important cause of insomnia in older adults (3), causing yin deficiency and excess of fire (4). An important feature of insomnia in older adults is the complexity of the pathological mechanism (3) with deficiency present along with phlegm, blood stasis and fire. This is partly due to the high number of functional (e.g., anxiety, depression) and organic (e.g., hypertension, cardiovascular diseases, diabetes) comorbidities (2). When the pathological mechanism is complex, the clinician should "grab the main pattern" (i.e., identify the core pathological mechanism) and treat it with a single formula, adding only a few herbs to treat the secondary patterns (1). The formula should be kept below 12 ingredients and not be changed unless significant improvement (1). The treatment should also be taken for a long time, using manufactured products or diet therapy if necessary (1). In case of blood stasis, the clinician should be careful about not using too many or too strong blood-activating herbs (1) and using a combination of blood-activating and blood-burturing herbs such as *danshen*, *danggui*, *yimucao*, *chuanxiong*, *sanqi* and *chishao* (1). As there is a risk of bleeding in order adults, *sanqi* can also be used in prevention (1). Finally, due to older adults' constitutional weakness, it is important to strengthen their spleen (1).

Quantitative analysis of different age groups was possible only for older adults. Compared to the treatment of the general insomnia population, the 23 formulae used specifically for insomnia in older adults included more *yang*-tonifying herbs (+175%), collecting and consolidating herbs (+146%), interior-warming herbs (+130%), liver-calming and wind-extinguishing herbs (+89%) and spirit-

calming herbs (+16%), and less food transforming herbs (-100%), qi-moving herbs (-77%), phlegm-transforming and anti-coughing herbs (-27%), and heat-clearing herbs (-12%). There are 21 individual herbs used more frequently for older adults than for the general population, i.e., *jiangcan* (+3695%), *daizheshi* (+743%), *yinyanghuo* (+743%), *juhua* (+623%), *fuxiaomai* (+462%), *tianma* (+406%), *shanyao* (+392%), *shanzhuyu* (+322%), *fuzi* (+289%), *huangbai* (+216%), *ganjiang* (+198%), *fushen* (+174%), *guizhi* (+174%), *gouqizi* (+171%), *hehuanpi* (+141%), *shudihuang* (+120%), *danpi* (+117%), *yejiaoteng* (+70%), *longgu* (+61%), *muli* (+60%), and *changpu* (+53%), and 18 herbs used less frequently for older adults than for the general population, i.e., *zhishi* (-100%), *renshen* (-100%), *zhuru* (-100%), *zhiqiao* (-100%), *muxiang* (-100%), *longchi* (-100%), *shenqu* (-100%), *chenpi* (-79%), *huanglian* (-64%), *shengjiang* (-60%), *maidong* (-57%), *zhizi* (-57%), *fuling* (-45%), *danggui* (-44%), *baizhu* (-41%), *chaihu* (-38%), *banxia* (-34%), *yuanzhi* (-31%).

9.4.1.2. Sex of the person

Insomnia in female is considered related to qi stagnation (3), blood deficiency (2) and blood stasis (1), while insomnia in male is related to liver fire (1). If the characteristics of male and female insomnia are rarely described, many clinicians focus on menopause-related insomnia and its characteristics. The main pathological factor of insomnia in menopausal women is liver and kidney *yin* deficiency (11) provoking fire (7). This is largely due to the consumption of essence and blood because women undergo menstruation, pregnancy, childbirth and breast-feeding (3). Liver stagnation (5) creating fire (2) is also a major mechanism. This is due to the stress menopausal women undergo in relation to longing for the years gone and the burden of social and familial roles (3). One clinician pointed out that kidney *yang* and kidney *yin* deficiency are not common and that most menopausal women with insomnia have heart deficiency and liver congested fire (1). Another clinician pointed out that many women had phlegm heat pattern, partly due to the fact that menopausal women are excessively treated with *yin*-nurturing herbs (1). Senile vaginitis, recurrent urinary tract infection and their treatment with heat-clearing dampness-draining herbs can also aggravate insomnia (1). In this case, *yin*-nurturing and fire-draining should be conducted (1). Finally, *gouqizi*, *nvzhenzi* and *ziheche* can be used in case of low oestrogen levels (1).

Participant Initials				Participant ID			

The 53 formulae used specifically for insomnia in perimenopausal women were compared to the treatment of the general insomnia population. These formulae included more *yang*-tonifying herbs (+222%), *yin*-tonifying herbs (+109%), collecting and consolidating herbs (+105%), liver-calming and wind-extinguishing herbs (+49%), blood-tonifying herbs (+23%) and heat-clearing herbs (+10%), and less food-transforming herbs (-100%), water-draining herbs (-41%), surface-liberating herbs (-38%), phlegm-transforming and anti-coughing herbs (-34%), and *qi*-tonifying herbs (-23%). There are 22 individual herbs used more frequently for perimenopausal women than for the general population, i.e., *lü'emei* (+3609%), *zibeichi* (+1754%), *meiguihua* (+1291%), *guijia* (+1225%), *bajitian* (+1136%), *digupi* (+1013%), *yinyanghuo* (+518%), *lianzixin* (+406%), *xiaomai* (+364%), *huangbai* (+248%), *jizihuang* (+165%), *baihe* (+158%), *hehuanpi* (+135%), *shanzhuyu* (+121%), *danpi* (+112%), *ejiao* (+100%), *shudihuang* (+88%), *yujin* (+85%), *yejiaoteng* (+78%), *zhimu* (+65%), *baishao* (+44%), and *huanglian* (+33%), and 18 herbs used less frequently for perimenopausal women than for the general population, i.e., *longdancao* (-100%), *shenqu* (-100%), *renshen* (-77%), *shengjiang* (-71%), *zhiqiao* (-67%), *xiangfu* (-67%), *muxiang* (-65%), *huangqi* (-56%), *banxia* (-52%), *dangshen* (-49%), *wuweizi* (-47%), *huangqin* (-38%), *yuanzhi* (-36%), *chuanxiong* (-29%), *fuling* (-27%), *chaihu* (-18%), *danggui* (-18%), *suanzaoren* (-16%).

Pregnancy-related insomnia is another type of female-specific insomnia. In pregnancy-related insomnia, the *yin*-blood is concentrated in the bottom which causes an excess of heart fire (1).

9.4.1.3. Constitution of the person

The constitution is defined by long-term psychological characteristics of one person. People with *yin* deficiency or *qi* stagnation constitutions are more vulnerable to insomnia (1). People with different constitutions are also susceptible to contract different patterns of insomnia. For example, people with liver deficiency are susceptible to kidney deficiency pattern (1), people with *yang* deficiency are susceptible to spleen deficiency pattern (1), people with fire-type constitution, as defined as being stressed, irritable and explosive, are prone to liver and heart fire (2), people with wood-type constitution are prone to heart and spleen deficiency pattern (1). Obese and depressed women are prone to stagnation and phlegm-fire (1). People with *banxia* constitution, as defined as being

perfectionist, doubtful, tensed, easily panicked and presented various autonomous system symptoms such as dizziness, palpitation, vomiting or numbness, are prone to phlegm-heat pattern (1).

When the symptoms are severe, one should focus on the symptoms but when the symptoms are mild, the treatment should be focused on the constitution (1). The pattern and the constitution have to be both taken into account. If they are aligned, the dose of the herbs corresponding to the constitution have to be increased, but if they are opposed, the treatment should be adjusted accordingly (1). After remission, it is better to continue to regulate the constitution in order to prevent relapse (2). Examples of treatment for the constitution after remission are shown in Table 9.19.

Constitution	Pattern	Pattern-specific treatment	Constitution-specific treatment
Qi deficiency	Heart, spleen and gallbladder deficiency	An Shen Ding Zhi Wan and Gui Pi Tang	Si Jun Zi Tang
Yang deficiency	Spleen and kidney deficiency	Gui Fu Di Huang Wan	Shen Qi Wan
Yin deficiency	Yin deficiency and excessive fire	Tian Wang Bu Xin Dan	Liu Wei Di Huang Wan
Blood stasis	Qi stagnation and blood stasis	Xue Fu Zhu Yu Tang	Taoren, danggui and cloud ear fungus
Qi stagnation	Liver stagnation creating fire	Long Dan Xie Gan Tang or Dan Zhi Xiao Yao San	Xiao Yao Wan

Table 9.5. Treatment before and after remission according to the pattern or the constitution

9.4.1.4. Personality of the person

Some personality traits such as sensitivity, introversion, emotional instability, and being conservative or stubborn traits all increase the vulnerability to insomnia (1). One of the reason is that being sensitive and not adaptive enough increases the probability of external stimuli to provoke emotions (1). More generally, different personality traits act as a “ground” for certain types of insomnia. For example, timid and coward people are subject to panic, which can lead to panic-type insomnia (1). This type of insomnia has to be treated with heavy-sedative spirit-calming herbs (1). More common patterns and their “ground” personality traits are summarized in Table 9.20.

Pattern	Personality trait

Participant Initials				Participant ID			

Heart and Spleen Deficiency	Introverted and prone to thorough consideration (1)
Heart and Gallbladder Deficiency	Introverted, easily frightened and timid (1)
Liver Qi Stagnation	Introverted (3), irritable (2), depressed (2) and sentimental (1)
Heart and Liver Fire	Irritable (1)
Congestion of Phlegm and Qi	Suspicious (1) and worried (1)

Table 9.6. Common patterns of insomnia and their "ground" personality traits.

9.4.1.5. Comorbidities of the person

Insomnia is often present along other medical conditions, i.e. comorbidities. These comorbidities are diabetes (12), depression (9), hepatic conditions (7), anxiety disorder (5), coronary heart disease (4), post-stroke (4), gastric conditions (4), respiratory conditions (3), hypertension (3), cardiac arrhythmias (3), cervical spondylosis (2), chronic kidney failure (1), female urethral syndrome (1), Parkinson's disease (1), prostatic hypertrophy (1), cerebral arteriosclerosis (1), brain trauma (1), autism (1), obsessive-compulsive disorder (1), AIDS (1), cancer (1), heart failure (1), myocarditis (1), and chronic diarrhoea (1).

According to the clinicians, these comorbidities are either present before the start of the insomnia or at the same time, but never developed on the basis of insomnia. The causality between insomnia and the comorbidity is more complex. Insomnia and the comorbidity can have the same aetiological and pathological pathway (Table 9.21).

Comorbidity	Common aetiological and pathological pathway
Diabetes	Phlegm-dampness and inner heat
Diabetes	Excessive diet, emotions, work-life imbalance
Diabetes	Yang deficiency
Anxiety	First liver stagnation producing fire, then phlegm, blood stasis, spleen deficiency and blood deficiency
Anxiety	Lack of *yin* and blood with deficient fire rising
Anxiety	Non-interaction between heart and kidney
Depression	Disharmony of heart and gallbladder
Obsessive-compulsive disorder	Stagnating fire of shaoyang
Coronary heart disease	Liver stagnation, spleen deficiency and blood stasis
Coronary heart disease	Phlegm and blood stasis
Cardiac condition (coronary heart disease, myocarditis, arrhythmia)	Emotions, mental strain or catching cold
Palpitation	Gallbladder or stomach impairment

Participant Initials				Participant ID			

Hypertension	Liver-kidney deficiency, hyperactive liver *yang*, phlegm-heat
Respiratory condition	Lack of rest and inappropriate treatment of cold, emotions and mental strain

Table 9.7. Common aetiological and pathological pathways of insomnia and the comorbidity.

Insomnia can be developed on the basis of the comorbidity (or primary disease). In this case there are five possibilities. The first possibility is insomnia being a symptom of the primary disease, i.e. depression (2) or chronic hepatitis B (1). The second possibility is the evolution of the pathology of the primary disease (Table 9.22). The third possibility is that the insomnia is caused by a symptom of the primary disease, i.e. stomach discomfort (4), frequent urination (4), bodily pain (3), cough or dyspnoea (2), itching (2), thoracic pain (1), diarrhoea (1), abdominal bloating (1), pain in the liver area (1), palpitations (1), sleep apnoea (1), and teeth pain (1). The fourth possibility is that the primary disease leads to emotional distress (i.e., excessive despair, anxiety and rumination), which then causes insomnia. This emotional distress is due to an incorrect view of the disease, worry about relapse or aggravation, financial burden, social despise and pressure, adverse reactions from treatment, the stress of constantly monitoring the disease (e.g., glycaemia for diabetics). The fifth possibility is that the treatment of the primary disease causes insomnia. For example, in the case of cancer, chemotherapy can harm the *qi* and blood, which leads to insomnia (1).

Primary disease	Aetiology and mechanism	Evolution
Diabetes (9)	*Yin* deficiency with dryness-heat (4); excessive diet creating phlegm-dampness overwhelming spleen and excessive emotions impairing the liver (1); *qi* and *yin* deficiency	Phlegm and phlegm-heat (6); blood stasis (4); liver stagnation producing fire (3); fire disturbing the heart (2); liver blood deficiency (1); *qi* and blood deficiency (1)
Stroke (3)	Heat, phlegm, blood stasis, deficiency and inner wind (1); phlegm-heat (1)	Blood stasis (1); phlegm-heat (1); *yin-yang* deregulation (1)
Hepatic condition (3)	Dampness-heat and liver stagnation (1)	Liver *qi* stagnation (2); dampness-heat in the liver meridian (2); liver blood deficiency (2); spleen unable to produce blood (1); *yin* deficiency with effulgent fire (1); liver stagnation producing fire (1) and phlegm-fire (1)
Digestive disorder (2)	Excessive emotions impairing the liver, which harms the spleen (1)	Stomach disharmony (1); *qi* and blood deficiency (1); phlegm-dampness (1)
Respiratory conditions (2)	Stagnation, heat, phlegm, dryness or coldness in the lung (1)	The lung *qi* cannot produce the blood (2)

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Chronic renal failure	The kidney is not able to transform the turbid, which blocks the three burners	The *qi* and blood are deficient or do not circulate well
Parkinson's disease	Liver-kidney yin deficiency	Excessive heart fire
Cervical spondylosis	External affection of wind, cold and dampness, trauma or chronic damage leads to contraction of tendons and joint displacement	The *qi* and blood cannot irrigate the brain
Cerebral arteriosclerosis, cervical spondylosis, brain trauma, hypertension		Blood stasis
Depression	Liver stagnation due to irregular emotions	Stagnating fire harming the *yin*
Autism	Heart, liver, spleen and kidney functions impairment, phlegm and blood stasis	*Yin-yang* imbalance and abnormal circulation of nutritive and protective

Table 9.8. Aetiology and mechanism of the primary disease and evolution leading to insomnia.

Insomnia can also aggravate the comorbidity (i.e., stroke, coronary heart disease) by disrupting the endocrine system (1), creating anxiety (2), exciting the sympathetic system (1), and increasing insulin antagonist hormones (1). As one of the clinicians put it "it is hard to differentiate which one is the cause and which one is the consequence".

Regarding treatment, it is difficult to extrapolate the different possible strategies when treating insomnia with comorbidities. This difficulty comes from the fact that pattern differentiation based on signs and symptoms is the main diagnostic approach in Chinese medicine. The SSs can be due to either insomnia or the comorbidity, and it is difficult to assess if the treatment targets insomnia, the comorbidity, or both. Despite this difficulty, we have been able to extract four strategies.

The first is the focus on the comorbidity, either on a pattern or disease basis. For example, insomnia induced by cervical spondylosis is treated with *gegen*, *chuanxiong*, *jianghuang* and *quanxie*, which mainly target the cervical spondylosis by releasing the tendons and unblocking the vessels. Insomnia provoked by respiratory conditions are treated according to the pattern with Er Chen Tang with San Zi Yang Qin Tang, Sang Bai Pi Tang or Bai He Gu Jin Tang. Spirit-calming herbs can be added to the treatment. The rationale behind this strategy might be that insomnia is directly caused by the comorbidity or its symptoms, and treating the comorbidity alone is enough to get rid of insomnia. Or

it might be that insomnia is not considered severe enough compared to the comorbidity. The comorbidities for which this approach is used are cervical spondylosis (1), respiratory conditions (2), chronic hepatitis (1), cardiac failure (1), and diabetes (1).

The second is the focus on insomnia with a pattern basis. In this case, the treatment is not different from the usual pattern-based treatment of insomnia. For example, insomnia in heroin addiction rehabilitation is treated according to the pattern with Gui Pi Tang, Huang Lian E Jiao Tang, Jiao Tai Wan, An Shen Ding Zhi Wan, Qing Re Di Tan Tang and Bao He Wan. The rationale behind this approach might be that the comorbidity and insomnia are not directly related, therefore there is no need to treat the comorbidity in order to improve insomnia. The comorbidities for which this approach is used are chronic renal failure (1), heroin addiction rehabilitation (1), diabetes (1), and AIDS (1).

The third is the treatment of both conditions with a pattern based or disease based treatment. In this approach, the common pathological mechanisms of the two conditions are targeted. For example, the common mechanism of stroke and insomnia, phlegm, is target by the phlegm-transforming formula Wen Dan Tang. The common mechanism of palpitations and insomnia, gallbladder and stomach impairment, is targeted by a set of formula including Huang Lian Wen Dan Tang, An Shen Ding Zhi Wan with Suan Zao Ren Tang, and Hao Qin Qing Dan Tang with Hua Gan Jian. The rationale behind this approach might be that there is an overlap between the pathological mechanism of the two conditions, or that insomnia is the result of the evolution of the comorbidity. The treatment targets directly that shared mechanism. The comorbidities for which this approach is used are diabetes (9), depression (4), stroke (3), palpitations (2), chronic hepatic disease (2), chronic hepatitis B (2), autism (1), anxiety (1), Parkinson's disease (1), obsessive-compulsive disorder (1), cardiac arrhythmia (1), pruritus (1), vertigo (1), mental disorders (1), chronic gastritis (1), and digestive conditions (1).

The fourth is the treatment of both conditions with a mixed pattern-disease approach. In this strategy, the main formula targets either insomnia or the comorbidity and the formula is modified according to the pattern of insomnia or the comorbidity. For example, in case of insomnia with comorbid coronary heart disease, *danshen*, *chuanxiong*, *gualou* and *xiebai* are used to target the coronary heart disease

and the formula is modified according to the pattern of insomnia. In case of insomnia comorbid with gastric condition, a basic formula composed of liver-inhibiting and liver-draining herbs is used for insomnia, and modified according to the pattern of the gastric condition. The rationale behind this approach might be that one of the condition presents patterns that are different from the core mechanism of the other condition. The comorbidities for which this approach is used are coronary heart disease (1) and chronic hepatitis B (1).

The fifth is the treatment of both conditions with a disease-treatment combining two formulae. For example, Suan Zao Ren Tang is combined to Dan Shen Yin in order to treat insomnia comorbid with coronary heart disease, the first formula treating the first condition and the second formula treating the second condition. The rationale behind this approach might be that the two conditions have a different core mechanism. The comorbidities for which this approach is used are coronary heart disease (1), hepatic diseases (1), chronic diarrhoea (1), female urethra syndrome (1), respiratory conditions (1), heart diseases (1), and liver cancer (1).

9.4.2. According to the season

The treatment itself is generally not based on the season. However, the formula can be adapted according to the season or climate. For example, in summer the rainy and humid weather can provoke spleen dampness, which is manifested by body heaviness, fatigue, nausea, etc. (1). In this case *huoxiang* and *peilan* can be added to the formula (1). In autumn, the lung-metal is excessive and inhibits the liver-wood, therefore *baibu* has to be used moisten the lung, nurture the *yin* and soften the liver (1). The five movements and six *qi (wuyun liuqi)* can also be taken into consideration. The five movements and six *qi* system is a system of correspondence between the time and global climatic tendencies according to the five movements (i.e., wood, fire, earth, metal and water) and related climates (i.e., wind, cold, summer-heat, dampness, dryness and heat). For example, the climatic characteristics of 2016 are an excess of fire and the inhibition of the earth by water (1). Therefore, in 2016 insomnia should be treated with Bai Le Mian capsule which nurtures the *yin*, clarifies heat, and drains excessive dampness (1).

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9.4.3. According to the location

According to the clinicians, the location can influence people's constitution in three ways, i.e. the climate, local food and local culture. For example, a humid climate tends to create dampness, high-fat and sweet local food creates dampness, and a high-paced culture tends to create liver congestion. Sometimes the combination of climatic and cultural factors creates the pathological mechanism, e.g. humid climate with spicy food and hot climate with high-fat food can both create dampness-heat. The location can be considered in three ways. It can be a direct cause of a pathological mechanism (i.e., a pattern), increase the vulnerability of the person to a certain pattern, or be considered as a background factor that has to be taken into consideration (e.g., adding *qi*-moving herbs such as muxiang and zisugeng when treating qi and blood deficiency in a patient from the humid South-of-Mountains region). The influence of the location on the pathological mechanism of insomnia is shown in Table 9.23.

Region	Local factor	Pattern
South-of-Mountains (Lingnan), roughly Guangdong and Guangxi provinces	Humid and hot climate (4), eating sweet food (1) and cold tea (1), high-paced and stressful lifestyle (1).	Phlegm-heat (4), dampness (2), spleen deficiency (1), liver congested fire (1) and *yin* deficiency (1)
Sichuan	Humid climate (1), high-fat and spicy food (1)	Phlegm-dampness (1)
Hunan	Humid climate (1) and spicy food (1)	Phlegm-heat (1)
Xinjiang	Hot and dry climate (1) and high-fat, sweet, meat-rich and roasted food (1)	Dampness-heat (1)
Yunnan	Cold and humid climate (1)	Cold-dampness (1)

Table 9.9. Local factors and pattern caused in different regions.

9.5. Treatment according to disease characteristics

9.5.1. Treatment according to the complaint

There are three main complaints of insomnia: difficulty falling asleep (DFA), frequent awakenings (FA), frequent dreams (FD) and early morning awakenings (EMA).

Insomnia with a complaint of DFA is associated with excess pattern (2). More specifically it is associated with liver or *shaoyang* stagnation (4), liver or heart fire/heat (5), phlegm (2), blood

deficiency (2), *yin* deficiency (2) with hyperactive *yang* (1), blood stasis (2), non-interaction between heart and kidney (1) and nutritive-protective disharmony (1). A main complaint of DFA is also associated with anxiety (2) and obsession (1).

Insomnia with a complaint of FA is associated with deficiency pattern (1), more specifically *yin*-blood deficiency (1), heart-gallbladder *qi* deficiency (1), liver blood deficiency (1), *qi* and blood deficiency (1), lung *yin* deficiency (1), lung *qi* deficiency (1), lung phlegm (1), and liver congestion with blood deficiency (1). It is also associated with depression (1).

Insomnia with a complaint of FD is associated with the liver (2) as the spirit *hun*, which is associated with dreams, corresponds to the liver. More specifically, it is associated with blood deficiency (5), blood stasis (3), liver stagnation (3), liver heat (2), phlegm-heat (1) and yin deficiency (1).

Insomnia with a complaint of EMA is associated with mostly deficiency patterns and the kidney. More specifically it is associated with *yin* deficiency and hyperactive *yang* (2), kidney yang deficiency (2), kidney *yin* deficiency (1), heart blood deficiency (1), heart-gallbladder disharmony (1), nutritive-blood heat and liver stagnation (1). This type of insomnia is also associated with depression (3) and cerebral vascular insufficiency (1).

Another way to classify insomnia subtypes is according to the time of the symptoms. In Chinese culture, *shichen* (i.e., couple of hours) are associated with organs. The *shichen* related to insomnia symptoms are *Zi* (from 11 pm to 1 am) which is associated with the gallbladder, *Chou* (1 am to 3 am) which is associated with the liver and *Yin* (3 am to 5 am) which is associated with the lung. Except the *shichen* system, the movement of the *yang* are also related to time, with the *yang* going inward in the evening, the *yin* being extreme at midnight and the yang going outward in the morning. According to the clinician, DFA occurring during the *Zi* hours (11 pm to 1 am) is caused by the gallbladder-pivot being blocked (1) and has to be treated with *chaihu*-type formula (1) or Chai Hu Jia Long Gu Mu Li Tang (1). If clinicians agree that awakenings during the *Chou* hours (1 am to 3 am) are related to the liver (3), there is no consensus on the mechanism, which can be either an impossibility for the liver-wood to move upward and outward (1), a deregulation of liver function caused by emotions (1) or an

imbalance with both heat and cold in the *jueyin* treated with Wu Mei Wan (1). EMA during the *yin* hours (3 am to 5 am) is linked with kidney-water cold (2), the kidney *yang* floating prematurely as it is pushed by the coldness. Also, the lung-metal cannot descend as it is blocked by the coldness (1). This condition has to be treated with warm-tonifying herbs and immersing-oppressing herbs (1).

9.5.2. Treatment according to the stage

Unsurprisingly, early-stage insomnia is associated with excess (2) while late-stage insomnia is associated with deficiency (2). In the first case, *zhenzhumu*, *hupo* and *duan longgu* are added to a perverse-removing formula and in the second case *xiyangshen*, *ejiao* and *guiban* are added to a regular-tonifying formula (1). This is contrasted by another clinician who believes that the mechanism of late-stage anxiety-type insomnia is either liver stagnation with spleen deficiency or phlegm and blood stasis creating fire (1). Long-term insomnia is indeed considered to have a complex pathological mechanism (1) and has to be treated with Chinese herbal medicine combined with either Western medicine or psychotherapy (1).

The treatment of acute insomnia was reported far less than chronic insomnia. Acute insomnia is associated with liver stagnation (5), liver and heart fire (4), phlegm-heat (2), disturbed *shen* (2) and non-interaction between heart and kidney (1).

As many as 77 articles focused on persistent insomnia. However, the definition of “persistent insomnia” varied greatly from one article to another. Persistent insomnia is defined by criteria of duration (14), resistance to treatment (7), relapse frequency (3), short total sleep time (3) and serious social impairment (3). The criterion for duration can be undefined (9), more than 1 month (1), more than 3 months (2) or more than 1 year (1). The criterion for short total sleep time can be less than 2 hours (2) or less than 3 hours (1). In some articles, “persistent insomnia” is used interchangeably with “insomnia” or directly defined as “insomnia”. In these case we did not consider it as “persistent insomnia”.

Persistent insomnia has a complex aetiology (2), including constitutional factors, the influence of the disease and its treatment (1). Mixed patterns of deficiency/excess and cold/heat can happen when for

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example a person with a yang-deficiency constitution gets congested fire because of emotions (1). As depression (4) and anxiety (4) are intertwined with persistent insomnia, a common pathway is insomnia-induced emotions (3) provoking liver stagnation (4) which in turn can provoke other mechanisms such as phlegm, blood stasis or fire. The most common patterns of persistent insomnia are blood stasis (12) and phlegm (6), followed by yang deficiency (3), yin deficiency with excessive fire (2), kidney deficiency (2) and qi deficiency (1).

The formulae of the 77 CERs in which the treatment of persistent insomnia was reported were compared to the treatment of the general insomnia population. They included more blood-activating herbs (+72%) and phlegm-transforming and anti-coughing herbs (+32%) and less water-draining herbs (-29%), blood-tonifying herbs (-12%) and spirit-calming herbs (-8%). There are 9 individual herbs used more frequently for persistent insomnia than for the general population, i.e., *yinyanghuo* (+554), *honghua* (+227%), *jiegeng* (+200%), *niuxi* (+170%), *taoren* (+170%), *cishi* (+145%), *chishao* (+121%), *zhiqiao* (+89%) and *shengdi* (+28%), and 9 herbs used less frequently for persistent insomnia than for the general population, i.e., *shudihuang* (-72%), *danpi* (-58%), *hehuanpi* (-53%), *wuweizi* (-44%), *fuling* (-37%), *zhimu* (-35%), *baizhu* (-32%), *suanzaoren* (-28%) and *baishao* (-24%).

9.6. Spirit-calming herbs

As the disturbance of the spirit is one of the main features of insomnia, using spirit-calming herbs for the treatment of insomnia is not surprising. In most cases, clinicians recommend to use spirit-calming herbs on the basis of pattern differentiation (25). Many clinicians recommended to avoid treatment with mainly spirit-calming herbs (10) or even to limit their use (3), especially the use of heavy-sedative herbs (3). They explained that the efficacy of this approach is low (2), especially for moderate and severe types of insomnia (1). Only one clinician recommended to use a spirit-calming formula as the main formula (1).

Except the two main categories of spirit-calming herbs (heart-nurturing and heavy sedative), two other categories of spirit-calming herbs have been proposed by the clinicians, i.e. stagnation-eliminating and orifice-opening. The stagnation-eliminating spirit-calming herbs are indicated when

there is both liver *qi* stagnation and a disturbed spirit, while the orifice-opening spirit-calming herbs are indicated when there is loss of memory. Some other herbs are known for their spirit-calming properties but are not classified in any category, therefore we labelled them "other typical spirit-calming" herbs. Finally, some herbs that are not considered to have spirit-calming properties were identified by the clinicians as spirit-calming. This is the case for *banxia* (5), *huanglian* (3), *chaihu* (1), *kushen* (1), *baishao* (1) and *chantui* (1). These herbs were identified as spirit-calming on the basis of both individual experience and pharmacological studies.

Spirit-calming category	Herbs
Heart-nurturing	*Suanzaoren, baiziren, yejiaoteng, hehuanpi, hehuanha, longyanrou, lianzirou, lingzhi*
Heavy-sedative	*Longgu, muli, zhenzhumu, cishi, hupo, zhusha, longchi, zibeichi, shengtieluo*
Stagnation-eliminating	*Huashengye, hehanhua, hehuanpi, gansong, suxinhua*
Orifice-opening	*Changpu, yuanzhi*
Other typical spirit-calming	*Fuling, fushen, xiecao, wuweizi*
Atypical	*Banxia, huanglian, chaihu, kushen, baishao, chantui*

Table 9.10. Different categories of spirit-calming herbs.

Figure 9.27. Spirit-calming herbs used in the pattern-differentiation approach. The size of the word is proportional to the frequency of use. The colour represents the category. Orange = heart-nurturing, Grey = heavy-sedative, Green = stagnation-eliminating, Red = orifice-opening, Blue = other typical spirit-calming.

The type of spirit-calming herb used has to be chosen according to the duration and severity of the disease, heavy-sedative herbs for short-term (2) and severe conditions (1), and heart-nurturing for long-term (2) and mild conditions (1). It has also to match the pattern of the patient (3), i.e., the type of stagnation (1), heavy-sedative for "moving" pattern and heart-nurturing for "quiet" pattern (1), or heavy sedative for excess pattern and heart-nurturing for deficiency pattern (1). There is a debate on this last point as some clinicians recommend to use heavy-sedative herbs (5) or heart-nurturing herbs (5) on a disease differentiation basis regardless of the pattern. A possible explanation is that specific type of spirit-calming herbs can be used for any type of insomnia but are more appropriate for some types of insomnia, as one clinician mentioned that *suanzaoren* is more appropriate for *yin* deficiency but can be used for other patterns when used in combination with other herbs.

The percentage of heart-nurturing, heavy-sedative, typical (including heart-nurturing, heavy-sedative, stagnation-eliminating, orifice-opening and other typical spirit-calming herbs) and all spirit-calming (including both typical and atypical spirit calming herbs) herbs according to the percentage of tonic herbs (which reflects the excessive of deficient nature of the pattern) is shown in Figure 9.26. The percentage of tonic herbs is positively correlated ($r=0.102$, $P=0.023$) with the percentage of heart-nurturing herbs, negatively correlated ($r=-0.243$, $P<0.001$) with the percentage of heavy-sedative herbs, negatively correlated ($r=-0.159$, $P<0.001$) with the percentage of all spirit-calming herbs, and not correlated ($r=-0.084$, $P=0.061$) with the percentage of typical spirit-calming herbs. The percentage of heart-nurturing herbs is significantly lower in the 10-19% tonic group than any other group except the 40-49% tonic group and the 70-79% tonic group, and significantly lower in the 70-79% tonic group than in any other group except the 10-19% tonic group (Table 9.25). The percentage of heavy-sedative herbs is significantly higher in the 0-9% tonic group than the 30-39%, 50-59%, 60-69% and 70-79% tonic groups, significantly lower in the 50-59% tonic group than the 10-19%, 20-29% and 40-49% tonic groups, and significantly lower in the 60-69% tonic group than the 10-19%, 20-29%, 30-

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39% and 40-49% tonic groups (Table 9.26). The percentage of typical spirit-calming herbs is significantly lower in the 60-69% tonic group than in the 0-9% tonic group, and significantly lower in the 70-79% tonic group than any other group (Table 9.27). The percentage of all spirit-calming herbs is significantly lower in the 60-69% tonic group than in the 0-9%, 10-19% and 30-39% tonic groups, and significantly lower in the 70-79% tonic group than any other group (Table 9.28).

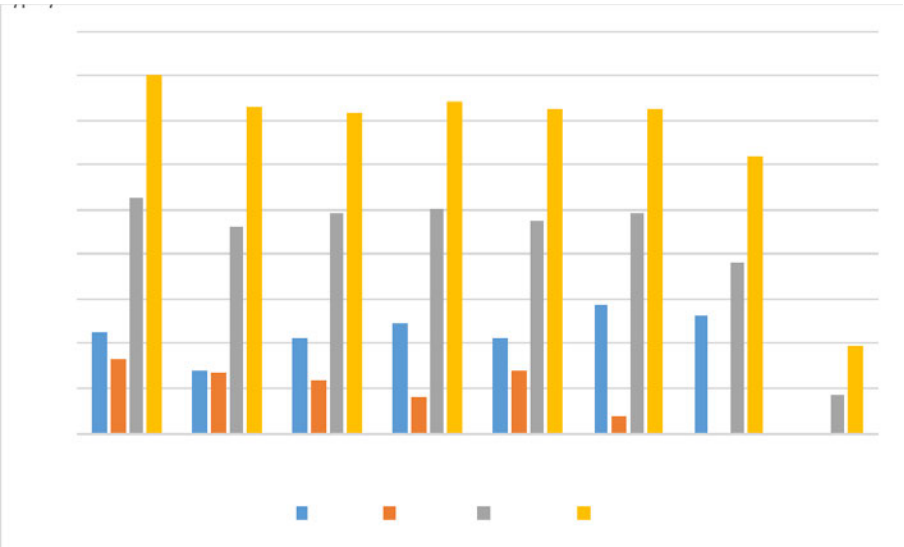

Figure 9.28. Categories of spirit-calming herbs used according to the percentage of tonic herbs. The Y-axis represents the proportion of spirit-calming herbs in the formula while the X-axis represents the percentage of tonic herbs in the formula.

%tonic	0-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%
10-19%	0.041*						
20-29%	0.005	-0.036*					
30-39%	-0.012	-0.053*	-0.017				
40-49%	0.006	-0.035	0.001	0.018			
50-59%	-0.032	-0.073*	-0.037	-0.020	-0.038		
60-69%	-0.020	-0.061*	-0.025	-0.01	-0.026	0.012	
70-79%	0.111*	0.070	0.106*	0.123*	0.105*	0.143*	0.131*

Table 9.11. Heart-nurturing herbs content differences according to the percentage of tonic herbs in the formula. * P<0.05.

%tonic	0-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%
10-19%	0.016						
20-29%	0.023	0.007					
30-39%	0.042*	0.026	0.019				
40-49%	0.012	-0.004	-0.011	-0.031			

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50-59%	0.065*	0.049*	0.042*	0.023	0.053*		
60-69%	0.084*	0.067*	0.060*	0.041*	0.072*	0.018	
70-79%	0.084*	0.067	0.060	0.041	0.072	0.018	0.000

Table 9.12. Heavy-sedative herbs content differences according to the percentage of tonic herbs in the formula. * P<0.05.

%tonic	0-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%
10-19%	0.032						
20-29%	0.017	-0.015					
30-39%	0.014	-0.019	-0.003				
40-49%	0.025	-0.007	0.008	0.011			
50-59%	0.017	-0.016	-0.000	0.003	-0.008		
60-69%	0.072*	0.039	0.055	0.058	0.047	0.055	
70-79%	0.222*	0.189*	0.205*	0.208*	0.197*	0.205*	0.150*

Table 9.13. Typical spirit-calming herbs content differences according to the percentage of tonic herbs in the formula. * P<0.05.

%tonic	0-9%	10-19%	20-29%	30-39%	40-49%	50-59%	60-69%
10-19%	0.036						
20-29%	0.043	0.007					
30-39%	0.031	-0.005	-0.012				
40-49%	0.040	0.004	-0.003	0.009			
50-59%	0.039	0.004	-0.003	0.009	-0.001		
60-69%	0.094*	0.058*	0.051	0.063*	0.054	0.054	
70-79%	0.304*	0.269*	0.262*	0.274*	0.265*	0.265*	0.211*

Table 9.14. All spirit-calming herbs content differences according to the percentage of tonic herbs in the formula. * P<0.05.

The percentage of heart-nurturing, heavy-sedative, typical spirit-calming and all spirit-calming herbs according to the pattern is shown on Figure 9.27. These percentages vary greatly between different patterns. The percentage of heart-nurturing herbs is significantly higher for Heart-Spleen Deficiency than any other pattern, significantly higher for Yin Deficiency with Effulgent Fire than any other pattern except Heart-Spleen Deficiency, and significantly lower for Liver-Spleen Disharmony than any other pattern (Table 9.29). The percentage of heavy-sedative herbs is significantly higher for Liver-Spleen Disharmony than any other pattern, and significantly higher for Liver Fire than for Heart-Spleen Deficiency (Table 9.30). The percentage of typical spirit-calming herbs is significantly higher for Heart-Spleen Deficiency than any other pattern, significantly higher for Yin Deficiency

with Effulgent Fire than any other pattern except Heart-Spleen Deficiency, and significantly lower for Blood Stasis than any other pattern except Liver Fire (Table 9.31). The percentage of all spirit-calming herbs is significantly lower for Blood Stasis than for any other pattern except for Liver Fire, significantly lower for Liver Fire than for any other pattern except for Liver-Spleen Disharmony and Blood Stasis, and significantly lower for Liver-Spleen Disharmony than Yin Deficiency with Effulgent Fire, Phlegm-Heat, Heart-Spleen Deficiency and Liver Stagnation (Table 9.32).

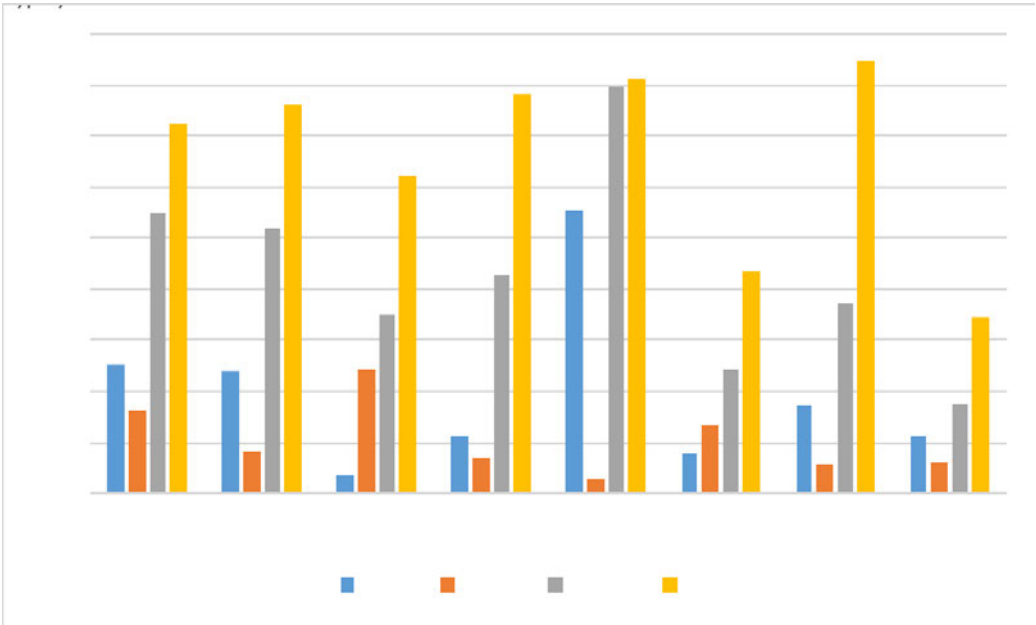

Figure 9.29. Categories of herbs used according to the pattern. The Y-axis represents the proportion of spirit-calming herbs in the formula while the X-axis represents the pattern. 0 = not classified, 1 = Yin Deficiency with Effulgent Fire, 2 = Liver-Spleen Disharmony, 3 = Phlegm-Heat, 4 = Heart-Spleen Deficiency, 5 = Liver Fire, 6 = Liver Stagnation, 7 = Blood Stasis.

Pattern	Not Cla	Yin Def	L-S Dis	Ph-Heat	H-S Def	Liv Fire	Liv Stag
Yin Def	0.004						
L-S Dis	0.107*	0.103*					
Ph-Heat	0.069*	0.065*	-0.038*				
H-S Def	-0.150*	-0.156*	-0.259*	-0.220*			
Liv Fire	0.085*	0.081*	-0.022*	0.016	0.236*		
Liv Stag	0.039*	0.035*	-0.069*	-0.030	0.190*	-0.046	
Blood Sta	0.068*	0.064*	-0.039	-0.000	0.220*	-0.017	0.029

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Table 9.15. Heart-nurturing herbs content differences between patterns. Not Cla = not classified, Yin Def = Yin Deficiency with Effulgent Fire, L-S Dis = Liver-Spleen Disharmony, Ph-Heat = Phlegm-Heat, H-S Def = Heart-Spleen Deficiency, Liv Fire = Liver Fire, Liv Stag = Liver Stagnation, Blood St = Blood Stasis. * P<0.05.

Pattern	Not Cla	Yin Def	L-S Dis	Ph-Heat	H-S Def	Liv Fire	Liv Stag
Yin Def	0.040*						
L-S Dis	0.040*	-0.080*					
Ph-Heat	0.046*	0.006	0.086*				
H-S Def	0.067*	0.027	0.107*	0.021			
Liv Fire	0.014	-0.026	0.054*	-0.032	-0.053*		
Liv Stag	0.054*	0.014	0.094*	0.008	-0.013	0.040	
Blood Sta	0.052*	0.012	0.092*	0.006	-0.015	0.038	-0.002

Table 9.16. Heavy-sedative herbs content differences between patterns. Not Cla = not classified, Yin Def = Yin Deficiency with Effulgent Fire, L-S Dis = Liver-Spleen Disharmony, Ph-Heat = Phlegm-Heat, H-S Def = Heart-Spleen Deficiency, Liv Fire = Liver Fire, Liv Stag = Liver Stagnation, Blood St = Blood Stasis. * P<0.05.

Pattern	Not Cla	Yin Def	L-S Dis	Ph-Heat	H-S Def	Liv Fire	Liv Stag
Yin Def	0.012						
L-S Dis	0.099*	0.087*					
Ph-Heat	0.061*	0.049*	-0.038				
H-S Def	0.124*	-0.136*	0.223*	-0.185*			
Liv Fire	0.152*	0.140*	0.053	0.091*	0.276*		
Liv Stag	0.088*	0.076*	-0.011	0.027	0.212*	-0.064	
Blood Sta	0.187*	0.174*	0.088*	0.126*	0.310*	0.035	0.099*

Table 9.17. Typical spirit-calming herbs content differences between patterns. Not Cla = not classified, Yin Def = Yin Deficiency with Effulgent Fire, L-S Dis = Liver-Spleen Disharmony, Ph-Heat = Phlegm-Heat, H-S Def = Heart-Spleen Deficiency, Liv Fire = Liver Fire, Liv Stag = Liver Stagnation, Blood St = Blood Stasis. * P<0.05.

Pattern	Not Cla	Yin Def	L-S Dis	Ph-Heat	H-S Def	Liv Fire	Liv Stag
Yin Def	-0.022						
L-S Dis	0.049	0.071*					
Ph-Heat	-0.032	-0.011	-0.081*				
H-S Def	-0.044	-0.022	-0.093*	-0.012			
Liv Fire	0.145*	0.167*	0.096*	0.177*	0.189*		

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Liv Stag	-0.064*	-0.043	-0.114*	-0.032	-0.020	-0.210*	
Blood Sta	0.189*	0.211*	0.140*	0.221*	0.233*	0.044	0.254*

Table 9.18. Spirit-calming herbs content differences between patterns. Not Cla = not classified, Yin Def = Yin Deficiency with Effulgent Fire, L-S Dis = Liver-Spleen Disharmony, Ph-Heat = Phlegm-Heat, H-S Def = Heart-Spleen Deficiency, Liv Fire = Liver Fire, Liv Stag = Liver Stagnation, Blood St = Blood Stasis. * $P<0.05$.

Spirit-calming herbs are considered to have adverse reactions, as cold-type spirit-calming herbs can damage the stomach (1), heavy-sedative herbs can damage the stomach (3) and have to be used in low quantity (below 30g for *longgu* and *muli*) (1), in combination with spleen-strengthening (1) or food-eliminating herbs (1), and not for long-term use (1). Mineral spirit-calming herbs can also lead to dementia (1). Sour-collecting herbs like *wuweizi* and *suanzaoren* can aggravate the phlegm-heat (1) or food, dampness and phlegm stagnation (1), they cannot be used in case of slimy fur (1). Finally, *yuanzhi* is slightly toxic and cannot be used on a long-term period (1).

Regarding the dose of the spirit-calming herbs, clinicians recommended to use high doses of *suanzaoren* (8), *banxia* (6) and *yejiaoteng* (2). The recommended dose of *suanzaoren* is minimum 15g (2), 20g (1), 30g (2) or 120g (1) and maximum 30g (1), 60g (2), 120g (3) or 180g (2). *Yejiaoteng* can be used up to 80g (1). The recommended dose of *banxia* is 15 to 30g (1) or more than 30g (2), and the dose can be progressively increased up to 50g. *Suanzaoren* (3) and *yejiaoteng* (1) are safe at high doses and do not provoke adverse reactions, however *banxia* can be toxic, therefore it has to be cooked longer (1) and the patient has to be careful about sensations in the lips, tongue, mouth and throat (1). In terms of preparation, one clinician mentioned that *suanzaoren* has to be stir-fried (*chao*) as raw (*sheng*) *suanzaoren* is indicated for hypersomnia, whereas another clinician explained that both can be used for insomnia, *sheng suanzaoren* being more appropriate for liver heat and *chao suanzaoren* being more appropriate for blood deficiency. The most appropriate type of *banxia* for insomnia is *fa banxia*, which is prepared with *gancao* and *shihui* (1).

For an optimal effect, spirit-calming herbs have to be used in the evening (4), half an hour before bedtime (1), as a form of granules (1).

Spirit-calming herbs can also be used to substitute to hypnotic treatments (1). In this case, they have to be used similarly to hypnotics, before bedtime, and the dose has to be reduced progressively (1).

9.7. General considerations

Several considerations should be taken regarding the use of Chinese medicine herbs for insomnia. These considerations cover the use and the limitation of certain herbs.

Several clinicians recommended to protect the spleen and stomach (10) as insomnia is a chronic condition which can impair the spleen and stomach (1). The use of certain herbs can also affect the spleen and stomach and should be used carefully. Rich tonifying herbs such as *shengdi* and *shudihuang* can block the stomach and qi-regulating herbs such as *chenpi*, *zhiqiao*, *muxiang*, dampness-removing herbs such as *fuling* and *sharen*, and food-transforming herbs such as *shanzha*, *jineijin* and *guya* can be added to the formula (1). Cold (1) and heavy (1) spirit-calming herbs can affect the spleen and stomach (2). In case of acid reflux and heartburn one can use *huanglian*, *wuzhuyu*, *haipiaoxiao* and *zhebeimu* (1), or *ganjiang* and *rougui* to warm the stomach (1), or use *baizhu*, *jineijin* and *sharen* to strengthen the spleen (1). Bitter-cold heat-clearing herbs damage the spleen and stomach (3) and should not be used for long-term (1) or in case of spleen-stomach *yang* deficiency (1). Low-doses of *ganjiang* (1) and spleen-protecting herbs such as *baizhu*, *jineijin* and *sharen* (1) can be used. One clinician pointed out that one should not use warm-dry-dispersing herbs or sweet-warm herbs when protecting the spleen and stomach in an insomnia population (1). Liver-draining and stomach-harmonising herbs such as *foshou*, *lvmeihua*, *meiguihua* and *bayuzha* should be used instead of *chenpi*, *muxiang*, *houpo* and *banxia* (1). Neutral herbs such as *taizishen*, *zhi gancao*, *shanyao*, *dazao* and *longyanrou* should be used instead of *huangqi* and *dangshen* (1).

Clinicians recommend to use liver-draining *qi*-regulating herbs such as *chaihu* and *xiangfu* carefully as they are pungent, warm, fragrant and dry and therefore damage the *yin* (4). They should not be used long-term (1), can be replaced by flower-type herbs (1) or can be combined with *yin*-nurturing herbs (1). Liver-calming and liver-clearing herbs can also damage the *yin* and have to be used with tonifying herbs (1). *Qi*-tonifying and *yang*-tonifying herbs have also to be used carefully (3) as they may worsen the excess (1) or damage the *yin* (1). The use of orifice-opening herbs is controversial as one

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clinician suggested they make activate the brain (1) while another clinician found them beneficial as the heart orifice of chronic insomniacs is blocked (1). Finally, the *yangqi* has to be protected when using rich and slimy herbs (1). More generally, there should be a balance in the formula, for example cold formulae must be supplemented with low-doses of *rougui*, *guizhi* or *wuzhuyu* and *tonifying* formulae must be supplemented with *qi*-moving herbs (1).

9.8. Preparation, intake methods and treatment regimen

Only a few recommendations were given concerning the treatment preparation method. These are cooking longer spirit-calming herbs and asking the family to cook the herbs in order to avoiding tiring the patient.

In terms of time of intake, it is usually recommended to take the herbs once in the afternoon and once in the evening (8) instead of the traditional morning-evening intake. The reason for this is to attain an optimum blood concentration (3), to adhere to the natural rise of the yin during the second half of the day (2), to increase the strength of the treatment without having to increase the dose (1), and to avoid daytime sleepiness (1). The precise time can be 2 pm (1) or 4 pm (1) for the afternoon and 8 pm (1), 9 pm (1), 1 to 1.5 hours before bedtime (1) or 2 hours before bedtime (1) for the evening. It is also possible to take the first cooking (which is more concentrated) 2 hours before bedtime and the second cooking (which is less concentrated) in the morning (3). Other alternative include taking the herbs three times a day, either before the meals (1) or twice during daytime and once at night (1), or to take all the herbs at once (2), especially in case of severe case (1). If the patient is weak (1) or if he/she has stomach conditions (1), he/she should take low doses of decoction frequently. If the patient cannot handle decoction, herbal infusions can be used instead (1). It is preferable to take the decoction before the meal in case of deficiency pattern such as Heart-Spleen Deficiency, Liver Blood Deficiency or Liver-Kidney Deficiency, and in case of Phlegm-Dampness or Phlegm-Heat as the herbs will help to regulate the stomach during the meal (1). It is preferable to take the decoction after the meal in case of congested fire in the upper part of the body as it would provoke vomiting if taken before the meal, and in case of blood stasis as the qi-moving and blood-activating herbs can damage the stomach (1).

Taking different formulas during daytime and night-time is another alternative (4). The night-time formula can either be the same formula added with heavy-sedative herbs (1) or a completely different formula (3). In this case, the daytime formula mainly regulates the movements of the qi (1), regulate the *yinyang* (1) or regulate the liver (1), and the night-time formula appeases the spirit (2) or drains the liver and appeases the spirit (1).

The treatment has to be taken for 1-2 weeks (1), 2 weeks (1) or 2-4 months (1).

9.9. Other herbal treatments

In addition to herbal decoctions taken orally, six types of herbal treatments are recommended, including herbal foot bath (9), herbal manufactured products (6), herbal pillow (3), herbal tea (3), paste (2) and injections (2).

Herbal footbath used either pattern-based formulae, reusing the herbs that had been cooked for herbal decoction (1), or using a standardised formula (4). The standardised formula is composed of spirit-calming herbs such as *yejiaoteng* (3), *cishi* (2) and *hehuanhua* (1), heat-clearing herbs such as *juhua* (2), *huangqin* (1) and *zhizi* (1), vessel-unblocking hers such as *honghua* (2), *tougucao* (1), *sumu* (1) and *jixueteng* (1) or warming herbs such as *fuzi* (1), *aiye* (1) and *shengjiang* (1). The average (range) dose is 76 (60-90) g of herbs (5). The herbs have to be cooked, then removed and 5000ml of warm water added (2). The temperature of the water should be 30-40 °C (1) or 40-45 °C (2). The water level should be above the ankles (1). The average (range) duration of the footbath should be 18 (10-30) minutes (8). The herbal footbath has to be conducted 1 hour (1) or just before bedtime (2) every evening (1) during 3 to 6 months (1). It is particularly adapted for patients with difficulty falling asleep (1).

Compared to herbal decoctions, herbal manufactured products are more convenient to use (1). They are used either on a pattern-differentiation basis (3) or on a disease-differentiation basis (3). Herbal manufactured products used on a disease-differentiation basis are shown in Table 9.33. Luo Hua An Shen mixture (1) and Tian Wang Bu Xin Dan (1) are used for all types of insomnia, and An Shen Bu Nao Ye is used for insomnia in older adults (1).

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Pattern	Product name (CN)
Blood Deficiency and Liver Excess	Yang Xue Qing Nao granules (2)
Non-Interaction between Heart and Kidney	Wu Ling capsule (2)
Heart-Spleen Deficiency	Gui Pi pills (1)
Liver Stagnation and Blood Deficiency	Xiao Yao pills (1)
Heart Qi Deficiency	Qi Ye Shen An tablet (1)
Yin Deficiency with Heat	Bai Le Mian capsule (1)
Blood Deficiency	Zao Ren An Shen capsule (1)
Heart Shen Disturbance	Xin Shen Ning tablet (1)
Kidney Deficiency	Tian Meng oral solution (1)
Hyperactive Liver Yang	Song Ling Xue Mai Kang (1)

Table 9.19. Herbal products used on a pattern-differentiation basis. CN = citation number.

For herbal pillows, different formulae have been proposed. The first formula is composed of *juhua* and *juemingzi* and is not modified (1). The second formula is composed of 100g of *juhua*, 100g of *cishi*, 100g of *yejiaoteng*, 30g of *zhu dengxincao*, 30g of *dingxiang*, 60g of *changpu*, 60g of *yuanzhi*, 60g of *fushen*, 20g of *tanxiang* and 10g of *bingpian* (1). In case of frequent dreams, 100g of *longgu* and 60g of *muli* are added to the formula (1). The last one is composed of *baiziren*, *yejiaoteng* and *cansha*, and is adapted according to the pattern (1). In case of Non-Interaction between Heart and Kidney *tusizi* and *yuanzhi* are added; in case of Blood Deficiency with Liver Excess *suanzaoren*, *juemingzi*, *juhua* and *hehuanhua* are added; in case of gallbladder deficiency and phlegm *hupo*, *yujin* and *changpu* are added; in case of kidney deficiency with blood stasis *shudi*, *danggui* and *hanliancao* are added (1). The herbs have to be grinded into gross powder and inserted into a fabric bag, and used as a pillow (2).

Herbal teas can be used according to the pattern such as *meiguihua* for Liver Stagnation and *maidong* for Yin Deficiency (1). Peanut stem extremities are used for postpartum insomnia (1) and a

combination of *gouqizi* and *meiguihua* for perimenopausal insomnia (1). The herbs have to be placed in 150 ml of boiling water and taken as a tea (1).

Paste are herbal decoction that are cooked for a long time until forming a paste. Usually, paste-like ingredients such as *ejiao* and *guijia* are added inside (1). The formula *Zi Shen Yang Xue* paste, composed of *nvzhenzi*, *hanliancao*, *gancao*, *xiaomai*, *dazao*, *baihe*, *shengdihuang*, *ejiao*, *guijia*, *taoren* and *heizhima* is used for perimenopausal insomnia in order to nurture the essence and the blood (1). Paste is also used for the more general insomnia population in case of deficiency in order to tonify *qi* and blood, or after the treatment in case of excess in order to help the patient recover (1). When preparing paste, attention should be paid to the taste, colour and smell of the paste (1). It can be also useful to regulate the spleen and stomach for one week before starting the treatment (1).

One clinician recommends to use *ciwujia* injection with intravenous drip for 7 to 10 days on the basis of other treatments for insomnia (1). Another clinician recommends to use vitamin B12 injections on GB20 *fengchi* in order to stimulate the point for treating perimenopausal insomnia (1). For the latter, 1 ml of vitamin B12 injection is injected in each points at 4:30 pm every day (1).

9.10. Psychological interventions

Psychological interventions were considered part of the treatment by 82 clinicians, however one clinician mentioned that insomnia “could not be treated only with a simple psychological induction”. In all the 82 reports that mention psychological interventions, there were used as a complementary treatment, not the main treatment. Unlike Chinese herbal medicine and acupuncture, the definition of psychological interventions in Chinese medicine is broad and vague. The terms to define psychological interventions are varied, including psychotherapy (*xinli zhiliao*), psychological dredging (*xinli shudao*), psychological tutoring (*xinli fudao*), psychological education (*xinli jiaoyu*), psychological care (*xinli huli*), emotional care (*qingzhi huli*) and mental regulation (*jingshen tiaoshe*). The distinction between these terms by the clinicians is not clear. These term can either refer to non-specific aspects of the consultation (such as the attitude, voice, etc.) or to specific therapies or techniques used to treat the patient. In most of the reports, the description of the psychological intervention is limited to a conceptual level (the name of the therapy and the goal of the treatment).

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The main goal of psychological interventions is to regulate emotions, which are closely associated with insomnia.

The non-specific aspects of the consultation include the voice and attitude of the clinician, a patient-centred approach, an active involvement in the emotional factors of the disease and a convincing communication (Table 9.34). The objectives of these non-specific aspects are to create confidence between the clinician and the patient, to control negative emotions, to improve adherence to treatment and make the patient more optimistic about the treatment outcome.

Non-specific aspect	Description
Voice, tone and attitude	The clinician should have a respectful, noble and humble attitude, be careful of his/her wording, be warm, gentle, caring, friendly and compassionate, and be optimistic.
A patient-centred approach	The clinician should put his attention on the patient, listen carefully and sincerely what the patient is saying, answering when appropriate, supporting, comforting, encouraging and praising the patient. The clinician should put himself at the place of the patient. The clinician should not explain excessively, make promises, neglect or despise the patient.
Active involvement	The clinician should look for and try to understand the psychological reasons and emotional factors underlying the symptoms. The clinician should have "heart-to-heart talk" (*tanxin*), which means discussing about what one's have in his heart, induce catharsis (*xuanxie*), "open and direct" (*kaidao*) the patient, which means guiding the patient to see things differently, for example "treating annoying events with a usual mind", and "open the nodes of the mind" (*jiekai xinjie*), which means letting go of the congestion of emotions and thoughts. The clinician should use reason to control the patient's emotions and use explanations to remove confusion (e.g. about the causes of insomnia or the harm of drugs).
Convincing communication	The clinician should use convincing knowledge, knowledge about physiology and pathology and suggestions of good prognosis in order to convince the patient.

Table 9.20. Description of the non-specific aspects of psychological interventions.

The psychological therapies proposed by the clinicians are reported in Table 9-35. Many of these therapies are similar to Western psychotherapy, such as psycho-education, cognitive therapy and sleep hygiene. However, the way of conducting these therapies is influenced by cultural specificities. For example, seeing the relativity of things is influenced by Daoist philosophy and the *yinyang* theory; Tai Chi and Qigong are culturally-adapted relaxation methods; creating a positive conditioning through habits is different from the Western view of avoiding sleep rituals; Morita therapy is also influenced by East-Asian culture.

Participant Initials				Participant ID			

Therapy (CN)	Protocol
Cognitive therapy (8)	Cognitive therapy targets the false beliefs about sleep, including the consequences of insomnia on health, dreams, worry about insomnia, excessive expectations about sleep, excessive attention on sleep, exaggeration of symptoms, the attribution of daytime symptoms (e.g. psychological factors) and the reasons of the failure of previous treatments. The patient must also understand the relativity of everything, including the relation between oneself and society, between public and private, between obtaining and loosing. In terms of technique, the preparation for the worst (i.e., not sleeping at all) and role play (i.e., explaining sleep knowledge to a friend who has insomnia).
Sleep hygiene (5)	Sleep hygiene include having a regular schedule, improving the sleep environment (comfortable bed, no light), relaxing before bedtime, avoiding strong tea, coffee, tobacco and alcohol, having a frugal dinner, and not using sleep time for entertainment activities such as playing video games.
Relaxation (4)	Relaxation training include muscular relaxation, deep-breathing relaxation, mental imagery, biofeedback, Tai Chi and Qigong.
Behavioural therapy (4)	Behavioural therapy includes (1) stimulus-control therapy recommendations such as avoiding to use the bed during the day and staying out of bed when awake; (2) sleep-restriction therapy recommendations such as controlling time in bed and avoiding sleeping during the day; (3) writing up a daily schedule; (4) creating sleep conditioning with habits such as foot bath, wearing pyjamas, low lights, listening to soothing music.
Education (3)	The clinician provides information about the cause, mechanism and characteristics of insomnia, the treatment of insomnia (including hypnotic drugs), and the relations between emotions and insomnia.
Hypnosis (1)	After inducing the patient into hypnosis state, negative ideas are changed into positive ideas, or the patient is asked to imagine a sleep-promoting situation such as travelling in a train, hearing the repetitive sounds of the train and the wind. Self-hypnosis can also be used. In this case, the patients repeat to himself sleep-promoting suggestions such as “sleep, I’m very sleepy, I will fall asleep, etc.”, but the patient should not use excessive suggestions such as “I need to sleep, just sleep now!”. Also, the patient should not fuss about the results.
Morita therapy (1)	Morita therapy is about going along with nature. The patient is recommended to think “If I stay in bed, I can rest even if I’m not sleeping”, and obey to his natural sleepiness instead of trying to control sleep.
Moving-attention-to-change-direction therapy (1)	The patient is recommended to conduct outdoor activities (travelling, hiking, sport, etc.) and hobbies to distract his attention. Other individualised approaches to disperse the attention can be used.

Table 9.21. Psychological therapies proposed by the clinicians. CN = citation number. Only the citations in which the protocol was described were counted.

9.11. Recommendations and self-treatment

Self-treatment is an important part of Chinese medicine treatment. As such, clinicians often make recommendations for lifestyle changes at the end of the session. These lifestyle changes can be categorised in four categories, i.e. activities, life attitude, sleep behaviours and environment, and diet. Self-treatment methods, food therapy and acupressure, are also recommended for insomnia patients.

Participant Initials				Participant ID			

9.11.1. Recommendations

The most common recommendations from the clinicians was to conduct more physical exercise (29), including sport, Tai Chi, Qigong, etc. Only one clinician mentioned the duration and frequency of the exercise, 30-60 minutes every day. It can be conducted either in the morning (1) or in the late afternoon or evening (1). Physical work is also recommended as a type of physical exercise (3). Physical exercise was recommended for insomnia as it can help to regulate emotions, including by distracting the patient from his/her symptoms, and also to improve the activity/rest balance, as more activity during the day are considered to improve the sleep at night. The second most common recommendation about activities is to have a regular schedule (19). Patients are also recommended to conduct more cultural and entertainment activities (9) such as painting, reading, making calligraphy, etc., having more social interactions (5) including group activities, staying in contact with nature (2), having hobbies (1), conducting cheerful activities and work (1), and staying in contact with happy events (1). A good work/life balance (4) was also recommended, which can be more work or less work depending on the condition on the patient, but always more physical exercise (1).

Life attitude recommendations were also common. The clinicians recommend that patients control their emotions (17), especially anger (1), to stay optimistic and happy (10), to keep a "smooth" or "flowing" (*shuchang*) mood (8), to control and reduce their thoughts and worries (6), to keep a peaceful and plain mind (5), to reduce their psychological pressure (4), to keep an open and not-competing attitude (3), to reduce external psychological stimuli (2), and to not look for fame and money (1) or for perfection (1).

More specifically about sleep, the patients are asked to stay away from exciting substances (i.e., strong tea, coffee, alcohol and tobacco) before bedtime (21), to improve their sleep environment (11), including having a calm and dark sleep environment with fresh air and adapted temperature, a comfortable bed and appropriate pillow, to avoid eating too much (8) and having a light meal (4) for dinner, and avoiding eating 3 hours before bedtime (1). According to the clinicians, the patients should go to bed early (3), preferably before 11 pm (1), and get up early as well (1). The patient should avoid excitement before bedtime (10), including intense exercise or emotional movies,

thinking less before bedtime (4), limit daytime sleep (2), and avoid watching TV at night (1), as these activities are harmful to sleep. Sleep-promoting activities that can be used before bedtime are having a hot foot bath (5) followed by the massage of KI 1 *yongquan* point (3), drinking hot milk (3), sugar water (1) or hot water with a spoon of vinegar (1), counting (2), using relaxation techniques (2), and having a hot shower (1).

These recommendations are adapted to all insomnia patients, yet some can be individualised according to the pattern. For example, meditation before bedtime is recommended for patients with non-interaction of heart and kidney (1) and the recitation of the Heart Sutra is recommended for patients with liver fire (1).

In terms of diet, a healthy (5), light (4), easily digested (2) and regular (1) diet is recommended for every patient. The patient should avoid spicy and irritating (6), cold (including cold nature) (4), high-fat (4), hard (2), sticky (1), hot-dry (1), raw (1), sweet (1) and gas-producing (1) food. Some recommendations are adapted to the pattern of the patient. Patients with Phlegm-Heat should have light (3) and easily digested (2) food, avoid high-fat (2), sweet (2), sticky (1) food and meat (1), as well as irritating food (1) such as onions, garlic and chili. Patients with Gallbladder and Heart Deficiency should avoid stimulants (1) such as alcohol and tobacco, and radish (1). Patients with Liver Fire should avoid spicy food (1). Patients with Yin Deficiency and Effulgent Fire should avoid spicy food (1) and alcohol (1). Patients with Spleen and Stomach Yang Deficiency should avoid cold (1), raw (1), high-fat (1) food and mung beans (1).

9.11.2. Food therapy

Food therapy can be used either on a disease or a pattern basis. Food that was considered beneficial regardless of the pattern are pork brain, pork heart, lotus seed (*lianzi*), celtuce, and jujube (*dazao*). The following recipes were also suggested:

1. **Sour jujube porridge**: 50g of sour jujube (*chao suanzaoren*) and rice cooked to make porridge.

2. **Polygalacea and sour jujube porridge**: use 15g of polygalacea (*yuanzhi*), 10g of sour jujube (*chao suanzaoren*) and 75g of rice to make porridge.

Participant Initials				Participant ID			

3. **Vinegar and millet porridge**: cook the millet to create porridge. Take the porridge one hour before bedtime. Take 10ml of vinegar half an hour after taking the porridge. Repeat every evening.

4. **Longan, lotus seed and pork heart soup**: boil 30g of lotus seed (*lianzi*), 30g of longan (*longyanrou*) and half a pork heart with a bit of salt until cooked. Take once every evening one hour before bedtime.

However, food therapy is mostly adapted to the situation of the patient. Food and recipes prescribed according to the pattern are shown in Table 9.36. Additionally, Mushroom soup are recommended for patients with stomach conditions, daylily and kaoliang porridge are recommended in case of spleen deficiency, seaweeds, onions and cabbage are recommended for menopausal women, and donkey skin paste is recommended for older adults with Qi and Blood Deficiency. Donkey skin paste is made of donkey skin (*ejiao*), walnuts (*hutaoren*), crystal sugar and glutinous rice alcohol cooked to make a paste. One spoon has to be taken every day.

Pattern	Food, dishes and recipes
Yin Deficiency with Effulgent Fire	Food such as longan (*longyanrou*), jujube (*dazao*), lotus seed (*lianzi*), wood ear, milk, low-fat meat.
Non-Interaction between Heart and Kidney	Food such as Mulberry (*sangshen*), lily flower (*baihe*), goji berry (*gouqizi*), tofu, celtuce, daylily. **Soup of mulberry and jujube**. Boil 15g of mulberry (*sangshen*) and 50g of jujube (*dazao*). Take once a day for 2 weeks.
Heart-Spleen Deficiency	Food such as wheat, lotus seed (*lianzi*), jujube (*dazao*), longan (*longyanrou*), yam, bergamot (*foshou*), papaya (*mugua*), hawthorn (*shanzha*). Dishes such as jujube (*dazao*) soup, poria (*fuling*) cake, yam (shanyao) and lotus seed (*lianzi*) porridge, jujube and wheat porridge. **Sour jujube seed porridge**. Boil 60g of sour jujube (*suanzaoren*), take the juice, then cook 100g of rice in the juice to make porridge. Add monosodium glutamate and white sugar as appropriate. Take in the morning and in the evening.
Stomach Disharmony	Food such as hawthorn (*shanzha*), white radish, water chestnut. **Pinellia root and kaoliang porridge**. Boil 10g of pinellia (*fa banxia*), take the juice and use it to cook 100g of kaoliang into porridge. When the porridge is half ready, add 150g of white radish and cook until ready. Take twice, morning and evening.
Phlegm Heat	Food such as white radish, water chestnut, jellyfish.
Spleen and Stomach Disharmony	Food such as millet, lotus seed (*lianzi*) and lily flower (*baihe*) porridge.
Qi Deficiency of Heart and Gallbladder	Food such as longan (*longyanrou*), jujube (*dazao*), lotus seed (*lianzi*). Dishes such as white ginseng (*bai renshen*) soup. **Codonopsis and atractylode rice**. Boil 10g of codonopsis (*dangshen*) and atractylode (*baizhu*) for half an hour. Take the codonopsis and the atractylode out and cook the rice in the decoction.

Participant Initials				Participant ID			

Liver Qi Stagnation	Food such as millet, oyster, milk and longan (*longyanrou*).
Liver Stagnation creating Fire	Food such as mandarin, orange, citron, kumquat and white radish.
Blood Heat	Food such as mung beans, coix seed, lotus (*oujie*), sophora japonica, crystal sugar. Drinks such as rehmannia (*shengdihuang*) and crystal sugar tea.
Liver and Heart Fire	Sour jujube (*suanzaoren*) porridge.

Table 9.22. Food, dishes and recipes according to the pattern.

9.11.3. Acupressure

Acupressure protocols follow also either a disease or a pattern basis. Disease-based protocols include the following points: KI 1 *yongquan* (2), HT 7 *shenmen* (2) SP 6 *sanyinjiao* (2), EX-HN 3 *yintang* (1), EX-HN 5 *taiyang* (1), GV 11 *shendao* (1), PC 6 *neiguan* (1), ST 36 *zusanli* (1), and the areas of the forehead (1), the upper back (1) and the stomach (1). The pattern based protocols include: GV 24 *shenting*, EX-HN 3 *yintang*, and the dorsal groove of the ear for Liver Stagnation creating Fire (1); SP 6 *sanyinjiao* and PC 6 *neiguan* for Yin Deficiency with Effulgent Fire (1); ST 36 *zusanli* for Heart and Spleen Deficiency (1); ST 36 *zusanli* and SP 6 *sanyinjiao* for Heart and Kidney Deficiency (1); SP 6 *sanyinjiao* for Phlegm-Heat (1).

9.12. Integrative Chinese medicine

Chinese medicine is sometimes integrated with non-Chinese medicine therapies such as Western medicine (i.e., pharmacotherapy) and psychotherapy.

Chinese medicine and Western medicine are integrated in a stepped-care manner. Hypnotics such as Estazolam are used first (6), especially if the insomnia is severe (3), in order to control the symptoms of insomnia quickly and efficiently, and also to relieve the anxiety of the patient. Chinese herbal medicine is then used in second place (6) in order to treat the root of the condition, reduce the dose of Western medicine drugs (which can bring side effects and dependency) and control the secondary symptoms (which can impair sleep) such as hot flushes, frequent urination, and agitation. If the patient is already dependent on hypnotics, CHM can be used to discontinue the use of hypnotics (3). In this case, it is important to not discontinue the use of hypnotics abruptly but progressively (3). The dose of hypnotics can be reduced at a pace of ¼ or 1/8 of a tablet each week (1). Spirit-calming herbs such as *zhenzhumu*, *yejiaoteng*, *longgu*, *muli*, and *suanzaoren* can be used before bedtime in order to replace hypnotic drugs. Additionally, anti-depressant and anxiolytics (4) such as Deanxit (1) can be

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used, especially in case of moderate-to-severe anxiety and depression (2). Finally, using Western medicine diagnostic methods to understand comorbidities allows the clinician to treat the patient more efficiently (2). For example, in addition to the treatment for insomnia, *qi*-tonifying herbs and blood-nurturing herbs can be used if there is anaemia (2).

Chinese medicine can also be combined with CBT-I (4) and hypnosis (1). Few details about the integration of these therapies were available in the reports.

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Chapter 10. Discussion and conclusion

10.1. Main findings

10.1.1. General findings

The clinician reported three main types of treatment modalities, i.e., CHM, acupuncture and tuina. As the subject of the thesis is the treatment of insomnia with CHM, acupuncture and tuina treatment protocols were not presented in this thesis. Additionally, psychotherapy, self-treatment and integrative approaches were found to be part of the clinician's arsenal to manage insomnia. Except the traditional pattern diagnosis and disease diagnosis modalities, we found the disease characteristics, the disease subtype and the specificities of the person, the location and the season to be important diagnostic considerations to create a complete overview of the patient's condition. Therapeutic considerations including the prevention of adverse reactions, treatment modalities, doses, method of preparation and administration were also discussed by the clinicians.

10.1.2. Chinese herbal medicine treatments based on patterns

In total, 498 formulae were extracted from 154 CERs. The formulae were clustered into seven patterns which were labelled "Yin Deficiency with Effulgent Fire", "Liver-Spleen Disharmony", "Phlegm-Heat", "Heart and Spleen Deficiency", "Liver Fire", "Liver Stagnation" and "Blood Stasis". However, these pattern are not equal in terms of characteristics. The "Yin Deficiency with Effulgent Fire" and "Liver-Spleen Disharmony" patterns have both a loose definition, covering several pathological mechanisms, having several major formulae, SSs and herbs with relatively low sensitivity and specificity levels and a relatively high number of formulae, and changing easily when the variables of the cluster analysis are changed. These patterns may be constituted of sub-patterns that are closely related. On the other hand, the "Phlegm-Heat", "Heart and Spleen Deficiency", "Liver Fire" and "Blood Stasis" patterns have a strict definition, having one pathological mechanism, one major formula, SSs and herbs with relatively high sensitivity and specificity levels and being immune to changes in cluster analysis variables.

10.1.3. Chinese herbal medicine treatments based on the disease

By analysing the content of CERs reporting the treatment of insomnia with CHM on a disease-based approach, we identified four major categories of main formulae, which are "Spirit-Calming" formulae, "Suan Zao Ren Tang", "Liver-Draining" formulae and "Big and Diverse" formulae. The

authors of the CERs also recommended to modify the main formula according to the pattern of the patient, including “Liver Stagnation”, “Phlegm-Heat”, “Liver Fire”, “Hyperactive Liver Yang”, “Heart-Spleen Deficiency” and “Non-Interaction Between Heart and Kidney”. As insomnia is generally considered as a condition in which “the spirit is disturbed” [75], it is not surprising that some clinicians use herbs with spirit-calming effects such as *suanzaore*n or s*houwuteng*. These herbs are known to have hypnotic and sedative effects [329, 442, 443]. Suan Zao Ren Tang is a classic formula (i.e., a formula that comes from the Chinese medicine classic Shanghan Zabing Lun) and was originally indicated specifically for insomnia. Suan Zao Ren Tang may be used as a main formula for insomnia for the potential reasons: (1) classic formulae are authoritative; (2) It works on core aspects of insomnia pathological mechanism (i.e., yin and blood deficiency, liver stagnation and fire); (3) *suanzaoren*, the main ingredient of the formula, is the most commonly used and a well-studied herb for insomnia [316, 329]. Liver-draining formulae may be used on a disease-differentiation basis as liver stagnation is the main primary mechanism of insomnia, leading to liver fire, phlegm-heat, blood stasis or blood deficiency. Draining the liver is the equivalent of “cutting the trunk” of insomnia pathological mechanism. The use of “Big and Diverse” formulae may represent the will to cover every aspect of insomnia pathological mechanism with herbs from many different categories.

10.2. Comparison with existing knowledge

10.2.1. Existing guidelines for the pattern-based treatment with CHM

The pattern classification from the present study is largely consistent with the current guidelines [6, 7, 426, 427] and the patterns used in clinical studies [253, 444]. However, several discrepancies can be pointed out. The Heart and Gallbladder Qi Deficiency (represented by An Shen Ding Zhi Wan) and the Stomach Disharmony (represented by Bao He Wan) patterns from current guidelines did not form major patterns in our CER-based classification. In the above sources, the Blood Stasis pattern is often considered as an additional pattern whereas it stands as a major pattern in our CER-based classification. The Liver Stagnation and Liver-Spleen Disharmony patterns are largely absent from current guidelines. As the methodology of the guidelines is unknown, it is difficult to conjecture on the reason of these discrepancies.

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10.2.2. Existing guidelines for the disease-based treatment with CHM

As the disease-approach of the treatment of insomnia with CHM is not reported in the literature, we can only compare the pattern-based modification of the main formula to existing pattern classifications of the treatment of insomnia with CHM. “Phlegm-Heat”, “Liver Fire”, “Heart-Spleen Deficiency” and “Non-Interaction Between Heart and Kidney” are widely considered as major patterns of insomnia [6, 7, 426, 427]. Hyperactive Liver Yang, which is of limited size in our study, is usually not considered as a major pattern of insomnia. The “Yin Deficiency and Effulgent Fire” pattern, which is a major pattern in the pattern-differentiation approach, was not detected in this study.

10.3. Strength and limitations

The main strength of this study is the novel and explicit methodological approach to the identification of insomnia patterns. This allowed the reader to appreciate the validity and the generalizability of the findings, and to reproduce the study. Another important advantage compared to existing manuals and guidelines is the flexibility of the definition of the patterns, which include different formulae and are defined by large ranges of herbs and SSs, as it has been shown that patterns do not have tight boundaries [445]. Moreover, reporting the pathological mechanism allows to understand the relationships between these patterns. Another important point is the hierarchy of herbs and SSs using sensitivity and specificity levels. The main limitation of this CES is that it relies on the assumption that the authors of CERs were able to detect effectively the patterns relevant to insomnia treatment as well as the related SSs and effective treatments. Large-scale clinical databases that are currently being built may help to validate these findings in the future [446, 447]. The quality of the reports has not been assessed as to date there is no assessment tool or guideline. Finally, the classification of patterns using the ingredients of the formula is an innovative method that may not be accepted by clinical experts.

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To our best knowledge, this is the first study that systematically collected and analysed clinical experience on the treatment of insomnia with Chinese medicine. As clinical experience is to date one of the main bases for clinical decisions by Chinese medicine clinicians, this study can provide valuable guidance for clinicians. The procedures used in this study set a precedent in the field for the synthesis of clinical experience and creation of guidance that is both relatively reliable and clinically relevant for clinicians. These procedures can be replicated for the synthesis of clinical experience on other conditions or other topics (e.g., the use of a specific formula). This basis can be further improved and lead to more reliable and clinically relevant guidance.

This CES was also able to identify elements that seem to be clinically relevant according to Chinese medicine clinicians, yet were not identified and described by current textbooks and guidelines. For example, the yang deficiency pattern of insomnia was mentioned by dozens of clinicians, yet it is completely absent from current textbooks and guidelines. It gives another perspective on the diagnosis of Chinese medicine as well. For example, current textbook and guidelines usually give a series of SSs as indications for a certain pattern. In this CES, the SSs are reported with sensitivity and specificity levels, which allow clinicians to make a more informed decision when conducting pattern diagnosis. Some important aspects of clinical reasoning developed in this CES such as the adaptation of the treatment according to the person, the location and the time, the management of comorbidities, the integration with biomedicine are also absent from current textbooks and guidelines. Hopefully, this could engage the dialogue on the necessity of integrating these elements in clinical practice, but also educational programs and clinical research in the field of Chinese medicine.

The use of quantitative analyses and quantitative data reporting methods allowed us to limit the influence of the beliefs of the reviewers on the study. Compared to current textbooks and guidelines which do not provide the methods for selection of main patterns (which results in different classifications in different documents), our approach is replicable and does not rely on the experience of one individual or a small group of individuals. The word clouds are also an innovative method to report the SSs, formulas, herbs and acupuncture points related with certain patterns. They allow to

present large quantity of information without overwhelming the reader and provide a relatively simple and instructive guidance. The decision tree is also relatively simple to follow and apply for clinicians.

Despite these important strengths, the current study also suffers from significant limitations. First, this method and the decision taken during the CES were based on a small number of authors. These decisions and the procedures themselves will have to be validated by a larger pool of peers in the field. One way to achieve this is to publish the results of the CES in peer-reviewed journals, which allows peers in the field to review the methods and content and provide comment and feedback. A Delphi study could also be conducted to validate the methods and results used in this CES and provide clarifications on certain important questions.

The use of CER as a main source for information is also subject to potential critics. One of these critics is that the content of the CER does not reflect the way the clinicians are ‘really’ working in the clinic. However, we could object that, even though the reason for dishonesty in reporting the results of a clinical trial is clear (a positive result is useful for the author’s career), there is no reason to be dishonest in a CER. For example, if a clinician reports using Gui Pi Tang for patients who present certain SSs, there is no reason for this clinician to report they do not use this formula, report they use another formula, or present different associated SSs. Future CES could incorporate clinical cases in addition to CERs to add evidence that the methods presented in the CERs are indeed implemented in clinical practice. If resources allow, interviews with actively practising clinicians could also be conducted and even observation in clinical settings.

Although the quantitative analyses increase the validity of the CES and provide valuable information, they present significant drawbacks. Because some patterns may include formulas that have a wide variety of herbs, the cluster analysis may have failed to identify important patterns that are used in the clinic. In this CES, we have overcome this problem by reporting qualitatively ‘atypical’ patterns that could be identified by the name of the formula but not the cluster analysis of the ingredients of the formula. K-mean cluster analysis tends to group together elements that do not belong to any other cluster and form together a large, highly heterogeneous cluster. In this CES, this was the case for the

'Classical Formula' pattern, which does not represent a pattern with a specific direction. This issue was reduced by discarding formulas which were distanced from the cluster centres. Yet, this method itself poses a problem as it needs decision from the author of the CES, which implies a risk of bias. This issue should be considered in the design of future studies and the methods to overcome this issue should be further standardised and validated. The word clouds allow the reader to grasp quickly the essence of a pattern, yet do not present the context of SSs. For example, a sign of 'headache' could reflect a problem of liver fire rising if the tongue is red, but it could reflect a problem of blood stasis if the tongue is purple. This issue is a global problem in the design of guidance material for Chinese medicine clinicians which is not limited to this CES. The design of future studies should also consider this issue. Finally, the decision tree was created through statistical analysis of the association between SSs and Chinese medicine patterns. It is unclear how well it can mimic the 'real' clinical reasoning of a human clinicians, and if it can help clinicians to improve the precision of their diagnosis. Future studies will be needed to validate the use of decision trees from CES in clinical practice.

10.4. Implications for clinical practice and research

One of the main achievements of our study is to use a new methodology involving the analysis of clinical experience reports which is both rigorous and adapted for a holistic medicine such as CHM. The next step will be to replicate this methodology to synthesize the experience of clinicians on other medical conditions. Future clinical trials will have to test a protocol based on the findings of this CES to ensure the effectiveness of the present classification. The creation of assessment tools and guidelines will also be needed to improve the quality of CERs.

The efficacy of Suan Zao Ren Tang used in a disease-based approach for insomnia is well understood (Liang *et al*., 2019, Ni *et al*., 2015, Zhou *et al*., 2018). However, the other categories of formulae for the disease-based approach are not well studied, despite the relative easiness to conduct RCTs with this approach. Future clinical studies will have to assess the efficacy of the "Spirit-Calming", "Liver-Draining" and "Big and Diverse" formulae.

The methodology used in this study is innovative and allows to produce guidance material on the individualisation of Chinese medicine treatment based on pooled experience, which is relevant for

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holistic practices such as Chinese medicine. In the future, this methodology can be replicated to provide guidance on the treatment of other medical conditions with acupuncture. Additionally, the treatment protocol we have built on the basis of the most commonly recommended points can be tested in future clinical trials. Assessment tools and guidelines are also needed to improve the quality of CERs. The findings of this study were relatively well accepted by Chinese medicine clinicians who attended a workshop in which these results were presented.

10.5. Conclusion

Through the systematic synthesis of CERs, we have developed a classification of seven patterns relevant to the treatment of insomnia with CHM. This classification is mostly consistent with current guidelines, but discrepancies exist. The CES is a promising methodology to create guidelines based on pooled clinical experience.

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Summary of key findings and discussion

1. Key findings

Sleep is a recurrent inhibition of the Ascending Reticular Activating System leading to a reversible state of altered consciousness. Insomnia is a chronic impairment of sleep, manifested with difficulty falling asleep and/or staying asleep. Hyperarousal is the core pathological mechanism of insomnia. This hyperarousal is related to complex behavioural, cognitive and physiological factors. Pharmaceutical drugs targeting the benzodiazepine receptors and CBT-I are currently recommended for insomnia. However, these interventions have significant drawbacks, including adverse reactions, long-term adverse outcomes, and difficult access. Due to these drawbacks and individual preferences, a significant proportion of insomnia patients use CAM to treat insomnia. Recent research pointed out the potential of Chinese herbal medicine as an alternative treatment for insomnia.

ZRAS is a Chinese herbal medicine product composed of *suanzaoren*, *danshen* and *wuweizi*. It is a promising treatment for insomnia due to the traditional clinical use of its ingredients for insomnia and the relatively convenience of the administration (i.e., capsules or pills taken orally). The results of our meta-analysis showed that ZRAS is more effective than placebo and that its efficacy is comparable to BzRAs, with relatively less adverse reactions. As none of the included studies used appropriate methods of blinding, there is a high risk of bias. Thus, the evidence for the efficacy of ZRAS is weak. We conducted a randomised-controlled trial with double blinding to compare the efficacy and safety of ZRAS capsule with placebo. We found that, although ZRAS capsule is highly acceptable and safe, the reduction in insomnia severity was not significantly higher in the active group. However, subjective SOL was significantly shorter in the active group at post-treatment.

We also conducted a clinical experience synthesis of the treatment of insomnia with Chinese herbal medicine. We found that insomnia is mainly treated with a pattern approach, i.e. using an individualised formula that addresses a pathological mechanism identified through signs and symptoms. There are

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2. Quality of Chinese medicine research

The systematic review showed that ZRAS performed better than placebo in improving insomnia severity yet the clinical trial was not able to replicate these findings. The results of the clinical trial and the systematic review are conflicting.

The most straightforward explanation is the quality of the research in the field of Chinese medicine. The quality of clinical trials testing Chinese herbal medicine and acupuncture treatments has been a concern for a long time [448]. In Western countries Chinese medicine is a marginal CAM and researchers in the field lack the access of resources from the mainstream medical system. As a results, clinical trials tend to be limited to pilot studies and randomised studies with small sample size. In China, Chinese medicine is part of the mainstream medical system and has access to resources such as grants and hospitals to conduct clinical trials. Although sample sizes are much larger, the methodological quality of the studies is generally poor. Indeed, appropriate randomisation procedures and blinding procedures are rarely implemented [449]. Non-validated measures of assessment are widely used [449]. As such, the results of these studies tend to be inflated due to bias. Due to the quasi absence of negative results, some scholars even mention a “cultural bias” [450]. This cultural bias is not only limited to the field of Chinese medicine and extends to other medical fields [451].

3. Conflicts between clinical practice and experimental research

ZRAS was tested in the systematic review and the clinical trial conducted as part this doctoral thesis. ZRAS is a standardised herbal treatment composed of herbs known to have sedative properties and it is taken once a day before bedtime. This standardised treatment approach is in sharp contrast with the treatment model proposed by the Chinese medicine clinicians in the CES. The clinicians tend to use a pattern differentiation (i.e., the identification of pathological mechanisms through the observation of signs and symptoms) approach in which herbal formulas are used to target a specific pattern. The spatio-temporal and social context is taken into account and the treatment individualised according to the gender, age, constitution, comorbidities and symptoms of the patient. This individualisation does not only apply to the formula itself but also to the treatment modality (e.g., decoction, paste, pill), the preparation methods and intake methods. Clinicians recommend to avoid using uniquely herbs with sedative properties and instead aim at balancing the physiological imbalances of the patient.

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We can see there are significant differences between clinical research and clinical practice in the field of Chinese medicine. Randomised-controlled trials tend to use one-size-fits-all treatment protocols while clinicians tend to use highly individualised treatment protocols. The standardisation of treatment protocols in clinical research is motivated by the need for the treatment to be replicable. However, this does not reflect clinical practice. As a result, these randomised controlled trials cannot support or reject the use of Chinese medicine as it is practised in the clinic [452].

This issue has been raised for a few decades now and some improvements have appeared. Many clinical trials include pattern diagnosis in the study design. This can be achieved by either using pattern diagnosis in the inclusion criteria of the clinical trial or by tailoring treatments according to the pattern diagnosis as decided by a Chinese medicine clinician. In the latter approach, it is not the treatment protocol that is tested but the medicine (knowledge and practices) itself. This approach is not conventional in the field of pharmaceutical drug research yet is the de facto approach of clinical research for surgery and behavioural interventions. (evidence that pattern approach better that standardised approach)

Another important divergence between clinical practice and clinical research in CHM is the non-pharmacological aspect of the therapeutic process. During a Chinese medicine consultation, the clinician takes the pulse of the patient, observes his/her tongue and conducts a thorough interview about his/her health condition (including diet, lifestyle, professional and interpersonal situation) in order to have an overview of the patient as a whole [453, 454]. According to our CES, there are many psychological aspect of the Chinese medicine consultation, including adjusting the voice, tone, flow of speech, listening with empathy, etc. The warmth, attention and confidence of the clinician are known to be important factors of the efficacy of the treatment [455, 456]. However, these aspects of the consultation are often overlooked in clinical research. As the treatment is usually standardised, there is no need for thorough diagnostic investigation.

4. Challenges and opportunities in Chinese medicine research

Randomised trials using a standardised treatment are relatively easy to implement. For example, a herbal medicine manufacturer can produce the herbal product and a placebo treatment that looks and tastes similar. The active and the placebo can be placed in the same type of container with an

identification number and provided directly to the patient without infringing the blinding. Designing randomised trials in which individualised treatments are used is relatively challenging. The clinician needs to assess the condition of the patient at each treatment session and modify the treatment accordingly. The use of decoction of raw herbs does not allow for participant blinding. However, these difficulties do not mean that implementing high-quality randomised trials to test individualised treatments is impossible. For example, granules (dehydrated and soluble form of herbal decoction) and ready-made decoction can be prepared by Chinese medicine pharmacies. Placebo granules and ready-made decoctions with a herbal "taste" but no active ingredients can be produced in advance and ready to be dispensed. After assessing the situation of the participant, the clinician can provide a prescription to the pharmacy. Based on the randomisation list, the pharmacy provides either the active treatment or the placebo treatment to the participant. In this situation, both the clinician and the participant are blinded to treatment allocation.

Due to the complexity of clinical practice, testing the efficacy of Chinese medicine treatments as they are implemented in the clinic is challenging. This is particularly true for testing the effect of Chinese medicine treatments on overall health and long-term consequences. As a holistic medicine, Chinese medicine does not aim only at improving symptoms but also improving the long-term constitution of the patient. The National Health Insurance Research Database (NHIRD) from Taiwan may help us to overcome these difficulties. The NHIRD includes medical data such as registry for beneficiaries, ambulatory care claims, inpatient claims, prescriptions dispensed at pharmacies, registry for medical facilities, and registry for board-certified specialists. It covers 99.9% of the population and has collected medical data over 20 years. As Chinese medicine is part of the mainstream medical system in Taiwan, this database provides us with an extraordinary opportunity to observe the long-term effect of Chinese medicine treatments, including preventive effects. For example CHM is associated with reduced mortality in pancreatic cancer [457], reduction of risk of breast cancer in women with type 2 diabetes [458] and reduction of risk of dementia in hypertensive patients [459].

In the CES, we observed different degrees of treatment individualisation. Some clinicians recommended a single formula targeting the disease (i.e., insomnia). Others recommended a disease-

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based formula that is modified according to the pattern. The most common approach was the use of a pattern-based formula that is adapted according to the patient's secondary pattern and symptoms. Additionally, the treatment can be modified according to the characteristics of the patient and the spatio-temporal context. The individualisation of the treatment is generally limited to the ingredients of the formula, yet some clinicians recommend to adapt the treatment modality and preparation or intake methods. It is unclear which degree of individualisation of treatment provides the best treatment outcomes. The risk with an exceedingly standardised approach is to not address properly the specificities of the clinical situation. The risk with an exceedingly individualised approach is to provoke clinical reasoning "mistakes" leading to an ineffective treatment. Future research should try to clarify the correlation between treatment individualisation and treatment outcome. This can be achieved by the observation of data from a clinical setting (e.g., hospital in China) in which different degrees of individualisation are implemented. Future clinical trials can test the relative efficacy of treatment approaches by using different degrees of individualisation in each treatment arm. For the latter, it is important to use at least three approaches as the optimal degree of individualisation may be a moderate degree.

Finally, the Clinical Experience Synthesis (CES) can provide clinical guidance that is both clinically relevant and relatively rigorous. The guidance produced by the CES can later be tested through clinical trials. For example, the CES can be provided to Chinese medicine interns and junior doctors (who have not yet developed an individual perspective on the diagnosis and treatment of insomnia). The clinician can then conduct diagnosis and provide an individualised prescription in a real-world setting. The pharmacist can then provide either the herbal prescription or a placebo that appears similar to the participant, ensuring proper blinding of both the clinician and the participant.

5. Conclusion

This doctoral thesis provided clarification about the treatment of insomnia with CHM. ZRAS was found effective for insomnia in the systematic review but not in the randomised-controlled trial. More research is needed to clarify these discrepancies. This thesis also highlighted the differences between clinical practice and experimental research in the field of Chinese medicine. As a result, experimental

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research may fail to support or reject the use of CHM as it is practiced in the clinic for the treatment of insomnia.

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ANNEXES

Annexe 1. Investigator's Brochure of ZRAS capsule

CLINICAL INVESTIGATOR's BROCHURE

Authors of the brochure: Yoann Birling, MMed

Lan Yang, MMed

Supervisors: A/Pr. Xiaoshu Zhu, PhD

Pr. Alan Bensoussan, PhD

Pr. Jerome Sarris, PhD

Trial name: Zao Ren An Shen capsule for insomnia: A mixed-methods study

Investigational Product: Zao Ren An Shen capsule

Trade Name: Zaoren Anshen

Edition Number: 1

Release Date: 13 March 2019

Sponsor: Western Sydney University

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CONFIDENTIALITY STATEMENT
This investigator's brochure is a confidential document for the sole information and use of the HREC, the investigator's team and external partners of the trial.

CONFIDENTIAL

Investigator's Brochure

Investigational Product

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LIST OF ABBREVIATIONS

5-HIAA: 5-HydroxyIndoleAcetic Acid
5-HT: Serotonin
5-HTTP: 5-Hydroxytryptophan
AEs: Adverse Events
AIS: Athens' Insomnia Scale
ARTG: Australian Register of Therapeutic Goods
AUCinf: Area Under the Curve to infinity
Bcl-xL: B-cell lymphoma-extra large
BLM: Bai Le Mian
BzRAs: Benzodiazepine Receptor Agonists
CAM: Complementary and Alternative Medicine
CBT-i: Cognitive-Behavioural Therapy for insomnia
CCMD: Chinese Classification of Mental Disorders
CGI: Clinical Global Improvement
CHD: Coronary Heart Disease
CL: CLearance
Cmax: maximum Concentration observed
CNS: Central Nervous System
CWJ: Ci Wu Jia
CYP450: CYtochromes P450
DBP: Diastolic Blood Pressure
DOPAC: 3,4-DihydrOxyPhenylacetic Acid
DS: Dan Shen
ECG: ElectroCardioGram
GABA: Gamma-aminobutyric acid
GMP: Good Manufacturing Practice
HAMA: HAMilton Anxiety rating scale
HARS: Hamilton Anxiety Rating Scale
HDRS: Hamilton Depression Rating Scale
HPLC: High Pressure Liquid Chromatography
HVA: HomoVanillic Acid
ICSD: International Classification of Sleep Disorders
IL-1 β: InterLeukin-1-beta
iNOS: inducible NO Synthase
LD50: median Lethal Dose
MMP-2: Matrix MetalloProteinase-2
NF-kB: Nuclear Factor kappaB
N-RCT: Non-Randomized Controlled Trial
NWAK: Number of aWAKenings
OB: Olfactory Bulb
PANSS: Positive And Negative Syndrome Scale
PCPA: Para-ChloroPhenylAlanine
PSG: PolySomnoGraphy
PSQI: Pittsburgh Sleep Quality Index
RCT: Randomized Controlled Trial
REM: Rapid Eye Movement

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RMS: Rostral Migratory Stream
ROS: Reactive Oxygen Species
SAE: Severe Adverse Event
SBP: Systolic Blood Pressure
SDRS: Sleep Dysfunction Rating Scale
SE: Sleep Efficiency
SOL: Sleep Onset Latency
SQS: Sleep Quality Scale
SVZ: SubVentricular Zone
SZR: Suan Zao Ren
T1/2: Terminal phase half-life.
TESS: Treatment Emergent Symptom Scale
TGA: Therapeutics Goods Administration
TNF-α: Tumour Necrosis Factor-alpha
TST: Total Sleep Time
V1/F: Volume of the central compartment
WAIS: Wechsler Adult Intelligence Test
WCST: Wisconsin Card Sorting Test
WL: Wu Ling
WWZ: Wu Wei Zi
ZRAS: Zao Ren An Shen

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1. SUMMARY

1. Summary

1.1. Background

Insomnia disorder is the most common sleep disorder and may have severe consequences on mental and physical health. It is usually considered as an arousal disorder, hyperarousal being the core pathological mechanism of this disease. Noradrenaline (NE), Acetylcholine (Ach), histamine, dopamine (DA), serotonin (5-HT), the neuropeptides orexin A and B, Gamma-aminobutyric acid (GABA) and adenosine are involved in the neurological mechanism of insomnia [460].

The treatments recommended by the guidelines are pharmacotherapy (mainly Benzodiazepine Receptor Agonists, BzRAs) and Cognitive-Behavioural Therapy for insomnia (CBT-i) [155, 461, 462]. Because of adverse reactions and concerns over dependency [145, 163, 168, 374, 461], BzRAs are not favoured by insomniacs [11, 463]. Though effective, CBT-I is largely unavailable to insomnia patients [211, 212, 464]. Due to these imperfections, Over-the-counter drugs and Complementary and Alternative Medicine (CAM) are adopted by an important number of insomnia patients [98, 213, 214], Chinese Herbal Medicine (CHM) being one of the most popular [12, 13, 214]. A recent systematic review [278] supports the use of CHM for insomnia, though calling for an evaluation of the evidence for individual formulas.

1.2. Overview of Investigational Product

Zao Ren An Shen (ZRAS) capsule is a Chinese herbal medicine composed of extracts from three herbs, namely suan zao ren (Ziziphi Spinosae Semen), wu wei zi (Schisandrae Chinensis Fructus) and dan shen (Salviae Miltiorrhizae Radix et Rhizoma). The main components of the product are Jujuboside A, Schisandrol A, Schisandrol B, Tanshinone II A, Gomisin F, Gomisin H, Schisantherin A, Deoxyschizandrin, Schisandrin B, Salvianolic Acid B.

The exact pharmacological mechanism of its sedative effects is unknown. However, it is considered to involve GABAergic and serotoninergic pathways of the Central Nervous System (CNS).

ZRAS capsule has to be taken orally once a day before bedtime.

1.3. Chemistry, Manufacturing and Controls

The investigational product has been manufactured in accordance with Good Manufacturing Practice (GMP) for clinical studies.

Participant Initials				Participant ID			

The manufacturing process of ZRAS capsule includes reflux extraction, solid/liquid separation, vacuum concentration, soft extraction, vacuum drying, and sieving.

Quality analyses were performed on both the single herbs extract and the finished product by Medipro Botanical and Ferngrove Pharmaceuticals, respectively. Herb authentication analyses have been performed by Southern Cross University.

1.4. Nonclinical Studies

1.4.1. Pharmacology

There is strong evidence that both ZRAS as a whole formula and each herb composing ZRAS can exert sedative-hypnotic effect through modulating GABA systems and serotonergic systems, as well as neuroprotective function, anti-depressive and anxiolytic function. Please report to **4.1. Pharmacology**.

1.4.2. Pharmacokinetics

The pharmacokinetic profile for several major components in ZRAS formula has been evaluated after single administration in rats. It revealed that the plasma concentration for spinosin peaked at 5h after administration and slowly metabolized in the body. Whereas sodium Danshensu reached peak faster than spinosin but eliminated slower in the body. There were double peaks in the blood drug concentration curves for schisandrin A and deoxyschizandrin which indicated that there might be liver-intestinal or stomach-intestine circulation during the metabolism [465]

1.4.3. Toxicology

No pre-clinical study on the acute/chronic toxicology, toxicokinetics about ZRAS formula has been found by the authors of this IB. Modern toxicology studies of each individual herbs or their main components reveal very low acute toxicity (Table 4-7) and long-term use within safety range (Table 4-8). These studies suggest that the ingredients of ZRAS, i.e., suan zao ren, dan shen and wu wei zi, are safe to apply in clinic in the dose of the product.

1.5. Clinical Experience

The Chinese herbal medicine formula ZRAS has been used in China for more than 30 years. Originally manufactured as a solution, the formula exists also in form of capsule and granule. Only one RCT has compared ZRAS to placebo, showing a significantly lower score for the ZRAS group than for the placebo group after three weeks of treatment. Twelve RCTs and one non-randomized controlled trial assessed the efficacy of ZRAS for insomnia compared to a BzRA drug. These studies found similar or better outcomes for ZRAS compared to BzRA drugs in term of self-reported sleep quality and insomnia severity, therapist-rated clinical efficacy, and sleep parameters measured with PSG. Patients treated with ZRAS reported mild adverse reactions such as fatigue, stomach discomfort, diarrhoea, acid reflux, and lips numbness. In the studies comparing ZRAS to BzRAs, adverse reactions were significantly less reported by patients in the ZRAS group, 0-11% of the patients taking ZRAS reporting adverse reactions compared to 14-87% of those who took BzRAs.

1.6. Development Plan

ZRAS capsule has already been approved for human consumption by the Therapeutics Goods Administration (TGA) and is listed in the Australian Register of Therapeutic Goods (ARTG). As a stage 3 trial, this clinical trial will provide high-quality evidence for potential efficacy and safety. No further development of ZRAS capsule is planned to date.

Participant Initials			

Participant ID			

2. INTRODUCTION

2.1 Overview of Targeted Disease and Indication

2.2 Investigational Product

2.3 Rationale for Clinical Development

2.4 Dose Justification

2. Introduction

2.1. Overview of Targeted Disease and Indication

According to the Chinese Pharmacopeia, ZRAS is indicated for insomnia, memory loss, dysphoria, dizziness, and for neurasthenia [289]. ZRAS capsule has been approved by the TGA for "sleeplessness".

Table 2-1: Known components of ZRAS and their content.

Component	Content
Jujuboside A	2.05-2.35 mg/g [466]
Schisandrol A	2.50-2.71 mg/g [467] 2.25 mg/g [468]
Schisandrol B	2.00-2.14 mg/g [467] 0.73 mg/g [468]
Tanshinone II A	1.50-1.61 mg/g [467] 1.73-1.76 mg/g [469]
Gomisin F	0.88 mg/g [468]
Gomisin H	1.65 mg/g [468]
Schisantherin A	0.43 mg/g [468]
Deoxyschizandrin	5.71 mg/g [468]
Schisandrin B	0.94 mg/g [468]
Salvianolic Acid B	9.51-10.53 mg/g [470]

2.2. Investigational Product

The name of the investigational product (IP) is Zao Ren An Shen (ZRAS) capsule. The original Chinese name of the formula is zǎorén ānshén 枣仁安神, which means "appeasing the spirit with suan zao ren (Ziziphi Spinosae Semen)".

The formula, composed of the extracts of three herbs, namely suan zao ren (Ziziphi Spinosae Semen), wu wei zi (Schisandrae Chinensis Fructus) and dan shen (Salviae Miltiorrhizae Radix et Rhizoma). All of the herbal ingredients are in common use in Australia, available over the counter and are pre-approved with the Therapeutic Goods Administration (TGA).

Originally manufactured as a solution [280], the formula exists also in form of capsule [281], granule [282], and tablet [471]. According to the SFDA database, there are 15 different manufacturers of ZRAS in China [472]. Other formulas with the same or a similar name such as Zao Ren An Shen decoction [283, 284], Huang Qi Zao Ren An Shen decoction [285], compound Zao Ren An Shen capsule [286],

Zao Ren An Shen tablet [287], and Quick-effect Zao Ren An Shen capsule [288] have actually different ingredients and should not be confused with ZRAS.

The main components of ZRAS capsule and their respective content are listed in table 2-1.

2.3. Rationale for Clinical Development

Li Peisong, a senior Chinese medicine pharmacist from Beijing Medicinal Herbs Company, designed this formula for the treatment of insomnia based on his clinical experience [280].

The three herbs of the formula, Suan Zao Ren (SZR), Wu Wei Zi (WWZ) and Dan Shen (DS) have been traditionally used in China for insomnia both individually and combined with other herbs [298].

SZR, which is the main ingredient of the formula, is the most commonly used Chinese medicine herb for insomnia [316, 473]. SZR sedative effects may be mediated through GABAergic and serotonergic systems [329, 378]. WWZ shows sedative and hypnotic effects, mediated through GABAergic and glutamatergic systems [474]. DS is better known for its effects on the vascular system [475], but it has been found to show a sedative effect as well [476].

2.4. Dose Justification

The origin of the dosage is the clinical experience of Li Peisong, the pharmacist who designed the formula. This dosage has been confirmed by experimental studies on animals (see **4. Non-clinical studies (in vitro and in vivo)**). The Chinese Pharmacopeia recommends a dose of 0.45g per capsule, with a posology of five capsules once a day before bedtime [289]. For this trial, the dose of the investigational product has been changed to 0.76g per capsule, with a posology of three capsules once a day before bedtime, which results in a dose equivalent to the Chinese Pharmacopeia's recommendations. ZRAS capsule complies with all relevant dosage limitations stipulated by the TGA.

Participant Initials				Participant ID			

3. INVESTIGATIONAL PRODUCT PROPERTIES & FORMULATION

3.1. Formulation

3.2. Manufacture

3.3. Analysis and characterisation of the investigational product

3.4. Posology

3.5. Container and packaging

3.6. Storage

3.7. Stability

3. Investigational Product Properties & Formulation

3.1. Formulation

The active ingredients of the IP, SZR, WWZ and DS, are shown in Table 3-1. All the three ingredients have been pre-approved by the TGA. As it is an herbal extract, the chemical compounds are not fully known. The known compounds are Jujuboside A, Schisandrol A, Schisandrol B, Tanshinone II A, Gomisin F, Gomisin H, Schisantherin A, Deoxyschizandrin, Schisandrin B, Salvianolic Acid B (see Table 2-1).

Table 3-1: ZRAS herbal ingredients.

Pin Yin Name	Pharmaceutical name	Common English Name	Content (raw herb equivalent)
Suan zao ren	Ziziphi Spinosae Semen	Spine Date Seed	2500 mg/capsule
Wu wei zi	Schisandrae Chinensis Fructus	Chinese Magnoliavine Fruit	500 mg/capsule
Dan shen	Salviae Miltiorrhizae Radix et Rhizoma	Danshen root	700 mg/capsule

The actual content of the active ingredients and excipients are shown in Table 3-2.

Table 3-2: Investigational product master formulation.

Ingredient	Specification	Purpose	Conc (mg/capsule)
SZR extract	Manuf.	Active	416.67
DS extract	Manuf.	Active	70.00
WWZ extract	Manuf.	Active	166.67
Carob pod powder	BP.	Excipient	90.00
Silicon	BP.	Excipient	10.00
Magnesium stearate	BP.	Excipient	6.66
Total			760.00

The capsule shell used in the investigational product is a clear hard vege capsule size “00” consisting of Hypromellose and water-purified. The weight of the capsule shell is 118mg.

Participant Initials				Participant ID			

3.2. Manufacture

ZRAS capsule was manufactured the 11th December 2017 through a series of proprietary processing steps which have been validated and performed in accordance with GMP under license at: Global Therapeutics pty. Ltd., PO. Box 1999 Byron Bay, NSW 2481.

Individual herbal extracts were sourced from Medipro Botanical Co., Ltd., No. 398 Meilian Road, Minhang District, Shanghai 201108, China. They were analysed at Southern Cross University via HPLC methods to ensure correct herbal identification, check concentrations of major constituents and that the samples are free from contaminants such as heavy metals.

The manufacturing processes included:

1. Cutting (for DS), steaming with vinegar (for WWZ), or stir baking (for SZR)
2. Reflux extraction with (i) 75% Ethanol/Water (ii) 60% Ethanol/Water (iii) Purified water
3. Solid/liquid separation
4. Vacuum concentration
5. Soft extract
6. Vacuum drying
7. Sieving
8. Packaging/labelling/samples
9. Final quality control, general aspect, analytical and microbiological quality

3.3. Analysis and characterisation of the investigational product

The investigational product physical appearance is a size “00” clear hard vege capsule containing brown coloured powder. The total weight of the product is 883.9 mg/capsule and the fill weight is 760.1 mg/capsule. The disintegration time is less than 14 minutes.

The identity of the three herbal extract was confirmed by High Pressure Liquid Chromatography (HPLC). Analyses using 70:30 Ethanol:Water by HPLC detection at 254 nm for DS, 330 nm for SZR and 254 nm for WWZ, against respective references, found the extracts to be consistent with the reference samples.

Analytical assay of the finished product using HPLC showed the presence of 2500 mg/capsule of SZR quantified by input, 0.87 mg/capsule of Tanshinone II A, and 1.46 mg/capsule of Schisandrin. It complies with the requirements of the manufacturer, which are 2500 mg/capsule of SZR, 0.7 mg/capsule of Tanshinone II A, and 1.33 mg/capsule of Schisandrin.

Microbiological test showed that the product is sterile, with a total aerobic microbial count of 1000 CFU/g, a total yeast and mould count inferior to 10 CFU/g, a bile-tolerant gram negative bacteria inferior to 100 MPN/g, the absence of Salmonella in 10g, the absence of Escherichia coli in 1g, and the absence of Staphylococcus aureus in 1g.

3.4. Posology

The posology of ZRAS capsule is 3 capsules per night, taken orally 1 hour before bedtime.

3.5. Container and packaging

The capsules are packaged in glass bottles, 65 capsules per bottle.

3.6. Storage

The vials are to be stored below 30ºC, away from direct heat and sunlight in a secure area with limited access to the study investigator.

Participant Initials			

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3.7. Stability

The stability of the investigational product will be assessed before the beginning of the trial and after the end of the trial at NICM Health Research Institute, Western Sydney University.

Participant Initials				Participant ID			

4. NON-CLINICAL STUDIES (IN VITRO AND IN VIVO)

4.1. Pharmacology

4.1.1. Studies on Zao Ren An Shen as a whole formula

4.1.2. Studies on individual herbs

4.1.2.1. Studies on suan zao ren

4.1.2.2. Studies on dan shen

4.1.2.3. Studies on wu wei zi

4.1.3. Summary of the pharmacological studies

4.2. Pharmacokinetics and Product Metabolism in Animals

4.3. Drug interaction

4.3.1. Danshen - warfarin interaction through protein binding competency

4.3.2. Dan shen- inhibitory potency against Cytochromes P450 (CYP450) enzyme

4.4. Toxicology and safety studies

4. Non-clinical studies (in vitro and in vivo)

4.1. Pharmacology

4.1.1. Studies on Zao Ren An Shen as a whole formula

Two studies, reported in Table 4-1, indicate that daily administration of ZRAS granule enhances drug-induced sleep [327]. This hypnotic effect seems to be not mediated by the cytokines InterLeukin-1-beta (IL-1 β) and Tumour Necrosis Factor-alpha (TNF-α), which are both sleep-promoting substances [477], as ZRAS was found to decrease IL-1 β and TNF-α levels in rat brain [327]. The effect increased with the duration of the intervention and an inversed U-shaped dose-effect relationship was found with an optimal effect at 2080 mg/Kg [327]. The hypnotic effect of ZRAS granule was found to be mediated through serotonin and benzodiazepine receptors [328], although the role of serotonin receptor is unclear as it is usually considered as a wake-promoting substance [330].

Table 4-1: Pharmacology studies on ZRAS. 5-HTP = 5-Hydroxytryptophan; PCPA = Para-ChloroPhenylAlanine.

Activity	Model	Intervention	Result	Ref.
Hypnotic effect	Rat	ZRAS granule, 2080 mg/kg/d * 7d, i.g.	1. Increased sleep duration shortened sleep latency in pentobarbital sodium-induced sleep. 2. Decreased IL-1 β and TNF-α brain levels.	[327]
	Rat	ZRAS granule, 2080 mg/kg/d * 3-9d, i.g.	Sedative effect started after 5 days of intervention and increased along with intervention duration.	[327]
	Rat	ZRAS granule, 260-4160 mg/kg/d * 7d, i.g.	Inversed U-shaped dose-effect relationship, with the sedative effect being statistically significant only at 2080 mg/kg.	[327]

Mice	ZRAS granule, 2080 mg/kg/d * 7d, i.g.	Increased sleep duration shortened sleep latency in pentobarbital sodium-induced sleep.	[328]
Mice	ZRAS granule, 2080 mg/kg/d * 7d, i.g., with or without flumazenil, 3.5 mg/kg, i.p.	Hypnotic effect decreased when ZRAS used in combination with flumazenil.	[328]
Mice	ZRAS granule, 2080 mg/kg/d * 7d, i.g., with or without 5-HTP, 25 mg/kg, i.p.	Hypnotic effect increased when ZRAS used in combination with 5-HTP.	[328]
Mice	ZRAS granule, 2080 mg/kg/d * 7d, i.g., with or without PCPA 300 mg/kg, s.c.	Hypnotic effect decreased when ZRAS used in combination with PCPA.	[328]

4.1.2. Studies on individual herbs

4.1.2.1. Studies on suan zao ren

Suan zao ren and its main known bioactive components, jujubosides, spinosin and sanjoinine A, show broad CNS effects, including sedative, hypnotic and anxiolytic effects, neurogenesis, neuroprotection and memory improvement [331, 394, 478-487].

1. $GABA_A$ receptor and 5-HT 1A receptors, and certain inflammatory cytokines are involved in the mechanism behind the sedative, hypnotic effects, and anxiolytic effect of SZR and its main components.
2. Neuronal protecting effect were seen in cell toxicity model experiment by inhibiting cell damage and Reactive Oxygen Species (ROS) generation; in naïve mice neuron, it also witnessed the neurogenesis function after administered a chief component of SZR for consecutive days.
3. It is found that a chief component of SZR can increase the levels of memory-related signalling molecules in order to ameliorate memory function.

Table 4-2: Summary of pharmacology studies on the psychopharmacological and neurological effects of suan zao ren and its components. REM = Rapid Eye Movement

Activity	Extract/ Component	Model /Assay	Intervention	Result	Ref
Sedative & hypnotic effect	Jujuboside A	Rat hippocampal neuron culture	0.05 -0.1g/l, 24h, 72h	Altered $GABA_A$ receptor subunits (α1, α5, β2) mRNA expression.	[478]
	Jujuboside A	Rat small intestine tissue / hippocampal neurons culture	0,200 mg/ml, 3h	Down-regulate the secretion of relevant inflammation cytokines on the intestinal mucosal system to affect the intercellular cytokine network between nerve cells in the brain	[479]
	Jujubosides	Rat	9 mg/kg/d * 3 d, p.o.	Influence circadian rhythm and the serotonergic system	[480]

	Ethanol extract	Pentobarbital-induced sleep in mouse	400, 800 mg/kg/d * 7d, p.o.	Shorten sleep latency, increase sleeping time and prolong movement convalescence time	[331]
	Spinosin	Pentobarbital-induced sleep in mice	0.1 ml/10g 60 mins before pentobarbital administration, p.o.	Augment sleep dose-dependently, increase the rate of sleep onset and exhibit a synergistic effect with 5-HTP.	[481]
	Spinosin	Pentobarbital-induced sleep in mice	0.1 ml/10g 1h before pentobarbital administration, p.o.	Potentiate effect on REM sleep. Relate to postsynaptic 5-HT 1A receptors.	[482]
Neuroprotection	Methanol extract	NMDA-induced neurotoxicity in rat cerebellar granule neuron	0.05–5 μg/ml, p.o.	Inhibit neuronal cell death, glutamate release into medium, elevation of cytosolic calcium concentration, and generation of reactive oxygen species.	[483]
Neurogenesis	Spinosin	Adult hippocampal neuron in normal naïve mice	5 mg/kg/d * 14 d, p.o.	Up-regulate adult hippocampal neurogenesis and activate the ERK-CREB-BDNF signaling pathway.	[484]
Memory improvement	Spinosin	Scopolamine-induced memory impairment in mice	2.5- 20 mg/kg, 1 h before the behavioral tests, p.o.	Relate to the 5-HT1A receptor. Increase the levels of memory-related signalling molecules	[485]
Anxiolytic effect	Spinosin	Anxiety model in mice	2.5, 5 mg/kg/d * 7d, p.o.	Modulate $GABA_A$ and 5-HT1A receptors.	[486]
	Sanjoinine A	Rat, cerebellar granule cells	0.5-2.0 mg/kg, p.o.	Mediated by GABAergic transmission.	[394, 487]

4.1.2.2. Studies on dan shen

Dan shen, a well-known traditional Chinese medicine, widely used for treating cardio-cerebrovascular diseases, such as Alzheimer's disease. Dan shen and its main component Tanshinone IIA exert multiple neuroprotective effects by inhibiting Aβ aggregation, antioxidant, anti-inflammation, enhancing cholinergic signaling, and decreasing cell apoptosis. Certain sedative-hypnotic and anxiolytic effect are also observed in rats and mice, through modulating $GABA_A$ receptor.

Table 4-3: Summary of pharmacology studies on dan shen. Bcl-xL = B-cell lymphoma-extra large; iNOS = inducible NO Synthase; MMP-2 = Matrix MetalloProteinase-2; NF-kB = Nuclear Factor kappaB

Activity	Extract/ Component	Model /assay	Intervention	Result	Ref.
Anxiolytic effect	Ethanol extract	Rats	0-100 mg/kg/d * 14d, p.o.	Produce robust anxiolytic effects at the Elevated Plus Maze test, suppress stress-induced hyperthermia response.	[394, 488]
Sedative-hypnotic effect	Ethanol extract	Pentobarbital-induced sleep in mice	100-1000 mg/kg 45 min before pentobarbital injection, p.o.	High-affinity bind at the benzodiazepine site of $GABA_A$ receptor in a concentration-dependent manner	[331]
	Ethanol extract	Pentobarbital-induced sleep in mouse	150- 600 mg/kg 40 min before pentobarbital injection, p.o.	Shorten sleep latency significantly, increase sleeping time and prolong movement convalescence time	[489]
Neuron protection & neurogenesis	Tanshinone IIA	Nerve transection injury in rats	6- 40mg/kg/d * 12 weeks, i.p.	Alleviate nerve injury and promote nerve regeneration	[490]
	Tanshinone IIA	Aβ25–35-induced cytotoxicity in cortical neurons	1- 60 μM for 30 min before co-incubated with Aβ25–35 for 48 h	Involve in calpain and the p35/Cdk5 pathway	[491]
	Tanshinone IIA	Aβ 1-42-induced cortical neurons	1.25–40 μM for 24 h	Inhibit apoptosis via activation of the Bcl-xL pathway	[492]
	Tanshinone IIA	Alzheimer's model in rats	50 mg/kg/d * 15d, p.o.	Inhibit iNOS and MMP-2 at a transcriptional and translational level through the NF-κB pathway	[493]

4.1.2.3. Studies on wu wei zi

Many studies showed that WWZ and its main component schisandrin manifest sedative-hypnotic effect by altering brain neuron receptors, neurotransmitters and their metabolites in GABA and serotonergic systems, as well as neurotrophic functions through multiple systems.

Table 4-4: Summary of pharmacology studies on wu wei zi. DOPAC = 3,4-DihydrOxyPhenylacetic ACid; HVA = HomoVanillic Acid; 5-HIAA = 5-HydroxyIndoleAcetic Acid; SVZ = SubVentricular Zone; RMS = Rostral Migratory Stream; OB = Olfactory Bulb.

Activity	Extract/ Component	Model /Assay	Intervention	Result	Ref.

Sedative and hypnotic effect	Carbon dioxide fluid extraction	Mice	50-200 mg/kg, 30 mins before pentobarbital, p.o.	Relevant to the serotonergic and GABA system.	[340]
	Ethanol crude extract	Rat brain homogenate samples	7.5 g/kg/d * 8 d	Elevates GABA, NE, DA, DOPAC and HVA, and reduce 5-HT, 5-HIAA levels in rat brain	[336]
	Schisandrin B	Mice	0.1 ml/10g/d *7d, p.o.	Up-regulate $GABA_A$ receptors expression and modulate GABA and glutamate content in the peripheral blood and brain tissues	[341]
	Schisandrin	Mice	5–45 mg/kg, i.p.	Modify serotonergic system in dose-dependent manner	[494]
Anti-depressive effect	Water extracts	Mice	300, 600 mg/kg 1h before the test, p.o.	Modify noradrenergic, dopaminergic, GABAergic and glutamatergic systems.	[392]
Enhancing neurogenesis	Schisandrin A and B	Rat	1-20mg/kg * d, p.o	Sch B enhances neurogenesis Sch A negatively regulates neurogenesis in the adult SVZ–RMS–OB system.	[495]
Neurotrophic effect	Purified compound schisandrin	Rat embryo hippocampal neurons	3 μmol/L	Mediate CaMKII-PKC Delta *e-MEK pathway	[495]

4.1.3. Summary of the pharmacological studies

There is strong evidence that both ZRAS as a whole formula and each herb composing ZRAS can exert sedative-hypnotic effect through modulating GABA systems and serotonergic systems, as well as neuroprotective function, anti-depressive and anxiolytic function.

4.2. Pharmacokinetics and Product Metabolism in Animals

Because each herb contains thousands of components, some of them being currently unknown, it is impossible to give the data referring to the whole formula. Single-dose administration studies on some important components of ZRAS are summarized in Table 4-5. To the knowledge of the authors of this IB, no study on multiple-dose administration has been published yet. Meanwhile, there are some pharmacokinetics studies focusing on the interactions among the main known components of ZRAS (Table 4-6).

Table 4-5: Mean plasma pharmacokinetic parameters for ZRAS after single-dose administration. AUCinf = Area Under the Curve to infinity; Cmax = maximum concentration observed; CL = Clearance; V1/F = Volume of the central compartment; T1/2 = Terminal phase half life.

Participant Initials				Participant ID			

Species	Parameter	Dose of ZRAS (g/Kg)	Route	Cmax (mg/l)	AUCinf (mg.h/L)	CL (l/kg/h)	V1/F (L/kg)	T1/2 (h)	Ref
Rat	Spinosa	6.7	p.o.	3.452	30.419 ±3.58	0.589	2.439 ±0.7	2.341± 2.63	[496]
Rat	Salvianic acid A sodium	6.7	p.o.	2.291	11.035 ±5.42	1.753	11.222 ±7.63	0.555 ±1.18	[496]
Rat	schisandrin	6.7	p.o.	2.292	23.645 ±8.72	0.846	0.449 ±0.02	1.312 ±3.45	[496]
Rat	Spinosa	10	p.o.	49.96	479.447	0.042	0.072	1.17	[497]
Rat	Ferulic Acid	10	p.o.	6.811	61.424	0.328	0.206	0.811	[497]
Rat	Salvianic acid A	10	p.o.	28.664	14.335	1.402	0.907	3.214	[497]
Rat	Protocatechuic acid	10	p.o.	13.959	15.748	3.253	1.767	2.686	[497]
Rat	protocaterchualdehyde	10	p.o.	3.524	19.302	1.041	1.041	0.337	[497]
Rat	Schizandrol A	10	p.o.	10.548	84.084	0.239	1.092	1.157	[497]
Rat	schizandrin	10	p.o.	5.86	47.65	0.422	1.862	1.728	[497]

Table 4-6: Summary of pharmacokinetic studies on ZRAS.

Targeted compounds	Species	Method	Results/conclusion	Ref.
Spinose, salvianic acid A sodium, schisandrin	Rat	HPLC	1. Spinosin conforms to the one-compartment model. 2. Both salvianic acid A and schisandrin conform to two-compartment open model.	[496]
Spinosin, ferulic acid	Rat	HPLC	1. Spinosin and ferulic acid can penetrate the blood-brain barrier into the cerebrospinal fluid. 2. Time for early detecting in the brain tissue is 0.25 h for spinosin, 1 h for ferulic acid. 3. Higher concentration of spinosin and ferulic acid can be found in the heart, liver and kidney tissue. 4. Certain chemical components in Salvia Miltiorrhiza promote the absorption and distribution of spinosin and ferulic acid 5. Certain components in Fructus schisandrae reduce the distribution of spinosin 6. The combination of these herbs can elevate the efficient concentration of ZRAS in brain tissue of rats.	[498]
Spinosin, salvianic acid A,	Rat	LC-MS/MS	1. A linear relationship between high dose and medium dose. All the indicator	[499]

protocatechualdehyde, 6W,-feruloylspinosin, salvianolic acid B, schisandrin, deoxyschisandrin	components were absorbed into the blood within 1 h. 2. Spinosin has a large area under the concentration-time curve and clearance rate in the rat 3. Salvianolic acid B has the highest content in the prescription, decline rapidly after the peak plasma concentration 4. Salvianic acid A generates via bond cleavage of the ftiran ring and two ester bonds in salvianolic acid B. 5. Schisandrin and deoxyschisandrin exhibit bimodal behaviours in plasma concentration-time profiles, may be caused by hepatoenteric circulation.

4.3. Drug interaction

Few studies on the interaction of ZRAS with drugs has been found. However, some studies on the herb-drug interaction of DS indicates its protein binding competency with warfarin and inhibitory potency against the CYtochromes P450 (CYP450) enzyme metabolic pathway.

4.3.1. DS - warfarin interaction through protein binding competency

Warfarin, an anticoagulant used to prevent the formation of blood clots, is highly bound (97-99%) with human serum albumin in plasma with selectivity to site I. Increased levels of free plasma warfarin could be observed when warfarin is combined with DS because of the replacement of warfarin by its constituents, which may potentiate the anticoagulant effect of warfarin.

Sodium tanshinone IIA sulfonate, a water-soluble derivative of tanshinone IIA used in the form of injection in China, displaced warfarin from the warfarin-human serum albumin complex [500].

Salvianolic acid B and rosmarinic acid can bind to bovine serum albumin at the site I with binding constants around 105 L/mol [501]. Salvianolic acid B, lithospermic acid, rosmarinic acid, salvianolic acid A, and salvianolic acid C can bind to human serum albumin at sites I and/or II with increasing binding constants at 298 K ranging from 0.18 to 16 × 105 L/mol [502-504]. The binding constant for tanshinone IIA at 303 K was 1.54 × 105 L/mol [505]. The plasma protein binding of salvianolic acid A, salvianolic acid B, and tanshinone IIA was 99.7% [506], 83.8-92.1% [502, 507], and 99.2% [508], while that of tanshinone was 2%[509] In the presence of the above-mentioned individual constituent, the human serum albumin binding constant of warfarin decreased by 1.4- to 8.7-fold [504] which may cause increased free warfarin concentrations.

4.3.2. Dan shen- inhibitory potency against CYP450 enzyme and transporters

Most drugs undergo metabolism by CYP enzymes in the liver after they enter the body and produce metabolites with or without pharmacological activities. In-vitro studies show that DS extracts and its individual constituents exert different effects on CYPs and transporters including, including CYP141, CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CE1, CE2, P-gp, OAT1, OAT2, OAT3, OAT4 [510]. There is a large scope of drugs metabolised by these enzymes and transporters, however the interactions with DS are only theoretical as there is not clinical report of interaction between these drugs and DS (see section 5.5.). Lipophilic components are more likely to induce potential DS-drug interactions than aquaphilic components [510].

Participant Initials				Participant ID			

4.4. Toxicology and safety studies

The safety of ZRAS has been pre-evaluated by the Therapeutic Goods Administration (TGA). No pre-clinical study on the acute/chronic toxicology, toxicokinetics about ZRAS formula has been found by the authors of this IB. Modern toxicology studies of each individual herbs or their main components reveal very low acute toxicity (Table 4-7) and long-term use within safety range (Table 4-8). This studies suggest that the ingredients of ZRAS, i.e., SZR, DS and WWZ, are safe to apply in clinic in the dose of the product.

Table 4-7: Summary of acute toxicology studies on animals. LD50 = median Lethal Dose. LD50>15 g/Kg suggests a practical nontoxicity, LD50=5-15 g/Kg a low toxicity, LD50=0.5-5 g/Kg a moderate toxicity, LD50=50-500 mg/Kg a high toxicity and LD50<5 mg/Kg a very high toxicity [511].

Herb/Chief component	Species	Route of admin.	Duration	Result	Ref.
Suan zao ren	Mice	i.v.	Single-dose	LD50 is 25.1-30.1 g/Kg	[409]
Dan shen	Rat	i.v.	Single-dose	LD50 is 68.7 g/Kg	[410]
Wu wei zi	Mice	p.o.	Single-dose	LD50 is 10.5 g/Kg	[411]

Table 4-8: Summary of chronic toxicology studies on animals.

Herb/Chief component	Species	Dose (g/Kg)	Route of admin.	Duration	Result	Ref.
Suan zao ren	Rat	20	p.o.	30 days	No toxic reaction	[512]
DS-MEF	Rat	8	p.o.	90 days	No significant toxic reaction	[513]
Wu wei zi lignanoids	Beagle	0.22	p.o.	91 days	The toxic reaction is mild, targeting at thymus gland and liver, and can be reversible after discontinuing.	[514]

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5. EFFECTS IN HUMANS

5. EFFECTS IN HUMANS

5.1. Clinical trials using ZRAS as a monotherapy for insomnia

5.1.1. Overview

Thirteen clinical trials have assessed the efficacy of ZRAS for insomnia [281, 299-310], including one three-arm Randomized Controlled Trial (RCT) comparing ZRAS to a Estazolam and placebo, one Non-Randomized Controlled Trial (N-RCT) comparing ZRAS to Estazolam, and eleven RCTs comparing ZRAS to BzRAs drugs, namely Estazolam, Alpazolam, Eszopiclone, and Clonazepam (Table 4-1). Only one study used ZRAS granule as an investigational product and the others used ZRAS capsule. Three studies only recruited older adults and one recruited insomniacs with heart and spleen deficiency pattern only. The sample size of these studies ranged from n=32 to n=150. The intervention period also varied, from 1 to 4 weeks.

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5.1.2. Efficacy

The only study in which ZRAS capsule was compared to placebo found a significantly lower (i.e., better) Pittsburgh Sleep Quality Index (PSQI; a self-report questionnaire used to assess subjective sleep quality) score for ZRAS capsule compared to placebo after 1 week and 3 week of treatment [299].

Nine studies assessed the efficacy of ZRAS compared to BzRAs drugs with PSQI, Sleep Quality Scale (SQS) and Sleep Dysfunction Rating Scale (SDRS), three self-report questionnaires used to assess subjective sleep quality. Most of these studies (8/9) showed no significant difference after 2 to 4 weeks of treatment [281, 299, 301-304, 306, 308] and one showed a better score for ZRAS capsule after 4 weeks of treatment [307]. One study found a similar decrease of PSQI score for ZRAS granule compared to Eszopiclone [300]. Interestingly, one RCT found a difference in PSQI score at a 7-day follow-up, despite an absence of significant difference after 16 days of treatment, suggesting a lower propensity for rebound insomnia [306].

Two studies used clinical efficacy assessed by the therapist as an outcome measurement, both finding a better efficacy for ZRAS capsule compared to Estazolam [309, 310]. Another found a similar Clinical Global Improvement (CGI; a therapist-rated scale) score for both groups at post-treatment but a better score at follow-up for ZRAS capsule[306].

Objective measures of sleep parameters using PolySomnoGraphy (PSG) were used only in one trial [305]. This trial found a longer Total Sleep Time (TST) in the group treated with ZRAS capsule compared to the group treated with Alpazolam, but no difference in Sleep Onset Latency (SOL), Number of aWAKenings (NWAK), sleep/wake ratio, Sleep Efficiency (SE), or sleep structure.

Only study assessed psychological status, finding a similar decrease in HAMilton Anxiety rating scale (HAMA; a therapist-rated scale used to assessed anxiety levels) score after 16 days of treatment and a better HAMA score at follow-up for ZRAS capsule compared to Estazolam [306].

In one trial, the severity of the Chinese medicine pattern was assessed with a scale designed for the purpose of the trial [307]. This trial found a lower Chinese medicine pattern score for the group that had taken ZRAS capsule compared to the group that had taken Eszopiclone after 4 weeks of treatment.

Finally, one study assessed the impact of ZRAS on hemorheological indexes of older adults, finding a lower low-shear whole blood viscosity and a lower high-shear whole blood reduced viscosity after 4 weeks of ZRAS capsule compared to Alpazolam. The relation between the effects on sleep and the effects on blood rheology were not clearly stated in the study.

5.1.3. Safety

Adverse Events (AEs) were not reported in the only trial in which ZRAS was compared to placebo. Among the 12 studies in which ZRAS was compared to a BzRA medication, nine studies reported the number and nature of adverse events, including two studies using a validated instrument, the Treatment Emergent Symptom Scale (TESS; a self-report scale used to assess adverse reactions). Patients treated with ZRAS reported mild adverse reactions such as fatigue, stomach discomfort, diarrhoea, acid reflux, and lips numbness. Adverse reactions were significantly less reported by patients in the ZRAS group (Table 4-1), 0-11% of the patients taking ZRAS reporting adverse reactions compared to 14-87% of those who took BzRAs. No Severe Adverse Event (SAE) was associated with the use of ZRAS. In one study, routine blood tests, routine urine tests, hepatic function blood tests, renal function blood tests and electrocardiograms were also performed before and after the intervention, showing no significant difference after 16 days taking ZRAS capsule [306]. Overall, ZRAS seems relatively safe, especially compared to BzRAs, however, there is a need to assess the adverse reaction in comparison with placebo in order to understand the safety of this medicine better.

Participant Initials				Participant ID			

Table 5-1: Characteristics and outcomes of the studies comparing ZRAS to a BzRA drug. FU = follow-up; SDRS = Sleep Dysfunction Rating Scale; TESS = Treatment Emergent Symptom Scale; N-RCT = Non-Randomized Controlled Trial; SQS = Sleep Quality Scale; HAMA = HAMilton Anxiety rating scale; CGI = Clinical Global Impressions scale

Author (date)	Design	Form of active	Control	Population (n)	Duration	Efficacy measurement	Efficacy outcomes	Safety measurement	Safety outcomes
Ren (2007)	RCT	Capsule	Estazolam 1mg	Older adults with insomnia (100)	16 days + 7-days FU	SDRS, HAMA, and CGI	No significant difference at post-treatment but favors ZRAS at follow-up	TESS	Significantly less adverse reactions for ZRAS
Liu (2009)	RCT	Capsule	Estazolam 1mg and placebo	Psychophysiologic insomniacs (90)	3 weeks	PSQI	No significant difference with active control at post-treatment; better than placebo	not reported	
Liu (2017)	N-RCT	Capsule	Estazolam 1mg	Older adults with insomnia (120)	2 weeks	PSQI	No significant difference at post-treatment	not reported	
Zhang (2007)	RCT	Capsule	Estazolam 2mg	Insomniacs with heart and spleen deficiency pattern	4 weeks	Therapist-rated clinical efficacy	Favors ZRAS at post-treatment	not reported	
Zhang (2016)	RCT	Capsule	Estazolam 1-2mg	Insomniacs (68)	3 weeks	Therapist-rated clinical efficacy	Favors ZRAS at post-treatment	Adverse reactions reports	Significantly less adverse reactions for ZRAS
Xu (2011)	RCT	Capsule	Alpazolam 0.4mg	Insomniacs (150)	2 weeks	SQS	No significant difference at post-treatment	Adverse reactions reports	Significantly less adverse reactions for ZRAS
Li (2012)	RCT	Capsule	Estazolam 1mg	Insomniacs (60)	2 weeks	PSQI	No significant difference at post-treatment	Adverse reactions reports	Significantly less adverse reactions for ZRAS
Wang (2017)	RCT	Capsule	Eszopiclone 3mg	Insomniacs (128)	4 weeks	PSQI and Chinese medicine pattern	Favors ZRAS at post-treatment	Adverse reactions reports	Significantly less adverse reactions for ZRAS
Gan (2013)	RCT	Capsule	Alpazolam 0.8mg	Older adults with insomnia (120)	4 weeks	PSQI	No significant difference at post-treatment	Adverse reactions reports	Significantly less adverse reactions for ZRAS
Qin (2007)	RCT	Capsule	Clonazepam 1mg	Insomniacs (125)	15 days	SQS	No significant difference at post-treatment	Adverse reactions reports	Significantly less adverse reactions for ZRAS
Qin (2015)	RCT	Capsule	Alpazolam 0.8mg	Insomniacs (62)	7 days	PSG	Longer TST for the ZRAS group but no significant difference in SOL, NWAK, SE, sleep/wake ratio, and sleep period ratio	not reported	
Chen (2014)	RCT	Granule	Eszopiclone 7.5mg	Insomniacs (120)	4 weeks	PSQI	No significant difference at post-treatment	Adverse reactions reports	Significantly less adverse reactions for ZRAS
Huang (2013)	RCT	Capsule	Estazolam 1mg	Insomniacs (90)	2 weeks	SDRS	No significant difference at post-treatment	TESS	Significantly less adverse reactions for ZRAS

5.1.4. Limitations

If one study used internationally recognised diagnostic criteria from the International Classification of Sleep Disorders (ICSD) and nine other studies used locally recognised criteria from the Chinese Classification of Mental Disorders (CCMD) to diagnose insomnia disorder, none of these study reported who establish the diagnosis and how. There is a possibility that the participants recruited in these studies do not meet internationally recognised insomnia disorder diagnosis criteria.

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Another important point is that the objective of these studies compared an active with an active control, i.e. showing superiority or non-inferiority, was not clearly stated. Since the efficacy of BzRAs is widely accepted, a non-inferiority trial design seems more relevant, however, these studies used inappropriate statistical analyses to show non-inferiority [515].

The majority of these studies presented unclear or high risk of bias in terms of sequence generation (9/13), allocation concealment (12/13), blinding of participant and personnel (12/13), blinding of outcome assessment (13/13), and selective reporting (6/13).

Moreover, the intervention was limited to maximum 4 weeks without long-term follow-up, which does not allow concluding about ZRAS's long-term efficacy and possible dependency issue.

Finally, except for one study [306] in which self-reported anxiety level was measured, psychological status, quality of life, fatigue, performance, and self-reported sleep parameters were not assessed, despite it is recommended by the guidelines for clinical trials on insomnia [311].

5.2. Clinical trials using ZRAS in combination with other treatments for insomnia

5.2.1. Overview

Six clinical trials have assessed the efficacy of ZRAS in combination with another treatment for the treatment of insomnia (Table 4-2). Two of these trials used a combination of acupuncture and a ZRAS formulation, one [313] without control and the other [312] controlled with Zopiclone. One trial [516] compared the efficacy of a combination of two patent Chinese medicine, i.e. Wu Ling capsule and ZRAS capsule, to Estazolam. Another [517] trial assessed the efficacy of ZRAS when added to conventional anti-hypertensive drugs for older adults with comorbid insomnia and hypertension. In the last two trials [282, 518], a ZRAS formulation was added to BzRA medication for the treatment of insomnia. The intervention period was variable in these six trials, ranging from 2 weeks to 3 months.

5.2.2. Efficacy

The combination of acupuncture and ZRAS capsule in the one-arm trial, but the absence of validation of the efficacy measurement and the lack of control prevents drawing conclusion from these results [313]. Interestingly, the outcomes at the 6-months follow-up were not recorded in the report, despite being stated in the protocol [313].

The combination of Wu Ling capsule with ZRAS capsule was found more effective than Estazolam after 30 days of treatment [516] and the combination of acupuncture with ZRAS solution was found as effective as Zopiclone [312]. In both case it is difficult to know the contribution of the ZRAS formulation alone. The benefits of combining the different treatments are also unclear.

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Table 5-2: Characteristics and outcomes of the studies using a combination of ZRAS and another treatment. WL = Wu Ling; FU = follow-up; SDRS = Sleep Dysfunction Rating Scale; RCT = Randomized Controlled Trial; AIS = Athen's Insomnia Scale; SOL = Sleep Onset Latency; TST = Total Sleep Time; SE = Sleep Efficiency; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure

Author (date)	Design	Active	Control	Population (n)	Duration	Efficacy measurement	Efficacy outcomes	Safety measurement	Safety outcomes
Xu (2014)	One-arm trial	Acupuncture plus ZRAS capsule	N/A	Insomniacs (30)	4-6 weeks with 6-month F-U	Clinical efficacy assessed by therapist	100% of the participants experienced improvement; 87% were clinically "cured"	Not assessed	
Zhu (2011)	RCT	WL capsule plus ZRAS capsule	Estazolam 1 mg	Insomniacs (61)	30 days	AIS	Significant efficacy (i.e.,50% reduction in AIS score) was achieved by more participants in the experimental group	Reports of side effects	More side effects in the control group, but statistical significance unclear
Gao (2014)	RCT	Acupuncture plus ZRAS solution	Zopiclone 7.5 mg	Insomniacs (120)	2 weeks with a 1-week F-U	SDRS	No significant difference at post-treatment between groups	Reports of adverse events, vital signs, blood metabolic index and physical examination	More adverse events in the control group. No significant difference in vital signs, blood metabolic index and physical examination at post-treatment
Zhang (2015)	RCT	ZRAS capsule plus Amlodipine or Levamlodipine	Amlodipine or Levamlodipine	Older adults with comorbid insomnia and hypertension (60)	8 weeks	Primary outcome: reported SOL, TST and SE; secondary outcomes: PSQI and blood pressure	Shorter SOL, longer TST, higher SE, lower PSQI score and lower SBP and DBP at post-treatment compared to control group	Not assessed	
Hu (2015)	RCT	ZRAS granule plus Estazolam 1-2 mg	Estazolam 1-2 mg	Insomniacs (93)	3 months	PSQI and Chinese medicine pattern score	Lower PSQI score and Chinese medicine pattern score at post-treatment for the experimental group	Routine blood, urine and fecal tests; cardiac, hepatic and renal functions blood tests; reports of adverse	More adverse events in the control group
Zhong (2018)	RCT	ZRAS capsule plus Oxazepam 15-30 mg	Oxazepam 15-30 mg	Insomniacs (96)	4 weeks	Clinical efficacy based on self-reported sleep parameters and PSQI	Better clinical efficacy and lower PSQI score at post-treatment for the experimental group	Not assessed	

ZRAS as an adjunctive treatment for insomnia in hypertension patients was found to be effective not only to improve subjective sleep parameters and sleep quality, but also to decrease blood pressure [517]. It is unclear if the effect on blood pressure was direct or indirect.

ZRAS capsule was found to be effective as an adjunctive treatment for insomnia compared to BzRAs alone in terms of subjective sleep quality [282, 518].

5.2.3. Safety

As for the studies in which ZRAS was used as a monotherapy, many of which ZRAS was used in combination did not assess safety measures. The study in which ZRAS capsule was combined with Wu Ling capsule reported less side effect than for Estazolam, without reporting if this difference was statistically significant however [516]. Adverse events were also less frequent when treated with ZRAS granule as an adjunctive of Estazolam [282]. It could be explained by a more moderate use of Estazolam associated with less severe symptoms because of the ZRAS formulation, or a positive impact of ZRAS on the adverse events caused by Estazolam. One study reported no significant difference between and after 2 weeks of ZRAS solution combined with acupuncture in terms of vital signs, blood metabolic index and physical examination [312]. Despite being assessed in one of the trials, routine blood, urine and faecal tests, cardiac, hepatic and renal functions blood tests results were not reported in the report of the trial [282].

5.2.4. Limitations

The combination of two types of Chinese medicine treatment (e.g., acupuncture and herbal medicine) is common in clinical practice. However, the design of the studies examined here does not allow concluding on the benefit of such a practice. The absence of matched placebo in the studies in which ZRAS was used as an adjunctive treatment also limits the interpretation of results.

Unclear and high risks of bias were present in most of the studies, especially in terms of sequence generation (4/6), allocation concealment (6/6), blinding of participant and personnel (6/6), blinding of outcome assessment (6/6), and selective reporting (5/6).

5.3. Clinical trials using ZRAS for other conditions

5.3.1. Overview

Different trials have assessed the efficacy of ZRAS for anxiety and depression in Coronary Heart Disease (CHD) patients [290, 291], major depression in post-stroke patients [296], neurasthenia [292], schizophrenia [294], and general reaction in cranial trauma patients [295] (See Table 4-3). The rationale for the use of ZRAS for these conditions is the effects of ZRAS and its ingredients on the central nervous system and on the blood circulation [329, 394, 519-522], which makes it particularly adequate for conditions involving the two systems.

5.3.2. Efficacy

ZRAS capsule was found effective in reducing anxiety and depression in CHD patients as an adjunctive treatment [290, 291]. However, it failed at improving significantly objective outcomes of depression and CHD, i.e. serotonin and myeloperoxidase blood levels. ZRAS capsule was also found to be effective as an adjunctive treatment in improving cognitive performances in schizophrenia patients after two years of treatment [294]. Compared to oryzanol, ZRAS granule was found more effective as a treatment of neurasthenia [292]. ZRAS was found to be efficient as an adjunctive treatment for major depression in post-stroke patients in terms of anxiety and depression levels [296]. Finally, the combination of Ci Wu Jia tablet and ZRAS solution was compared to standard treatment for the treatment of general reaction in cranial trauma patients, but significance was not reported [295].

Table 4-3. Characteristics and outcomes of the studies using a combination of ZRAS and another treatment. WCST = Wisconsin Card Sorting Test; WAIS = Wechsler Adult Intelligence Test; PANSS = Positive And Negative Syndrome Scale; NRT = Non-Randomized Trial; CWJ = Ci Wu Jia; HARS = Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale

Author (date)	Design	Active	Control	Population (n)	Duration	Efficacy measurement	Efficacy outcomes	Safety measurement	Safety outcomes
Qi (2018)	RCT	ZRAS capsule plus Sertraline, Diazepam, conventional CHD treatment and psychotherapy	Sertraline, Diazepam, conventional CHD treatment and psychotherapy	CHD patients with anxiety and depression (214)	3 months	Blood Serotonin and Myeloperoxidase levels; therapist-assessed clinical efficacy for CHD, anxiety and depression respectively	No significant difference in efficacy for CHD and in serotonin and myeloperoxidase levels between groups; better efficacy for anxiety and depression in the experimental group	Adverse events report	Significantly less adverse events in the experimental group
An (2014)	RCT	ZRAS capsule plus Quetiapine	Quetiapine	Schizophreniacs (70)	2 years	Cognitive and executive performance measured with WCST; Intelligence measured with WAIS; Schizophrenia severity measured with PANSS	Better cognitive and executive performance, better intelligence and lower symptom severity for the experimental group	Not reported	
Yang (1994)	NRT	CWJ tablet plus ZRAS solution	1. Piracetam, Vitamin B1, Oryzanol; 2 Piracetam, Vitamin B1, Oryzanol, CWJ tablet and ZRAS solution	Cranial trauma patients with general reaction (664)	3 weeks	Therapist-rated clinical efficacy	Better improvement of general reaction for experimental group but statistical significance not reported	Not reported	
Yang (2016)	RCT	Conventional CHD treatment, psychological counselling and ZRAS capsule	Conventional CHD treatment and psychological counselling	Angina pectoris patients with anxiety and depression (100)	4 weeks	Therapist-rated clinical efficacy for angina; HAMD reduction; duration of hospitalisation	No significant difference in clinical efficacy for angina between group; higher HAMD reduction in the experimental group; no significant difference in hospitalisation duration	Not reported	
Shen (2011)	RCT	ZRAS granule	Oryzanol	Neurasthenia (100)	4 weeks	Therapist-assessed clinical efficacy	Better efficacy for experimental group	Not reported	
Zhu (2007)	RCT	ZRAS capsule plus paroxetine	Paroxetine	Post-stroke patients with major depression (62)	4 weeks	HARS and HDRS	Better efficacy for experimental group after 1 week, 2 weeks and 4 weeks of treatment	Not reported	

5.3.3. Safety

Safety outcomes were assessed only in one study [290], which reported less adverse reactions for the experimental group in which ZRAS capsule was added to the conventional treatment received by the

control group. According to the results of this study, ZRAS may have the potential to diminish the adverse reactions caused by Sertraline, Diazepam, or conventional CHD treatment.

5.3.4. Limitations

All these studies presented high risk of bias. None of these studies had appropriate blinding, including participant blinding, personnel blinding, and assessor blinding. The use of non-validated criteria for therapist-reported clinical efficacy is particularly preoccupying as the therapist was not blinded to the participant's condition. The targeted population was not clearly defined, as for "cranial trauma" patients with "general reaction", or "neurasthenia", which is a disease classification that has been abandoned for years.

5.4. Clinical trials using ZRAS as a control intervention for insomnia

5.4.1. Overview

Five clinical trials have used ZRAS as a control intervention for other Chinese medicine treatments. The experimental intervention were other herbal formulas taken orally in form of granule [317], decoction [318] or capsule [319], herbal foot bath [320], and tai chi [321], a traditional physical exercise also known as "shadowboxing" (Table 4-4). Three of these trials were RCTs and two were Non-randomized Controlled Trials (NCTs).

5.4.2. Efficacy

The efficacy of ZRAS capsule was found to be lower than all control interventions [317-321], except for an absence of significant difference in terms of sleep parameters measured with polysomnography between insomniacs treated with ZRAS capsule and those treated with An Shen Fang granule [317]. The effect sizes in terms of TST, SOL and NWAK measured by polysomnography were 1.95 SD, -0.54 SD and -0.44 SD after 1 week of ZRAS as an experimental intervention [305] and only 0.72 SD, -0.71 SD and -0.63 SD after 4 weeks of ZRAS as a control intervention [317]. This discrepancy is even more obvious in sleep quality measured with PSQI, with an effect size of 2.31 SD [281] and 2.18 SD [303] after 2 weeks of ZRAS as an experimental treatment and only 0.12 SD after 2 weeks of ZRAS used as a control intervention [321].

5.4.3. Safety

Safety outcomes were reported in two trials only. The adverse events caused by ZRAS when used as a control intervention were found similar in nature and frequency with the ones in the trial with ZRAS as an experimental intervention [317, 320]. Routine blood, urine and stool test, hepatic and renal functions blood tests, and ECG were not significantly different after treatment with ZRAS capsule, except for one case who presented white and red cells in urine.

5.4.4. Limitations

Severe methodological flaws can be observed in these studies, such as an absence of randomization, difference between the two groups at baseline, inappropriate blinding of participants and personnel and ineffective blinding of outcome assessors. Non-validated criteria of clinical efficacy were used, which is troublesome as assessors were not appropriately blinded.

Table 5-4: Characteristics and outcomes of the studies using ZRAS as a control intervention. TST = Total Sleep Time; SOL = Sleep Onset Latency; NWAK = Number of aWAKenings; ECG = ElectroCardioGram; NCT = Non-randomized Controlled Trial; BLM = Bai Le Mian

Author (date)	Design	Active	Control	Population (n)	Duration	Efficacy measurement	Efficacy outcomes	Safety measurement	Safety outcomes
Wu (2010)	RCT	An Shen Fang granule	ZRAS capsule	Insomniacs (40)	4 weeks	Polysomnography; therapist-reported clinical efficacy	Not significantly different TST, SOL and NWAK between groups; longer deep sleep, longer REM sleep and shorter light sleep in experimental group; better clinical efficacy for the experimental group	Adverse reactions report; routine blood, urine and stool test, hepatic and renal functions blood tests, ECG	No adverse reaction or abnormal result in any group, except for one case of white and red cells in urine
Zhang (2018)	RCT	An Shen Fang foot bath	ZRAS capsule	Insomniacs (120)	10 days	PSQI; clinician-assessed clinical efficacy	Better PSQI score and better clinical efficacy in the experimental group	Adverse events	More adverse events (4 cases of stomach discomfort) in the control group
Zhang (2014)	RCT	Tai chi 24 form plus ZRAS capsule	ZRAS capsule	Insomniacs (60)	2 weeks	PSQI	Better PSQI score in the experimental group	Not reported	
Xu (2013)	NCT	Jie Yu Yi Hao Fang modified	ZRAS capsule	Insomniacs (100)	3 weeks	Clinician-assessed clinical efficacy	Better clinical efficacy for the experimental group	Not reported	
Yang (2015)	NCT	BLM capsule	ZRAS capsule	Insomniacs (55)	30 days	Chinese Medicine Psychological Disorder State Scale	Better psychological state in the experimental group at post-treatment	Not reported	

5.5. Interactions with other drugs in humans

Literature databases (pubmed, CNKI, Wanfang, VIP), drug-herb interaction databases (Medscape, National Center for Complementary and Alternative Health, NIH Office of Dietary Supplement), drug-herb interactions handbooks [523-525] and systematic reviews on herb-drug interactions [526-530] were searched for potential interactions between ZRAS and its ingredients and other drugs in humans.

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No interaction was found between ZRAS and other drugs in humans.

Potential interactions between DS and warfarin were widely reported. These potential interactions are based on three cases of interactions reported in China [531, 532]. In both the cases, an increase of the INR was observed after oral administration of DS in cardiac diseases patients taking warfarin, the INR being stabilised after the cessation of the administration of DS. This interaction was later established by a clinical trial in which DS was used on atrial fibrillation patient using warfarin with a stable INR [533]. The interaction between DS and warfarin is considered to not be related to CYP450 activity and the exact mechanism is unknown [510]. The effects of DS on CYP3A4 activity were tested in clinical trials in humans, with negative and positive results [534-538]. Therefore, there are theoretical interactions between DS and CYP3A4 substrates, including some immunosuppressants, chemotherapeutics, azole antifungals, macrolides, antidepressants, antipsychotics, opioids, BzRAs, statins, calcium channel blockers, etc. It is worth noting that these studies used much higher dose of DS extract, especially lipophilic components (which are suspected of affecting CYP450), than ZRAS. Moreover, no adverse reaction was observed in these trials. In the present search, no case of interaction between DS and other drugs was found, except the two cases of interaction with warfarin.

A retrospective, cross-sectional study including 1795 patients with schizophrenia from 17 psychiatric hospitals in China found an association between WWZ use and the frequency of adverse events caused by quetiapine, clozapine, and olanzapine [539]. No other case of interaction between WWZ and other drugs in human was found in the present search.

No case of interaction between SZR and other drugs in human was found in the present search.

5.6. Registration and Marketing Experience

ZRAS capsule was the second most commonly used sedative-type herbal patent medicine in 2006 according to a report on drugs sells in a general hospital in China [540].

ZRAS capsule has been register in the ARTG the 3rd April 2018 for “sleeplessness”.

A similar product consisting of the three herb formula ZRAS in liquid form is approved for use in Australia and marketed under the name “Sleep Inducer Formula” by Beijing Tong Ren Tang Pty Ltd.

5.7. Summary of the human research on ZRAS

Several clinical trials have found ZRAS efficient in improving subjective and objective measures of sleep when used as a monotherapy or an adjunctive treatment. According to these studies, the efficacy of ZRAS is better than placebo and similar or better than BzRAs drugs. ZRAS seems also promising for conditions in which the circulatory system and the central nervous system are both impaired. However, severe methodological flaws in these studies prevent a firm conclusion on ZRAS efficacy, especially as discrepancies have been found between studies in which ZRAS was used as an experimental intervention and those in which it was used as a control intervention.

ZRAS has been found to be a relatively safe treatment as only mild adverse reactions were reported in these trials, no matter if ZRAS was used as an experimental or control intervention. The safety profile of ZRAS seems to be better than the one of BzRA drugs. Laboratory and physical tests after the use of ZRAS were mostly negative.

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Participant Initials			

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Participant Initials			

Participant ID			

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Participant Initials			

Participant ID			

Annexe 2. Case Report File template

Efficacy and safety of Zao Ren An Shen capsule for the treatment of chronic insomnia: A randomized -controlled trial

Case Report File

Version 2

Investigator: Yoann Birling

Supervisors: A/Prof. Xiaoshu Zhu

Prof. Alan Bensoussan

Dr. Caterina Tannous

Co-investigator: Dr. Nicole Ableson

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Participant Initials			

Participant ID			

PRE-SCREENING PHONE CALL (W-2)

Date (dd/mmm/yyyy): _____/_____/ 20_____

Actions checklist

- ☐ Presented and discussed the trial
- ☐ Completed pre-screening checklist
- ☐ Recorded participant's contact (if applicable)
- ☐ Asked how the participant heard about the study (if applicable)
- ☐ Set the first visit time and venue
- ☐ Asked the participant to question bed partner about sleep conditions
- ☐ Reminded the participant to not take any sleep aid during the 7 days before the visit
- ☐ Asked to bring medication instructions (if applicable)
- ☐ Asked the participant if he/she has done any blood test in the past 6 months and ask him/her to bring it during the visit if relevant
- ☐ Booked the room for the visit (if applicable)
- ☐ Sent the first survey
- ☐ Sent the confirmation email/mail with PIS/ICF, campus map and parking permit (if applicable)
- ☐ Created the fatigue science account and paired the actigraph

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Participant Initials			

Participant ID			

PRE-SCREENING CHECKLIST

- ☐ 18 years old or older.
- ☐ Presence of difficulty initiating, difficulty maintaining sleep (i.e., frequent awakenings or problems returning to sleep after awakening) or early-morning awakening with inability to return to sleep
  Note: shallow sleep or non-restorative sleep in the absence of sleep initiation and maintenance difficulty does not apply. The difficulty initiating or maintaining sleep has to be perceived by the potential participant and not only measured or observed.
- ☐ The above symptoms occur at least **three times a week** every week since at least **three months**.
- ☐ The above symptoms occur despite adequate opportunity to sleep.
  Note: there is no excessive noise or temperature in the sleep environment; the bed is not uncomfortable.
- ☐ The above symptoms cause significant distress or impairment (e.g., negative impact on social relationships, work, studies, etc.).
- ☐ Agreement to abstain from any other treatment for insomnia, including pharmaceutical treatment, complementary and alternative medicine, and psychotherapy, during the trial (6 weeks).
- ☐ No known mental disorder or treated and stable for at least two years (schizophrenia and bipolar disorder) or one month (other mental disorders).
- ☐ Not taking warfarin, quetiapine, clozapine, or olanzapine.
- ☐ Ability to understand and speak English.
- ☐ Willing to use birth control methods and to not donate sperm during the baseline and intervention periods, or sterile.

For women only

- ☐ Not pregnant or breast-feeding.

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Participant Initials			

Participant ID			

FIRST VISIT (W-1)

Date (dd/mmm/yyyy): _____/_____/ 20_____

Actions checklist

- ☐ Presented and discussed the trial in details
- ☐ The participant signed the informed consent form
- ☐ Provided a copy of the PIS/ICF (if required)
- ☐ The participant completed the Insomnia Severity Index and the Credibility and Expectancy Questionnaire
- ☐ Insomnia Severity Index checked
- ☐ Measured blood pressure
- ☐ Conducted the medical interview (including SCID and MINI interviews)
- ☐ Completed the medical eligibility checklist
- ☐ Explained how to use the sleep diary
- ☐ Provided the actigraph, with explanations
- ☐ Provided the blood test form (if applicable)
- ☐ Provided the oximeter (if applicable)
- ☐ Provided the investigational product A
- ☐ Provided the $20 voucher
- ☐ Provided paper version of the questionnaires and sleep diary (if applicable)
- ☐ Set up time and venue for next visit

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Participant Initials			

Participant ID			

Participant Information Sheet

Project Title: ***Investigation on the Safety and Effectiveness of Chinese Herbal Medicine for the Treatment of Insomnia.***

Project Summary:

You are invited to take part in this research project. The aim is to test an herbal treatment for insomnia. This treatment is called Zao Ren An Shen (ZRAS) capsule.

This project is conducted by Yoann Birling, PhD candidate at NICM Health Research Institute (NICM). He is supervised by Associate Professor Xiaoshu Zhu (School of Science and Health, NICM), Professor Alan Bensoussan (NICM), and Professor Jerome Sarris (NICM).

Insomnia disorder is a common disease. It may severely affect people's body, mind and daytime performance. Current advised treatments include drugs and psychotherapy. Drugs such as sleeping pills can improve insomnia symptoms. However, they may also bring about side effects and dependency. Psychotherapy can benefit people with insomnia, but it requires a lot of time, energy and involvement. It is also largely not available. Thus, there is a need for other treatments.

Zao Ren An Shen (ZRAS) capsule is an herbal medicine. It has been used in China for insomnia for more than 30 years. It is composed of Suan zao ren (Ziziphi Spinosae Semen), Wu wei zi (Schisandrae Chinensis Fructus), and Dan shen (Salviae Miltiorrhizae Radix et Rhizoma). Previous studies have shown that this drug is efficient. Its effect is better or similar to that of sleeping pills. Its side-effects are mild and relatively rare.

This aim of the project is to assess the benefits and limitations of ZRAS capsule for insomnia.

How is the study being paid for?

This research is funded by Western Sydney University.

ZRAS capsules and placebos were provided by Global Therapeutics Pty Ltd.

The principal investigator (Yoann Birling) is a recipient of a Blackmores-NICM Scholarship.

What will I be asked to do?

Participation in any research is voluntary. If you agree to participate in this study, you may be asked to sign a Participant Consent Form; one copy retained by the researcher/s and copy given to keep.

In this study, you may receive either the treatment or a placebo. You cannot choose or change group. The look, taste and smell of the placebo are similar with the tested medicine. However, it has no medical effect. Neither you nor your investigator will know which treatment you are receiving. We aim at including 90 people in this study.

For this study, participants will be contacted twice over the phone and will be required to attend a Western Sydney University campus (Westmead, Campbelltown, Parramatta or Bankstown) three times. At these clinic visits, you will be asked questions about your health, including current diseases, medication, and substance use. You will also be asked to complete questionnaires about your sleep, mood and health. Additionally, your blood pressure will be measured and the investigator will examine your tongue and pulse.

Participants will need to complete a sleep diary every morning for seven weeks. You will need to complete a survey on your beliefs about different medicines and your opinion about the

treatment as well as electronic questionnaires about your sleep, mood and overall feeling. You will need to take three blood tests (at no cost); if you have done these tests in the past six months, you should give the results to the investigator.

Participants will be provided with a five-week treatment, and will be required to take three capsules of ZRAS (or a placebo) once a day, one hour before bedtime. During five weeks, you will not be allowed to start any other treatment for insomnia. These treatments include drugs and psychotherapy. You can take your regular medication if not used to treat insomnia. A treatment for insomnia can only be used occasionally as a rescue.

Participants will be required to wear an actigraph, a device used to detect movement, for 24-hour every day and may also be required to wear an oximeter, a device used to measure oxygen levels, every night for one week. You will be asked to take good care of these devices during the study and to recharge the actigraph when necessary. For the duration of the study, you will also be asked to control your caffeine, alcohol and nicotine consumption to your usual levels. You may still donate blood and if you are fertile, you will be asked to use birth-control methods and to not donate sperm for the duration of the study.

If you fall under one or more of the following situations, you **will not be eligible** to take part in this study:

- Are aged under 18.
- Do not have an insomnia disorder.
- Unwilling or unable to stop other treatments for insomnia for the duration of the trial.
- Are fertile and unwilling to use birth control methods for the duration of the trial.
- Unable to read and understand English.
- Imminent need of mental or medical care.
- Abnormal blood test results within the last six months, if not approved by a general practitioner.
- The symptoms can be explained by another disease or the use of a substance.
- Have undergone a treatment for insomnia less than 14 days prior to the second visit.
- Have any psychotic or bipolar disorder, if not treated or unstable.
- Have alcohol or drug addiction.
- Other mental disorders such as depression or anxiety, if the disease is not treated or stable for less than one month.
- Cognitive problems that prevent you from following the trial instructions or giving informed consent.
- Taking a Warfarin-type drug.
- Allergy history to any of the ingredient of the ZRAS capsule or the placebo.
- Are pregnant or breastfeeding.
- Considered not suitable for the trial by the investigator.

How much of my time will I need to give?

- About 1 to 1.5 hours for each of the three visit of the study. During the visits, you will be asked questions about your characteristics and your health.
- About 40 to 50 minutes for each of the two phone interviews. During these phone calls, questions about your symptoms and health status will be asked.
- About 3 to 10 minutes per day to complete the sleep diary.
- About 30 minutes for the survey.

30-60 minutes to take the blood tests, if needed (only once).

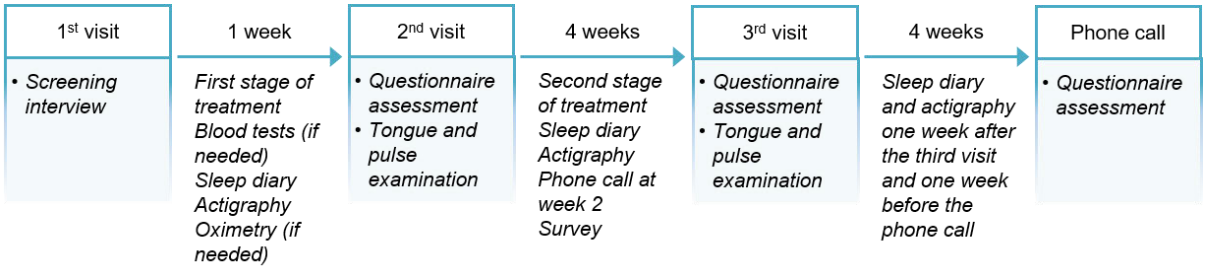

Figure 1 Flowchart of the trial procedure.

What benefits will I, and/or the broader community, receive for participating?

There is the potential that you may experience improvement in your insomnia symptoms and overall health. The study may also help you to understand your condition better, and may also help other insomnia patients, health practitioners and policy makers better understand the benefits and limitations of ZRAS as an alternative treatment for insomnia.

You will be given reimbursement for your travel costs (up to $20 per visit) for participating in this study.

Will the study involve any risk or discomfort for me? If so, what will be done to rectify it?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below. They may be mild, moderate, or severe. If you have any of these side effects, or are worried about them, talk to your investigator. Your investigator will also be looking out for side effects. Previous studies have identified the following side effects for this treatment. The incidence rate is about 0 to 10.67%.

- Fatigue
- Stomach discomfort
- Acid reflux
- Diarrhoea
- Lip numbness

There may be side effects that the investigator does not expect or does not know about. It could be serious. Tell your study investigator immediately about any new or unusual symptom/s that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your investigator may need to stop your treatment. You may be referred to a general practitioner or a hospital.

The effects of ZRAS capsule on the unborn child and on the newborn baby are not known. Because of this, it is important that participants are not pregnant or breastfeeding and do not become pregnant during the course of the research project.

How do you intend to publish or disseminate the results?

Participant Initials				Participant ID			

The results of this study will be published and/or presented as part of the investigator PhD thesis, journal articles, and conference presentations. In any publication and/or presentation, it will be impossible to identify you, except with your permission.

Identified data allow someone to be identified, such as a name or an address. These data will be kept confidential. Electronic identified data will be stored in a computer. The computer is protected by a password. Hardware identified data will be stored in a locked cabinet. Both type of data can only be reached by the investigator.

The monitor(s), the auditor(s), the Human Research Ethics Committee, and the regulatory authority(ies) will be granted access to your original medical records. They will verify the clinical trial procedures and/or data. They will not violate the confidentiality of the participants, to the extent permitted by the applicable law and regulations. By signing this form, you authorise such access.

The raw data collected from the actigraph will be stored and managed in Amazon servers. They are in the USA. This data cannot reveal your identity.

Will the data and information that I have provided be disposed of?

No. Your data will be used as per Western Sydney University's Open Access Policy. The non-identified data from this study can be made available online and worldwide. Identified data will be kept for 15 years in a shared drive with restricted access, however please be assured that only the researchers will have access to the raw data you provide.

Can I withdraw from the study?

Participation in the research is voluntary. You are not obliged to be involved. If you do participate you can withdraw at any time. You will be asked to come to the visit site to return all equipment. You will be asked to detail the reasons for wishing to withdraw. If provided, these will be recorded. If willing, you will complete the questionnaires of the study. If willing, you may be contacted to provide the information of the other assessments as well. If you do choose to withdraw and specify, any information that you have supplied can be destroyed and not included in the analysis.

Whatever your decision, it will not affect your future care or your relationship with the research staff.

Under the following circumstances, you may be withdrawn from the study:

- If you start a new treatment for insomnia;
- If your insomnia condition gets worse and additional treatment is required;
- If a serious medical condition occurs,
- If you fall pregnant.

Can I tell other people about the study?

Yes, you can tell other people about the study. You can provide them with the investigator's contact details. They can contact the investigator to discuss their participation in the research project and obtain a copy of the information sheet.

What if I require further information?

If you wish to discuss the research further before deciding whether or not to take part in, please contact the investigator.

Participant Initials			

Participant ID			

If there is any information relevant to your willingness to continue the study, you will be informed in time.

Yoann Birling
NICM Principal Investigator
p. +61 2 9685 4752
e. y.birling@westernsydney.edu.au

What if I have a complaint?

If you have any complaints or reservations about the ethical conduct of this research, you may contact the Ethics Committee through Research Engagement, Development and Innovation (REDI) on Tel +61 2 4736 0229 or email humanethics@westernsydney.edu.au.

Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.

This study has been approved by the Western Sydney University Human Research Ethics Committee. The Approval number is H12990.

Participant Initials			

Participant ID			

Consent Form

Project Title: *Investigation on the Safety and Effectiveness of Chinese Herbal Medicine for the Treatment of Insomnia*

I hereby consent to participate in the above named research project.

I acknowledge that:

- I have read the participant information sheet (or where appropriate, have had it read to me) and have been given the opportunity to discuss the information and my involvement in the project with the researcher/s
- The procedures required for the project and the time involved have been explained to me, and any questions I have about the project have been answered to my satisfaction.

I consent to:

☐ *My blood being tested*

☐ *My activity levels being measured*

☐ *My blood pressure being measured*

☐ *My oxygen saturation being monitored*

☐ *Provide information on my sleep and my health*

I consent for my data and information provided to be used for this project.

I understand that my involvement is confidential and that the information gained during the study may be published but no information about me will be used in any way that reveals my identity.

I understand that I can withdraw from the study at any time without affecting my relationship with the researcher/s, and any organisations involved, now or in the future.

Signed:

Name:

Date:

This study has been approved by the Human Research Ethics Committee at Western Sydney University. The ethics reference number is: H12990

What if I have a complaint?

If you have any complaints or reservations about the ethical conduct of this research, you may contact the Ethics Committee through Research Engagement, Development and Innovation (REDI) on Tel +61 2 4736 0229 or email humanethics@westernsydney.edu.au.

Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.

Participant Initials			

Participant ID			

MEDICAL INTERVIEW NOTESHEET

Sleep interview

- When did you start to have trouble sleeping? _____
- Any reason? _____

Current comorbidities review

Guiding questions: have you been diagnosed of any medical condition or illness, including physical and mental disorders? When have you been diagnosed? Is this disorder related to your insomnia? When the symptoms of this disorder get better or worse, do the symptoms of insomnia evolve in the same way?

Comorbidity 1:	Diagnosis date:
End date:	Suspected through the interview ☐
Evidence that the disorder does not adequately explain the predominant complaint of insomnia:	

Comorbidity 2:	Diagnosis date:
End date:	Suspected through the interview ☐
Evidence that the disorder does not adequately explain the predominant complaint of insomnia:	

Comorbidity 3:	Diagnosis date:
End date:	Suspected through the interview ☐
Evidence that the disorder does not adequately explain the predominant complaint of insomnia:	

Participant Initials			

Participant ID			

Comorbidity 4:	Diagnosis date:
End date:	Suspected through the interview ☐
Evidence that the disorder does not adequately explain the predominant complaint of insomnia:	

Comorbidity 5:	Diagnosis date:
End date:	Suspected through the interview ☐
Evidence that the disorder does not adequately explain the predominant complaint of insomnia:	

Comorbidity 6:	Diagnosis date:
End date:	Suspected through the interview ☐
Evidence that the disorder does not adequately explain the predominant complaint of insomnia:	

Comorbidity 7:	Diagnosis date:
End date:	Suspected through the interview ☐
Evidence that the disorder does not adequately explain the predominant complaint of insomnia:	

Participant Initials			

Participant ID			

Concomitant medication, caffeine consumption and alcohol consumption

Guiding questions: have you taken any medication or substance to improve your health in the last 30 days?

Medication 1:	
Route of administration:	
Dose:	Frequency:
Start date (dd/mmm/yyyy): / /	Stop date (dd/mmm/yyyy): / / Ongoing
Can the use of the medication explain the complaint of insomnia? Yes No	
Is the product used to treat insomnia? Yes No	

Medication 2:	
Route of administration:	
Dose:	Frequency:
Start date (dd/mmm/yyyy): / /	Stop date (dd/mmm/yyyy): / / Ongoing
Can the use of the medication explain the complaint of insomnia? Yes No	
Is the product used to treat insomnia? Yes No	

Medication 3:	
Route of administration:	
Dose:	Frequency:
Start date (dd/mmm/yyyy): / /	Stop date (dd/mmm/yyyy): / / Ongoing
Can the use of the medication explain the complaint of insomnia? Yes No	
Is the product used to treat insomnia? Yes No	

Medication 4:	
Route of administration:	
Dose:	Frequency:
Start date (dd/mmm/yyyy): / /	Stop date (dd/mmm/yyyy): / / Ongoing
Can the use of the medication explain the complaint of insomnia? Yes No	
Is the product used to treat insomnia? Yes No	

Participant Initials				Participant ID			

Medication 5:	
Route of administration:	
Dose:	Frequency:
Start date (dd/mmm/yyyy): / /	Stop date (dd/mmm/yyyy): / / Ongoing
Can the use of the medication explain the complaint of insomnia? Yes No	
Is the product used to treat insomnia? Yes No	

Medication 6:	
Route of administration:	
Dose:	Frequency:
Start date (dd/mmm/yyyy): / /	Stop date (dd/mmm/yyyy): / / Ongoing
Can the use of the medication explain the complaint of insomnia? Yes No	
Is the product used to treat insomnia? Yes No	

Medication 7:	
Route of administration:	
Dose:	Frequency:
Start date (dd/mmm/yyyy): / /	Stop date (dd/mmm/yyyy): / / Ongoing
Can the use of the medication explain the complaint of insomnia? Yes No	
Is the product used to treat insomnia? Yes No	

Complements and herbal products:
Is any of the above products used to treat insomnia? Yes No

Participant Initials				Participant ID			

Caffeine consumption:

Drink or food description	Caffeine content	Daily consumption	Caffeine consumption
Coffee (150 ml)			
Ground roasted	85 mg		
Instant	60 mg		
Decaffeinated	3 mg		
Tea (150 ml)			
Leaf/bag	30 mg		
Instant	20 mg		
Decaffeinated	2 mg		
Colas (500 ml)	52 mg		
Cocoa/hot chocolate (150 ml)	4 mg		
Chocolate (100g)			
Milk chocolate	20 mg		
50% cocoa dark chocolate	43 mg		
80% cocoa dark chocolate	80 mg		
Chocolate snacks	8 mg		
Energy drink (250 ml)	80 mg		
Total daily caffeine consumption			

Alcohol weekly consumption:

Type of alcohol	Weekly consumption (standardized drinks)
340 ml of 5% alcohol beer	
140 ml of 12% alcohol wine	
40 ml of 40% alcohol spirits	
Other:	
Total weekly consumption	

Nicotine consumption

Smoking: Yes No	If Yes, daily consumption:

REMIND THE PARTICIPANT TO MAINTAIN A REGULAR USE OF CAFFEINE/ALCOHOL

Participant Initials			

Participant ID			

List of drugs and substances known to affect sleep-wake:

Cannabis

Amphetamines

Opioids:
Fentanyl, Oxycodone (Oxycontin®), Hydrocodone (Vicodin®), Codeine, Oxymorphone (Opana®), Morphine (Kadian®, Avinza®), Heroin.

Benzodiazepines receptor agonists:
Chlordiazepoxide (Librium), Diazepam (Valium, Valrelease), Flurazepam (Dalmane), Chlorazepate (Tranxene), Clonazepam (Klonopin, Rivotril), Quazepam (Doral), Bromazepam (Lectopam, Lexotan) Halazepam (Paxipam), Lorazepam (Ativan), Temazepam (Restoril), Oxazepam (Serax, Serapax), Alprazolam (Xanax), Triazolam (Halcion), Estazolam (Prosom), Midazolam (Versed), Zolpidem (Ambien) or Zolpidem CR, Zaleplon (Sonata), Eszopiclone (Lunesta).

Carbamates: Meprobamate (Miltown, Equanil), Carisoprodol, Tybamate And Lorbamate.

Antihistamines:
Hydroxyzine (Atarax), Doxylamine, Chlorpheniramine (Chlor-Trimeton), And Diphenhydramine (Benadryl).

Other anxiolytics:
Mebicar (mebicarum), Fabomotizole (Afobazole), Selank, Bromantane, Emoxypine, buspirone (Buspar) and tandospirone (Sediel), Pregabalin, Menthyl isovalerate (Validol), Propofol, Racetams.

Melatonin and receptor agonists (e.g., ramelteon)

Barbiturates:
Amobarbital (Amytal), Butabarbital (Butisol), Pentobarbital (Nembutal), Secobarbital (Seconal), Belladonna, And Phenobarbital (Donnatal), Butalbital/Acetaminophen/Caffeine (Esgic, Fioricet), Butalbital/Aspirin/Caffeine (Fiorinal Ascomp, Fortabs).

Serotonine selective reuptake inhibitors:
Citalopram (Celexa), Escitalopram (Lexapro), Fluoxetine (Prozac), Paroxetine (Paxil, Pexeva), Sertraline (Zoloft), Vilazodone (Viibryd), Fluvoxamine

Tricyclics:
Amitriptyline (Endep, Entrip), Clomipramine (Anafranil, Placil), Dosulepin/dothiepin (Dothep), Doxepin (Deptran, Sinequan), Imipramine (Tofranil, Tolerade), Nortriptyline (Allegron, NortriTABS)

Other antidepressants: Trazodone, and Mirtazapine

Antipsychotics: Quetiapine and Olanzapine

Anticonvulsants: Gabapentin, Pregabalin, Valproic Acid, and Tiagabine.

Corticosteroids: Methylprednisolone (Medrol), Prednisolone, And Prednisone.

Thyroid hormone:
Levothyroxine Sodium (Levothroid, Levoxyl, Synthroid, Tirosint, Unithroid), Liothyronine Sodium (Cytomel, Triostat), Liotrix (Thyrolar).

Anti-arrhythmics: Procainamide (Procanbid), Quinidine (Cardioquin), Disopyramide (Norpace)

Beta blockers: Atenolol (Tenormin), Metoprolol (Lopressor), Propranolol (Inderal)

Participant Initials			

Participant ID			

Diuretics:
Chlorothiazide (Diuril), Chlorthalidone (Hygroton), Hydrochlorothiazide (Esidrix, Hydrodiuril, Others).

Medications containing caffeine: NoDoz, Vivarin, Caffedrine, Anacin, Excedrin, Midol.

Nicotine replacement products:
Nicotine patches (Nicoderm), gum (Nicorette), nasal spray or inhalers (Nicotrol), and lozenges (Commit).

Sympathomimetic stimulants:
Dextroamphetamine (Dexedrine), Methamphetamine (Desoxyn), Methylphenidate (Ritalin)

Clonidine (Catapres)

Atorvastatin (Lipitor)

Interferon alpha

Levodopa

Phenytoin (Dilantin)

Lamotrigine (Lamictal)

Bupropion

Theophylline

Protriptyline (Vivactil)

Cimetidine (Tagamet)

Pseudophedrine (Sudafed)

Warfarin-type anticoagulants:

Acenocoumarol, Dicoumarol, Ethyl Biscoumacetate, Phenprocoumon, Warfarin

Antipsychotics:

Quetiapine, Clozapine, or Olanzapine

Participant Initials			

Participant ID			

Comorbid sleep disorders

1. Sleep apnoea and hypopnoea

Guiding questions:

- Have you or your bed partner ever noticed snoring, gasping or breathing pauses during sleep?
- Do you wake up at night because of trouble breathing?
- Do you feel refreshed after waking up?
- Do you feel sleepy during daytime even if you had enough sleep time?

☐ Sleep apnoea/hypopnoea is considered absent

☐ Sleep apnoea/hypopnoea is suspected

If sleep apnoea/hypopnoea is suspected, the participant will have to undergo oximetry for one week.

Oximetry result: _____

2. Circadian rhythm sleep-wake disorders

Guiding questions:

- Do you have trouble getting asleep, wake up often or wake up too early in the morning?
- Do your symptoms improve if you advance or delay your sleep schedule?
- How many times do you sleep usually in 24h?
- Do your symptoms evolved cyclically through time (e.g., asymptomatic – sleep onset difficulty – daytime sleepiness – early morning awakening)?
- Do you do shift work?

☐ Circadian rhythm sleep-wake disorders are considered absent

☐ A circadian rhythm sleep-wake disorder is considered present

Please specify: _____

Participant Initials				Participant ID			

3. Parasomnias (NREM sleep arousal disorders, nightmare disorder, REM sleep behaviour disorder)

Guiding questions:

- Have you or your bed partner ever noticed you getting up and walking during nigh time?
- Have you or your bed partner ever noticed you having abrupt terror episodes when sleeping?
- Do you experience nightmares or unpleasant dreams frequently?
- Have you or your bed partner ever noticed you speaking and moving in the bed while sleeping?

☐ Parasomnias are considered absent

☐ Parasomnias are considered present

Please specify: _____

4. Restless legs syndrome

Guiding questions:

- Do you sometimes feel unpleasant or uncomfortable sensations in the legs?
- Do you feel sometimes an urge to move your legs?
- If yes, does the urge begins or worsens while resting?
- Is it relieved by movements?
- Is it worse during the day or at night?

☐ Restless legs syndrome is considered absent

☐ Restless legs syndrome is considered present

5. Narcolepsy

Guiding questions:

- Do you sometimes feel an irrepressible need to sleep during daytime?
- If yes, how often and for how long?
- Have you ever experienced an episode of sudden difficulty or impossibility to move?

☐ Narcolepsy is considered absent

☐ Narcolepsy is considered present

Participant Initials			

Participant ID			

Comorbid medical disorders

Are you aware of having any of these diseases?

- Chronic obstructive pulmonary diseases
- Diabetes mellitus
- Chronic kidney diseases
- Malignancy
- Rheumatic disorders
- Chronic pain
- Neurodegenerative diseases (e.g. Alzheimer's, Parkinson's, Huntington's)
- Fatal familial insomnia
- Cerebrovascular diseases (i.e. ischemic or haemorrhagic stroke)
- Multiple sclerosis
- Traumatic brain injury

Allergy history

Does the participant have any known allergy history to any of these substances?

1. Suan zao ren (Ziziphi Spinosae Semen)
2. Wu wei zi (Schisandrae Chinensis Fructus)
3. Dan shen (Salviae Miltiorrhizae Radix et Rhizoma)
4. Carob pod powder
5. Silicon dioxide
6. Magnesium stearate
7. Hypromellose
8. Microcrystalline cellulose
9. Calcium hydrogen phosphate dehydrate

Yes		No	

Blood pressure

Systolic blood pressure: _____

Diastolic blood pressure: _____

Contact of attending physician

Name: _____ Number:_____

Email address:_____

Postal address:_____

Participant Initials			

Participant ID			

Medical eligibility checklist

Inclusion criteria (The answer to ALL the following items should be Yes)	
ISI score ≥ 10	Yes ☐ No ☐
Meet the diagnosis criteria of insomnia disorder according to the SCID	Yes ☐ No ☐

Exclusion criteria (The answer to ALL the following items should be No)	
Imminent need of psychiatric (e.g. suicide risk) or medical care (e.g. stroke).	Yes ☐ No ☐
Evidence that a substance, a mental disorder or a medical condition can explain the predominant complaint of insomnia.	Yes ☐ No ☐
Use of any other treatment for insomnia within 7 days before the first visit.	Yes ☐ No ☐
Caffeine consumption >600 mg/day.	Yes ☐ No ☐
Alcohol or drug addiction.	Yes ☐ No ☐
Cognitive impairment preventing the participant to understand the trial instructions, complete questionnaires or provide informed consent.	Yes ☐ No ☐
Allergy history to any of the ingredient of the ZRAS capsule or the placebo.	Yes ☐ No ☐
Taking a Warfarin-type anticoagulant, quetiapine, clozapine, or olanzapine	Yes ☐ No ☐

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Participant Initials			

Participant ID			

SECOND VISIT (W0)

Date (dd/mmm/yyyy): _____/_____/ 20_____

Actions checklist

- ☐ Received the signed medical verification form
- ☐ Collected the oximeter (if applicable)
- ☐ Synced actigraph data
- ☐ The participant completed the baseline questionnaires (including ISI, LTE, pain VAS, DASS, FSS and AQoL)
- ☐ Checked medical eligibility
- ☐ Checked for adverse events
- ☐ Conducted the Chinese medicine examination
- ☐ Provided the investigational product B
- ☐ Provided the $20 voucher
- ☐ Set up time and venue for next visit
- ☐ Provided the paper version of the questionnaires and sleep diary (if applicable)

Participant Initials			

Participant ID			

Medical eligibility checklist

Inclusion criteria (The answer to ALL the following items should be Yes)	
ISI score ≥ 10	Yes ☐ No ☐
Medical eligibility accepted by the study doctor	Yes ☐ No ☐

Exclusion criteria (The answer to ALL the following items should be No)	
The oximetry test is positive and sleep apnoea can explain the predominant symptoms of insomnia.	Yes ☐ No ☐
Use of any other treatment for insomnia within 14 days before the second visit.	Yes ☐ No ☐

Participant Initials			

Participant ID			

Chinese Medicine examination

The pulse is:

- ☐ Wiry (xuan) and rapid (shuo)
- ☐ Slippery (hua) and rapid (shuo)
- ☐ Thready (xi) and forceless (wuli)
- ☐ Wiry (xuan) and thready (xi)
- ☐ Thready (xi) and rapid (shuo)
- ☐ None of the above

The tongue is:

- ☐ Red
- ☐ Light
- ☐ With a yellow coating
- ☐ With a yellow and greasy coating
- ☐ Lacking of coating
- ☐ None of the above

The eyes are:

- ☐ Red
- ☐ None of the above

The complexion is:

- ☐ Dull
- ☐ None of the above

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Participant Initials			

Participant ID			

MID-TREATMENT PHONE CALL (W2)

Date (dd/mmm/yyyy): _____/_____/ 20_____

Actions checklist

- ☐ Completed the questionnaires (including ISI, DASS, FSS, and AQoL) on REDCap according to the participant's answers
- ☐ Checked for adverse events
- ☐ Reminded the participant to recharge the actigraph

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Participant Initials			

Participant ID			

THIRD VISIT (W4)

Date (dd/mmm/yyyy): _____/_____/ 20_____

Actions checklist

- ☐ Checked if the second survey was completed
- ☐ Synced data from the actigraph
- ☐ The participant completed the baseline questionnaires on REDCap (including ISI, LTE, pain VAS, DASS, FSS, AQoL and CEQ)
- ☐ Checked for adverse events
- ☐ Conducted the Chinese medicine examination
- ☐ Provided the $20 voucher
- ☐ Provided envelope for returning the actigraph
- ☐ Provided the paper version of the questionnaires and sleep diary (if applicable)

Participant Initials			

Participant ID			

Chinese Medicine examination

The pulse is:

- ☐ Wiry (xuan) and rapid (shuo)
- ☐ Slippery (hua) and rapid (shuo)
- ☐ Thready (xi) and forceless (wuli)
- ☐ Wiry (xuan) and thready (xi)
- ☐ Thready (xi) and rapid (shuo)
- ☐ None of the above

The tongue is:

- ☐ Red
- ☐ Light
- ☐ With a yellow coating
- ☐ With a yellow and greasy coating
- ☐ Lacking of coating
- ☐ None of the above

The eyes are:

- ☐ Red
- ☐ None of the above

The complexion is:

- ☐ Dull
- ☐ None of the above

Participant Initials			

Participant ID			

FOLLOW-UP PHONE CALL (W8)

Date (dd/mmm/yyyy): _____/_____/ 20_____

Actions checklist

- ☐ Completed the questionnaires (including ISI, DASS, FSS, and AQoL) on REDCap according to the participant's answers
- ☐ Checked for adverse events
- ☐ Asked the participant to return the actigraph

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Participant Initials			

Participant ID			

ADVERSE EVENT FORM

Visit: First visit / second visit / mid-treatment phone call / third visit / follow-up phone call

Form _____ on _____

<table>
<tr><td colspan="4">Adverse event description:</td></tr>
<tr><td colspan="2">Date of onset (dd/mmm/yyyy): / /</td><td colspan="2">Time of onset (hh:mm): :</td></tr>
<tr><td colspan="4">Duration of event:</td></tr>
<tr><td colspan="4">Date the event resolved (dd/mmm/yyyy): / / or ongoing O</td></tr>
<tr><td>Seriousness:
☐ Not serious
☐ Serious</td><td>Severity:
☐ Mild
☐ Moderate
☐ Severe</td><td>Causality relationship:
☐ Unrelated
☐ Possibly
☐ Probably
☐ Definitely
☐ Not assessable</td><td>Expectedness:
☐ Expected
☐ Unexpected</td></tr>
<tr><td colspan="4">Treatment and/or medication given for the event, if any:</td></tr>
<tr><td colspan="4">Action taken regarding study drug, if any:</td></tr>
<tr><td colspan="4">Event outcome:</td></tr>
<tr><td colspan="4">Changes in medication since the first visit, if any:</td></tr>
</table>

Participant Initials			

Participant ID			

Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence (e.g., abnormal laboratory finding, symptom, or disease) in a clinical investigation participant, administered a medicinal product/ device, that does not necessarily have a causal relationship with the medicinal product/ device. A worsening in a concomitant illness must be recorded as an AE. Pre-planned procedures and pre-existing conditions should not be recorded as AEs.

Adverse Reaction (AR)

Any untoward and unintended response to an investigational medicinal product related to any dose administered. All adverse events having a reasonable possibility of a causal relationship (i.e., there is evidence to suggest a causal relationship) to an investigational medicinal product would qualify as adverse reactions.

Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR)

An SAE/ SAR is any event that meets any of the following criteria:

- Results in death;
- Is life-threatening;
- Requires hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Other important medical events that are thought to jeopardize the participant and/or require intervention to prevent one of the other outcomes defining an SAE/ SAR.

Significant Safety Issue (SSI)

A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction that is both serious and unexpected.

Safety reporting

SAEs should be reported to the HREC and TGA.

The Investigator must report to the institution (site) within 72 hours of learning of the event, all SSI and SUSARs arising at the local site.

Severity	**Definition**
Mild	Easily tolerated and causing minimal discomfort
Moderate	Interfere with normal everyday activities
Severe	Prevents normal everyday activities

Causality	**Definition**
Unrelated	Not considered related
Possibly	Cannot be completely ruled out, but a better explanation exists
Probably	Reasonable relationship (administration/discontinuation) with investigational product (IP) and no better explanation
Definitely	Clear relationship with IP (administration, discontinuation, re-exposure)
Not assessable	E.g., insufficient evidence, conflicting data or poor documentation

Expected adverse events of ZRAS capsule: fatigue, stomach discomfort, diarrhoea, acid reflux, and lips numbness

Participant Initials			

Participant ID			

ADVERSE EVENT FORM

Visit: First visit / second visit / mid-treatment phone call / third visit / follow-up phone call

Form _____ on _____

<table>
<tr><td colspan="4">Adverse event description:</td></tr>
<tr><td colspan="2">Date of onset (dd/mmm/yyyy): / /</td><td colspan="2">Time of onset (hh:mm): :</td></tr>
<tr><td colspan="4">Duration of event:</td></tr>
<tr><td colspan="4">Date the event resolved (dd/mmm/yyyy): / / or ongoing O</td></tr>
<tr><td>Seriousness:
☐ Not serious
☐ Serious</td><td>Severity:
☐ Mild
☐ Moderate
☐ Severe</td><td>Causality relationship:
☐ Unrelated
☐ Possibly
☐ Probably
☐ Definitely
☐ Not assessable</td><td>Expectedness:
☐ Expected
☐ Unexpected</td></tr>
<tr><td colspan="4">Treatment and/or medication given for the event, if any:</td></tr>
<tr><td colspan="4">Action taken regarding study drug, if any:</td></tr>
<tr><td colspan="4">Event outcome:</td></tr>
<tr><td colspan="4">Changes in medication since the first visit, if any:</td></tr>
</table>

Participant Initials			

Participant ID			

Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence (e.g., abnormal laboratory finding, symptom, or disease) in a clinical investigation participant, administered a medicinal product/ device, that does not necessarily have a causal relationship with the medicinal product/ device. A worsening in a concomitant illness must be recorded as an AE. Pre-planned procedures and pre-existing conditions should not be recorded as AEs.

Adverse Reaction (AR)

Any untoward and unintended response to an investigational medicinal product related to any dose administered. All adverse events having a reasonable possibility of a causal relationship (i.e., there is evidence to suggest a causal relationship) to an investigational medicinal product would qualify as adverse reactions.

Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR)

An SAE/ SAR is any event that meets any of the following criteria:

- Results in death;
- Is life-threatening;
- Requires hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Other important medical events that are thought to jeopardize the participant and/or require intervention to prevent one of the other outcomes defining an SAE/ SAR.

Significant Safety Issue (SSI)

A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction that is both serious and unexpected.

Safety reporting

SAEs should be reported to the HREC and TGA.

The Investigator must report to the institution (site) within 72 hours of learning of the event, all SSI and SUSARs arising at the local site.

Severity	**Definition**
Mild	Easily tolerated and causing minimal discomfort
Moderate	Interfere with normal everyday activities
Severe	Prevents normal everyday activities

Causality	**Definition**
Unrelated	Not considered related
Possibly	Cannot be completely ruled out, but a better explanation exists
Probably	Reasonable relationship (administration/discontinuation) with investigational product (IP) and no better explanation
Definitely	Clear relationship with IP (administration, discontinuation, re-exposure)
Not assessable	E.g., insufficient evidence, conflicting data or poor documentation

Expected adverse events of ZRAS capsule: fatigue, stomach discomfort, diarrhoea, acid reflux, and lips numbness

Participant Initials			

Participant ID			

ADVERSE EVENT FORM

Visit: First visit / second visit / mid-treatment phone call / third visit / follow-up phone call

Form _____ on _____

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<tr><td colspan="4">Date the event resolved (dd/mmm/yyyy): / / or ongoing O</td></tr>
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Not assessable	E.g., insufficient evidence, conflicting data or poor documentation

Expected adverse events of ZRAS capsule: fatigue, stomach discomfort, diarrhoea, acid reflux, and lips numbness

Participant Initials			

Participant ID			

ADVERSE EVENT FORM

Visit: First visit / second visit / mid-treatment phone call / third visit / follow-up phone call

Form _____ on _____

Adverse event description:			
Date of onset (dd/mmm/yyyy): / /		Time of onset (hh:mm): :	
Duration of event:			
Date the event resolved (dd/mmm/yyyy): / / or ongoing O			
Seriousness: ☐ Not serious ☐ Serious	Severity: ☐ Mild ☐ Moderate ☐ Severe	Causality relationship: ☐ Unrelated ☐ Possibly ☐ Probably ☐ Definitely ☐ Not assessable	Expectedness: ☐ Expected ☐ Unexpected
Treatment and/or medication given for the event, if any:			
Action taken regarding study drug, if any:			
Event outcome:			
Changes in medication since the first visit, if any:			

Participant Initials			

Participant ID			

Definitions

Adverse Event (AE)

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Participant Initials			

Participant ID			

WITHDRAWAL FORM

Visit: First visit / second visit / mid-treatment phone call / third visit / follow-up phone call

Date of withdrawal (dd/mmm/yyyy): / / 20
The decision of the withdrawal originates from: the participant / the investigator
Reason(s) for withdrawal originating from the participant: ☐ Lack of improvement ☐ Adverse reactions ☐ Wishing to start a new treatment ☐ Unable to attend the visits at the trial site ☐ Other reason: _____ ☐ No reason given
Reason(s) for withdrawal originating from the investigator: ☐ Beginning of a new treatment ☐ Deterioration of insomnia condition requiring additional treatment ☐ Occurrence of serious medical condition ☐ Pregnancy ☐ Other reason: _____

I wish my data to be destroyed and not used in the analysis.

Participant signature: _____ Date (dd/mmm/yyyy): / /20

I agree for being contacted by the investigator and to provide my data for the remaining assessment procedures of the study.

Participant signature: _____ Date (dd/mmm/yyyy): / /20

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Participant Information Sheet

Project Title: Investigation on the Safety and Effectiveness of Chinese Herbal Medicine for the Treatment of Insomnia

Project Summary:

You are invited to take part in this research project. The aim is to test an herbal treatment for insomnia. This treatment is called Zao Ren An Shen (ZRAS) capsule.

This project is conducted by Yoann Birling, PhD candidate at NICM Health Research Institute (NICM). He is supervised by Associate Professor Xiaoshu Zhu (School of Science and Health, NICM), Professor Alan Bensoussan (NICM), and Professor Jerome Sarris (NICM).

Insomnia disorder is a common disease. It may severely affect people's body, mind and daytime performance. Current advised treatments include drugs and psychotherapy. Drugs such as sleeping pills can improve insomnia symptoms. However, they may also bring about side effects and dependency. Psychotherapy can benefit people with insomnia, but it requires a lot of time, energy and involvement. It is also largely not available. Thus, there is a need for other treatments.

Zao Ren An Shen (ZRAS) capsule is an herbal medicine. It has been used in China for insomnia for more than 30 years. It is composed of Suan zao ren (Ziziphi Spinosae Semen), Wu wei zi (Schisandrae Chinensis Fructus), and Dan shen (Salviae Miltiorrhizae Radix et Rhizoma). Previous studies have shown that this drug is efficient. Its effect is better or similar to that of sleeping pills. Its side-effects are mild and relatively rare.

This aim of the project is to assess the benefits and limitations of ZRAS capsule for insomnia.

In this study, you may receive either the treatment or a placebo. You cannot choose or change group. The look, taste and smell of the placebo are similar with the tested medicine. However, it has no medical effect. Neither you nor your investigator will know which treatment you are receiving. We aim at including 90 people in this study.

This research project has been designed carefully. We want to make sure that the results are interpreted in a fair and appropriate way. We also want to avoid researchers or participants jumping to conclusions.

How is the study being paid for?

This research is funded by Western Sydney University.

The ZRAS capsules and the placebos were provided by Global Therapeutics Pty Ltd.

Except for potential transportation fees to undergo blood tests, there won't be any cost for you.

What will I be asked to do?

Participation in any research is voluntary. If you do decide to take part in this research project you will sign this present form. You will be given a copy to keep.

If you fall under one or more of the following situations, you won't be allowed to take part in this study:

1. Age less than 18 years old.
2. Not having insomnia disorder.

3. Unwilling or unable to stop other treatments for insomnia during the time of the trial.

4. Being fertile and unwilling to use birth control methods while taking the study treatment.

5. Unable to understand and read English.

6. Imminent need of mental or medical care.

7. Abnormal blood tests within the last six months, if not approved by a general practitioner.

8. The symptoms can be explained by another disease or the use of a substance.

9. Use of a treatment for insomnia less than 14 days prior to the second visit.

10. Any psychotic or bipolar disorder, if not treated or unstable.

11. Alcohol or drug addiction.

12. Other mental disorders such as depression or anxiety, if the disease is not treated or stable for less than one month.

13. Cognitive problems that prevent you from following the trial instructions or giving informed consent.

14. Taking a Warfarin-type drug.

15. Allergy history to any of the ingredient of the ZRAS capsule or the placebo.

16. Women being pregnant or breastfeeding.

17. Considered not suitable for the trial by the investigator.

You will be asked to control your caffeine, alcohol and nicotine consumption to your usual levels during the study.

You will need to take three blood tests (at no cost). If you have done these tests in the past six months, you should give the results to the investigator.

You will need to take three capsules of ZRAS or a placebo once a day one hour before bedtime. You will take this treatment for five weeks.

You will need to wear an actigraph 24-hour every day during five weeks. If necessary, you may have to wear another actigraph and an oximeter every night during one week. An actigraph is a wrist-worn bracelet used to detect movement. An oximeter is a device placed on the fingertip used to measure oxygen levels. You will be asked to take good care of these devices during the study. You will have to recharge the actigraph when necessary.

You will need to complete a sleep diary every morning during six weeks.

You will need to complete a survey on your beliefs about different medicines and your opinion about the treatment.

You will need to come to the visit site three times in total. Travel cost will be reimbursed in a limit of $20.

You will be contacted two times by phone.

During five weeks, you will not be allowed to start any other treatment for insomnia. These treatments include drugs and psychotherapy. You can take your regular medication if not used to treat insomnia. A treatment for insomnia can only be used occasionally as a rescue.

You can still donate blood.

If you are fertile, you will be asked to use birth-control methods and to not donate sperm for the duration of the study.

How much of my time will I need to give?

About 1 hour to 1 hour and a half for each of the three visit of the study. During the visits, questions about your characteristics and your health. Your blood pressure will be measured. Your investigator will examine your tongue and pulse. You will also be asked to complete electronic questionnaires on an iPad. The questionnaires will be about your sleep, your mood and your overall feeling.

About 40 to 50 minutes for each of the two phone interviews. During these phone calls, questions about your symptoms and health status will be asked.

About 3 to 10 minutes per day to complete the sleep diary.

About 30 minutes for the survey.

30-60 minutes to take the blood tests, if needed (only once). Time for transportation is not included.

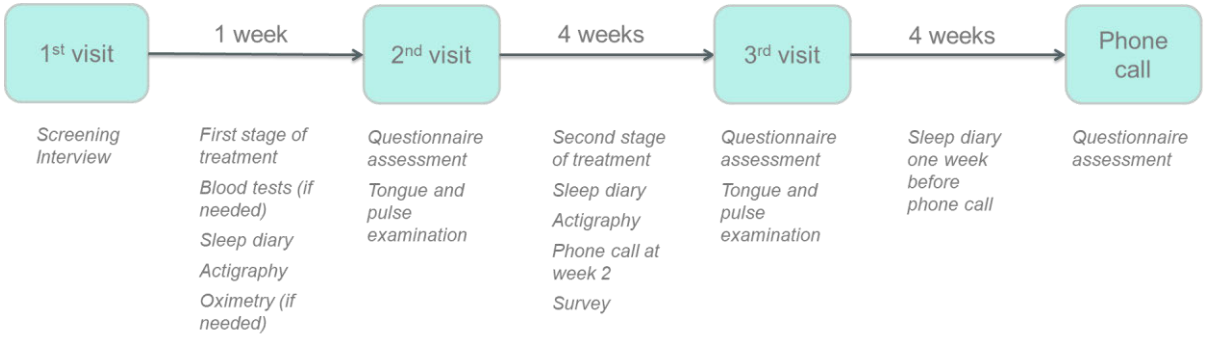

Figure 1. flowchart of the trial procedures

What benefits will I, and/or the broader community, receive for participating?

Your insomnia symptoms and overall health may improve.

You will understand your condition better through the free medical assessment. An unknown disease could be detected. In this case your health may improve if this disease is treated.

Your participation will allow the society to better understand the benefits and limitations of ZRAS as an alternative treatment for insomnia. It may interest other insomnia patients, health practitioners, and policy makers. If good results are obtained, millions of people across the world could benefit from it.

Will the study involve any risk or discomfort for me? If so, what will be done to rectify it?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below. They may be mild, moderate, or severe. If you have any of these side effects, or are worried about them, talk to your investigator. Your investigator will also be looking out for side effects. Previous studies have identified the following side effects for this treatment. The incidence rate is about 0 to 10.67%.

- Fatigue
- Stomach discomfort
- Acid reflux

- Diarrhoea
- Lip numbness

There may be side effects that the investigator does not expect or do not know about. It could be serious. Tell your study investigator immediately about any new or unusual symptom that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your investigator may need to stop your treatment. You may be referred to a general practitioner or a hospital.

If an unknown disease is uncovered during the study, you will be referred to your general practitioner for further management. If imminent care is needed for this condition, you will not be able to participate in this project until the condition is stable. The discovery of an unknown disease may affect your future health insurance.

The effects of ZRAS capsule on the unborn child and on the newborn baby are not known. Because of this, it is important that participants are not pregnant or breastfeeding and do not become pregnant during the course of the research project.

How do you intend to publish or disseminate the results?

The results of this study will be published and/or presented as part of the investigator PhD thesis, journal articles, and conference presentations. In any publication and/or presentation, it will be impossible to identify you, except with your permission.

Identified data allow someone to be identified, such as a name or an address. These data will be kept confidential. Electronic identified data will be stored in a computer. The computer is protected by a password. Hardware identified data will be stored in a locked cabinet. Both type of data can only be reached by the investigator.

The monitor(s), the auditor(s), the Human Research Ethics Committee, and the regulatory authority(ies) will be granted access to your original medical records. They will verify the clinical trial procedures and/or data. They will not violate the confidentiality of the participants, to the extent permitted by the applicable law and regulations. By signing this form, you authorise such access.

The raw data collected from the actigraph will be stored and managed in Amazon servers. They are in the USA. This data cannot reveal your identity.

Will the data and information that I have provided be disposed of?

No. Your data will be used as per Western Sydney University's Open Access Policy. The non-identified data from this study can be made available online and worldwide. Identified data will be kept for 15 years in a shared drive with restricted access.

Can I withdraw from the study?

Participation in the research is voluntary. You are not obliged to be involved. If you do participate you can withdraw at any time. You will be asked to come to the visit site to return all equipment. You will be asked to detail the reasons for wishing to withdraw. If provided, these will be recorded. If willing, you will complete the questionnaires of the study. If willing, you may be contacted to provide the information of the other assessments as well. If you do choose to withdraw and specify, any information that you have supplied can be destroyed and not included in the analysis.

Whatever your decision, it will not affect your future care or your relationship with the research staff.

Under the following circumstances, you may be withdrawn from the study:

- If you start a new treatment for insomnia;
- If your insomnia condition gets worse and additional treatment is required;
- If a serious medical condition occurs,
- If you get pregnant.

Can I tell other people about the study?

Yes, you can tell other people about the study. You can provide them with the investigator's contact details. They can contact the investigator to discuss their participation in the research project and obtain a copy of the information sheet.

What if I require further information?

If you wish to discuss the research further before deciding whether or not to take part in, please contact the investigator.

If there is any information relevant to your willingness to continue the study, you will be informed in time.

Chief investigator: Yoann Birling, PhD candidate
Tel: (02) 9685 4752

What if I have a complaint?

If you have any complaints or reservations about the ethical conduct of this research, you may contact the Ethics Committee through Research Engagement, Development and Innovation (REDI) on Tel +61 2 4736 0229 or email humanethics@westernsydney.edu.au.

Any issues you raise will be treated in confidence and investigated fully. You will be informed of the outcome.

This study has been approved by the Western Sydney University Human Research Ethics Committee. The Approval number is H12990

Consent Form

Project Title: *Investigation on the Safety and Effectiveness of Chinese Herbal Medicine for the Treatment of Insomnia*

I hereby consent to participate in the above named research project.

I acknowledge that:

- I have read the participant information sheet (or where appropriate, have had it read to me) and have been given the opportunity to discuss the information and my involvement in the project with the researcher/s
- The procedures required for the project and the time involved have been explained to me, and any questions I have about the project have been answered to my satisfaction.

I consent to:

☐ *My blood being tested*

☐ *My activity levels being measured*

☐ *My blood pressure being measured*

☐ *My oxygen saturation being monitored*

☐ *Provide information on my sleep and my health*

I consent for my data and information provided to be used for this project.

I understand that my involvement is confidential and that the information gained during the study may be published but no information about me will be used in any way that reveals my identity.

I understand that I can withdraw from the study at any time without affecting my relationship with the researcher/s, and any organisations involved, now or in the future.

Signed:

Name:

Date:

This study has been approved by the Human Research Ethics Committee at Western Sydney University. The ethics reference number is: H12990

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Annexe 3. Search terms for the CES

Search terms in English

Search terms for EMBASE

#1 insomnia

#2 experience

#3 #1 AND #2

Search terms for PubMed

Insomnia (title/abstract) AND experience (title/abstract)

Search the Cochrane Library

Insomnia (title/abstract/keywords)

AND experience (title/abstract/keywords)

Search terms for CINAHL

(insomnia [title] OR insomnia [abstract]) AND (experience [title] OR insomnia [abstract])

Search terms for PsychINFO

S1 TI insomnia OR AB insomnia

S2 T1 experience or AB experience

S3 S1 AND S2

Search terms for CNKI

SU = insomnia and SU = experience

Search terms for Wanfang

(题名:"insomnia" and 题名:"experience")*Date:-2019

Search terms for CQVIP

M=insomnia AND M=experience

Search terms for China Biomedical Literature

"insomnia"[标题] AND "experience"[标题]

Search terms in Chinese

Search terms for CNKI

(TI=失眠 or TI=不寐 or TI=睡眠障碍)and(TI=教授 or TI=大师 or TI=主任 or TI=老师 or TI=导师 or TI=经验 or TI=体会 or TI=心得 or TI=学术思想 or TI=学术观点 or TI=思路 or TI=思考 or TI=证治规律 or TI=用药规律 or TI=论治 or TI=探讨 or TI=探析 or TI=浅谈)

Search terms for Wanfang

(题名:("失眠" or "不寐" or "睡眠障碍") and 题名:("教授" or "大师" or "主任" or "老师" or "导师" or "经验" or "体会" or "心得" or "学术思想" or "学术观点" or "思路" or "思考" or "证治规律" or "用药规律" or "论治" or "探讨" or "探析" or "浅谈"))*Date:-2019

Search terms for CQVIP

M=(失眠 OR 不寐 OR 睡眠障碍) AND M=(教授 OR 大师 OR 主任 OR 老师 OR 导师 OR 经验 OR 体会 OR 心得 OR 学术思想 OR 学术观点 OR 思路 OR 思考 OR 证治规律 OR 用药规律 OR 论治 OR 探讨 OR 探析 OR 浅谈)

Search terms for China Biomedical Literature

("失眠"[标题] OR "不寐"[标题] OR "睡眠障碍"[标题]) AND ("教授"[标题] OR "大师"[标题] OR "主任"[标题] OR "老师"[标题] OR "导师"[标题] OR "经验"[标题] OR "体会"[标题] OR "心得"[标题] OR "学术思想"[标题] OR "学术观点"[标题] OR "思路"[标题] OR "思考"[标题] OR "证治规律"[标题] OR "用药规律"[标题] OR "论治"[标题] OR

Annexe 4. Definition and identification of CER

A CER is an article describing the experience of a clinician. The article can include theoretical analysis and reviews of the literature if the main point of the article (as described in the title, abstract or introduction) is to describe clinical experience. It can also include clinical trial reports and case reports if used to illustrate a particular point of experience or if the experience was drawn from this clinical trial/case.

Example of articles that are NOT CERs:

Theoretical discussion: an article that describe a particular aspect of the disease (i.e., insomnia) aetiology, pathology, semiology, comorbidities or treatment. The content is not drawn from clinical observation but from the literature and/or reflection.

Ex: "从脾郁角度探析失眠从中焦论治", "基于八纲辨证和脏腑辨证探讨针刺从肝论治亚健康失眠", "从六经系统浅谈失眠的病机".

Difference between CER and theoretical discussion

CER	Theoretical discussion (including discussion on the treatment of insomnia NOT based on experience)
Reference to experience in the title or the introduction "Zhang XX treating insomnia from the perspective of the liver", "after 30 years of experience, prof Li found that …"	Reference to analysis or discussion in the title or the introduction
There is a specific point of experience (i.e., originality). E.g., using Gui Zhi Tang to treat insomnia.	The treatment is common, such as using Huang Lian E Jiao Tang for yin deficiency with fire, or Wen Dan Tang for phlegm-heat. Or the knowledge is vague and theoretical "treating from the perspective of the liver", "regulating the spleen and stomach" without further specific description.
Use of clinical vocabulary "in clinic, we observed that …", "the patient present often …"	Use of theoretical vocabulary such as "reasoning 思路", "discussion 探讨" or "analysis 分析". Or general statements such as "Chinese medicine considers …中医认为"
Clinical details are included: "this type of patient present headaches in the morning", "the reaction of the patient is …"	The description of clinical information is vague or has a very high level of similarity to textbooks/original text.
Use of a clinical case relevant to the point of experience	No clinical case or the clinical case is copied from another article/book.
Few references, references limited to the "aetiology and pathology" section or references coming from the same clinician	Frequent references to ancient and modern literature, especially in the treatment section.

Case report: in these articles, one or multiple cases are presented. In a case report, the main objective is to show how these particular patients were treated, not to draw general conclusions about the treatment of insomnia.

Ex: "陈建杰教授治疗慢性肝病的不寐验案 3 则", "刘爱东教授辨证论治不寐医案举隅"

The difference between CER and case report is that in a CER, a point of experience is proposed (e.g., different patterns with corresponding treatment, use of a specific herb, etc.) and ALL the cases are used to illustrate this point of experience. It can be one of the three situation (only one situation is required).

CER	Case report
A point of experience is proposed in the introduction or the conclusion.	There is no general point of experience, or not all the cases are linked to that point of experience.
Before the clinical case/clinical trial there is a description of the method/pattern/formula "Xiao Chai Hu Tang is used when the patient presents … "	Subheadings with methods/pattern/formula such as "clearing liver heat" but no further description
The analysis after all of the cases includes general statements that go beyond the range of the case.	The analysis is focused on the case(s).

Clinical trial: In clinical trials, the main objective is to prove that a treatment is effective, not to create global theories based on the observation of these cases.

Ex: "养心安神催眠导寐法——按摩: 附 30 例不寐病人按摩护理体会", "中药与针灸联合治疗失眠体会"

Difference between CER and clinical trial

CER	Clinical trial
There is a clear reference to clinical experience, especially in the title, abstract or introduction.	No clear reference to clinical experience.
There is a point of experience.	There is an hypothesis, but the hypothesis is not linked to the clinical experience of the clinician.
The clinical trial is mentioned in one paragraph of the CER, generally in the introduction or the discussion.	The whole article is structured around the clinical trial: objective, methods, results and discussion.
The patterns and corresponding treatment are described in details. The aetiology/pathology section and the treatment section form the main part of the article.	The treatment is described roughly in the "methods" section.

Literature review: the objective of a literature review is to combine and summarize the results of various studies or the opinions of different scholar about a particular topic.

Ex: "从肝论治失眠的文献研究", "针灸对失眠症治疗的研究探讨", "针灸治疗失眠症选穴思路".

Difference between CER and literature review

CER	Literature review
Reference to experience in the title or the introduction "Zhang San treating insomnia from the perspective of the liver", "after 30 years of experience, prof Li found that …"	Reference to the literature or review methodology in the title or the introduction "the recent articles about the treatment of insomnia with acupuncture have been reviewed".
Reference are limited to the aetiology/pathology of the disease. References are used to discuss the point of experience of the author "another scholar has also found out that …"	The main content of the article comes from references.
The main content of the articles comes from clinical observation.	Clinical experience is used to discuss a particular point of the review and does not concern the article as a whole.

Literature analysis: the author analyses a book, clinical cases or a CER produced by another scholar. There is no evidence that the author is a student/peer directly involved in the clinical observation process (i.e., following the clinician in clinic).

Ex: "施今墨论治失眠探析"

Guidelines: clinical guidelines showing the aetiology/pathology, diagnosis and treatment of a disease (i.e., insomnia). There is no clear reference to clinical experience.

Ex: "浅谈中医对不寐的认识", "中医对失眠的分型论治".

Consensus: a consensus about the treatment of the disease is developed through discussion between specialists. The raw experience of individual clinicians is not the main point of the article.

Educational material: a document, usually a power point, that is used for education purposes. The document can include the author's experience but the objective of the document is to teach general knowledge about a specific condition, not to describe the clinician's experience.

Annexe 5. Standardisation of signs and symptoms

Part 1. Symptoms/signs compounds

The following table show compounds of signs and symptoms and proposes an identification of individual signs/symptoms.

复合表现	分开后
大小便可	大便正常，小便正常
二便自利	小便清长，大便溏泻
小漫频数而清长	尿频，小便清长
小便短赤而痛；小便短赤疼痛	小便短赤，尿痛，尿血
小便灼热黄赤	尿热，小便短赤
小便频数或癃闭不通	尿频，小便不利
燥结大肠；大便燥结；大便干结；大便易干结	便秘、大便干
大便溏黏	大便溏泻，大便黏
大便秘或溏	便秘，大便溏泻
纳食及大便正常	纳可，大便正常
不欲饮食	纳呆，不渴
急倦	急躁，乏力
心中烦热；胸中烦热	心烦，心胸热
五心烦热	心烦，心胸热，手足心热
烦热	心烦，身热
易烦惊；烦惊	心烦、易惊
心胸烦闷； 烦闷	心烦，郁闷
手心热而汗出	手心热，手汗出
口干而苦；口干苦；口干且苦；口苦而干；口中干苦	口干，口苦
口苦而粘；口苦黏腻	口苦，口粘
口臭粘腻	口臭，口粘
口咽干	口干，咽干
口腻或干苦	口粘，口干，口苦
夜间口干多饮	夜间口干，夜间多饮
咽喉干痛	咽痛，咽干
目赤肿痛	目赤，目肿，目痛
目胀干涩	目胀；目干
喜热饮食	喜热饮，喜热食
头晕或痛	头晕，头痛

头昏胀痛	头昏、头胀、头痛
头昏重；头昏沉重；头目昏沉；头重昏蒙；头脑昏沉	头昏，头重
头晕且胀	头晕，头胀
头部胀痛；头胀而痛；头胀痛	头胀，头痛
头重昏眩	头重，头昏，眩晕
头晕胀痛	头晕，头胀，头痛
四肢酸乏	肢体酸楚，乏力
后背、前胸、腹部等闷痛、窜痛及刺痛	背胸腹闷痛、背胸腹窜痛、背胸腹刺痛
胸胁脘腹胀闷不适	胸闷，胁胀，胃胀，腹胀
胸胁或胃脘胀痛	胸痛，胁胀，胃胀，胁痛，胃痛
两胁及胃院胀痛	胁胀，胁痛，胃胀，胃痛
胸胁疼痛	胸痛，胁痛
胸胁胀痛	胸闷，胁胀，胸痛，胁痛
胸脘痞闷	胸闷；胃胀
胸脘胁痛	胸痛，胃痛，胁痛
胸肋满；胸胁痞闷不舒；胸次痞胀；胸胁不适；胸胁胀满；胸胁满闷；胸胁不舒；胸胁部胀满不适；胸胁苦满；胸肋胀满	胸闷，胁胀
胸闷隐痛	胸闷、胸痛
胸闷刺痛	胸闷，胸刺痛
两胁及胃脘胀痛	胁胀；胁痛；胃胀；胃痛
胸胁、少腹胀痛；胸胁少腹胀痛	胸痛，胁痛，少腹痛，胁胀，少腹胀
脘腹不适	胃不适，腹不适
脘腹胀满；脘腹痞满；脱腹胀闷不舒	胃胀，腹胀
脘腹胀痛	胃痛，腹痛；胃胀；腹胀
胁肋胀痛；两胁胀痛	胁痛，胁胀
腹胀或痛；腹中胀痛	腹胀，腹痛
胃脘胀满不舒	胃胀，胃不适
胃脘胀痛	胃胀，胃痛
心胸憋闷疼痛	胸闷，胸痛
腰膝酸痛	腰膝酸软、腰痛、膝痛

腰背部怕冷	腰冷，背冷
肢体酸痛	身痛，肌肉酸
月经量多、色淡	月经量多，月经色淡
月经量少色淡	月经量少，月经色淡
【月经不调，量少色黑】	月经不调，月经量少，月经色黑
月经量少、推迟	月经量少，月经推迟
唇甲色淡	口唇淡，指甲色淡
指甲枯白不润	指甲枯萎、指甲色淡

Part 2. Individual signs/symptoms

1. Sleep related symptoms

彻夜不寐	All-night insomnia	彻夜 XX；整夜 XX；通宵难寐；彻底
入睡困难	Difficulty falling asleep	不能人寐，迟寐；难以入睡；入睡困难；入睡难；入睡时间延长；难寐；不易入睡；难睡；难于人睡；不易入眠；入睡时间长；不易人睡；难以入眠；难眠；失眠以入睡困难为主；不能入睡；不能人眠；夜难入寐；入睡较难；难以入眠
中途醒	Frequent awakenings	醒后难以再睡；易寤；频寤；易醒；时睡时醒；时醒时寐；屡睡屡醒；寐而多醒；忽寐忽醒
惊醒	Nocturnal panic	惊醒；寐中惊悸；惊则醒；寐而易惊；易于惊醒；梦魇纷纭；梦魔；寐中惕惕然如惊；梦中易惊；寐而易惊；睡后易惊醒
早醒	Early-morning awakening	早醒；早寤
睡眠浅	Light sleep	睡眠浅；寐而不实，寐而不酣；眠浅（眠眠=>眠）；似睡非睡；睡眠轻浅；睡眠浮浅；寐浅；睡眠不实
1-3 点失眠	1-3 am insomnia	1-3 点失眠
梦多	Frequent dreams	梦多；多梦；乱梦纷云；乱梦纷纭；合目则梦；合目而梦；夜梦纷纭；梦境杂乱；梦多纷纭；寐中多梦；梦扰；入睡梦多；睡眠梦多
梦不多	No frequent dreams	梦不多

噩梦	Nightmares	多恶梦；恶梦纷纭；恶梦；梦多不祥；噩梦；寐中梦境惊险；噩梦惊扰
异梦	Abnormal dreams	异梦
梦游	Sleep walking	梦游
梦呓	Sleep talking	梦呓；呓语；梦艺；梦呓缠绵
打呼噜	Snoring	常打呼噜；鼾重
不得卧	Impossibility to lie	不得卧【因为身体不适】
眠中流涎	Drooling during sleep	夜间睡觉流涎
磨牙	Grinding teeth during sleep	磨牙

2. Somatic symptoms

2.1. Excrements

大便正常	Normal stools	大便正常；大正常
大便秘结	Constipation	大便秘结；便秘；便结；大便不通；数日一行；（大大=）大；结结=》结）
大便干	Dry stools	大便干；大便偏干；大便干燥；便燥
大便黏	Sticky stools	大便黏
排便不爽	Difficult defecation	大便不爽；排便不爽
大便馊臭	Stool with rancid smell	大便馊臭
大便溏泻	Diarrhoea	便溏（大大=>大；泻泻=）泻）；溏泄；大便偏稀；大便稀溏；便不成形；大便塘泄；便稀；便不成型；大便澹薄；腹泻；便塘；大便偏溏
痛泻	Painful diarrhoea	腹痛则泻，泻后痛减
大便不调	Irregular stools	大便不调；时干时稀；大便干稀不调；大便干稀不定；大便干湿不调；大便时硬时溏

小便正常	Normal urine	小便正常
小便清长	Light and abundant urine	尿清；尿多
小便短赤	Dark and scanty urine	小便短赤；小便黄赤；溲赤；溲黄；小便色黄；尿赤；小便红赤；小便黄；尿少；小便发黄或短赤
夜尿频	Frequent night urination	夜间小便次数多；夜尿频多；夜尿多
小便频数	Frequent urination	尿频；小便频数
遗尿	Enuresis	遗尿；遗尿失禁
尿后余沥不尽	Post micturition dribble	尿后余沥不尽
小便不利	Dysuria	小便不利；小便淋沥；溺不得出
尿热	Burning urination	尿热
尿痛	Painful urination	尿痛
尿血	Haematuria	尿血

2.2. Spleen and stomach

纳呆	Lack of appetite	【饮食无味，不欲食】；饮食呆少；饮食无味；纳差；少食；纳呆；不思饮食；食少；纳少；食欲不振；纳滞；饮食不佳；纳食无味；纳食差；食欲不佳；胃纳差；饮食量少；纳谷不香；胃纳不佳；纳谷不馨；食欲减退；食欲不香
纳可	Normal appetite	纳食可
厌食	Aversion to food	厌食；恶食
善饥	Increased appetite	善饥
胃胀	Stomach bloating	胃胀；脘痞；胃部饱胀；脘闷；胃脘胀满；胃脘痞满
胃不适	Stomach discomfort	胃不适；胃脘不适

胃痛	Stomach pain	胃痛；胃脘痛
食后胃胀	Stomach bloating after eating	食后胃脘痞胀；食后腹胀
腹部胀	Abdominal bloating	腹胀
腹痛	Abdominal pain	腹痛
腹不适	Abdominal discomfort	腹不适
腹部刺痛	Abdominal stabbing pain	腹刺痛
嘈杂	Upset stomach	嘈杂
呃逆	Hiccup	呃逆；呃气
嗳气	Belching	嗳气；打嗝；噫气；嗳气频频
嗳腐	Putrid belching	嗳腐
恶心呕吐	Nausea and vomiting	【恶心、欲呕】；恶（恶心呕吐心=>恶心呕吐）；欲呕；泛恶（泛恶=）恶心呕吐）；呕（恶心恶心呕吐吐=）恶心呕吐）；呕吐（恶心恶心呕吐=）恶心呕吐）
反胃	Stomach reversion	反胃
反酸烧心	Acid reflux and heartburn	吞酸；酸腐；烧心（反酸反酸=）反酸）
喜热食	Preference for warm food	喜热食
矢气恶臭	Smelly intestinal gas	矢气恶臭
消化不良	Indigestion	消化不良
肠鸣	Borborygmi	肠鸣

2.3. Orifices

耳鸣	Tinnitus	耳鸣；耳鸣；脑鸣；脑响
耳聋	Hearing loss	耳聋；重听失聪；失聪；

目干	Dry eyes	目涩；双目干涩；两目干涩；眼干涩；眼干
雀盲	Night vision loss	雀盲
目胀	Eye distension	目胀
目赤	Eye redness	目赤
目肿	Eye swelling	目肿
目痛	Eye pain	目痛
视物不清	Blurred vision	视物不清；视物模糊；瞻视昏吵
鼻干	Dry nose	鼻干
口中干	Dry mouth	口干少津；口干；口中燥；口燥；口干舌燥；口舌干燥；口中干少津
夜间口干	Dry mouth at night	夜间口干
口不苦	No bitter taste in mouth	口不苦
口苦	Bitter taste in mouth	口苦
口吐苦水	Vomiting bitter liquid	口吐苦水
口粘	Sticky sensation in mouth	口粘；口中黏腻
口淡	Bland taste in mouth	口淡
喜食辛辣	Preference for spicy food	喜食辛辣
喜食油腻	Preference for oily food	喜食油腻
口臭	Bad breath	口臭
口干不渴	Dry mouth without thirst	口干不渴；口干而不渴；口干不欲饮；口干不思水饮
口渴	Thirst	渴；欲饮；喜饮；引饮
口不渴	No thirst	口不渴

夜间多饮	Abundant water intake at night	夜间多饮
夜间口干	Dry mouth at night	夜间口干；夜间口中干
喜冷饮	Preference for cold drinks	喜冷饮;喜凉饮
喜热饮	Preference for hot drinks	喜热饮；喜温饮
口水多	Abundant saliva	满口津液
流口水	Drooling	口流涎沫；口吐清水
唇干	Dry lips	唇焦
口疮	Mouth ulcer	口舌生疮；口舌糜烂；口腔溃疡
舌疮	Tongue ulcer	舌面生疮
牙痛	Teeth pain	牙痛
牙齿松动	Loose teeth	齿浮；齿摇
咽喉不利	Discomfort in the throat	咽喉不利；咽喉不适；咽不利；喉痹
咽干	Dry throat	咽干；咽燥；咽干少津
咽中异物感	Foreign object sensation in the throat	异物感；咽中如有物梗塞；咽中自觉有异物所阻；咽中如有炙脔
咽痛	Throat pain	咽痛；咽喉痛；喉痛
咽苦	Bitter taste in the throat	咽苦
声音嘶哑	Hoarse voice	声音嘶哑；音哑
上火	Elevation of fire	升火

2.4. Gynaecology and andrology

不孕不育	Sterility	不孕；不育；生殖功能低下；精冷；精少
性欲减退	Loss of libido	性欲减退

乳房胀痛	Breast distension and pain	经前乳房胀痛；乳房胀痛
月经不调	Irregular menstruation	月经失调，月经不调；月经的紊乱；经不调（月月=>月）；妇女月经不调；女子月经不调
月经先期	Early menstruation	月经前期
月经推迟	Delayed menstruation	不能应时而至
闭经	Amenorrhea	经闭；闭经
崩漏	Uterine bleeding	崩漏
月经量多	Abundant menstruation	月经量多
月经量少	Scanty menstruation	月经量少；月经稀少
经量多少不定	Indefinite menstruation quantity	经量多少不定
月经色淡	Light-coloured menstruation	月经色淡
月经色红	Red menstruation	月经色红
月经色暗	Dark-coloured menstruation	月经色黑；月经色暗
月经有血块	Blood clots in menstruation	有血块
经行不畅	Menstruation with irregular flow	经行不畅
妇女少腹痛	Lower abdominal pain in women	妇女少腹疼痛
痛经	Dysmenorrhea	痛经
带下	Leucorrhoea	带下
阳痿	Impotence	阳痿；阳萎；性功能衰退
遗精	Emission	遗精，滑精；男子遗精；失精

梦遗	Nocturnal emission	梦遗；梦而遗
早泄	Premature ejaculation	早泄

2.5. Body symptoms

水肿	Oedema	身体浮肿
身痛	Generalised pain	身痛
身窜痛	Generalised running pain	身窜痛；周身窜痛；身痛无定处
关节酸痛	Joint pain	骨节酸痛
过电感	Electricity sensation	身体的过电感
身困重	Body heaviness	身困；肢体沉重；身重；一身困重
震颤	Tremor	震颤
背胸腹闷痛	Oppressive pain in the back, chest and abdomen	背胸腹闷痛
背胸腹窜痛	Running pain in the back, chest and abdomen	背胸腹窜痛
背胸腹刺痛	Stabbing pain in the back, chest and abdomen	背胸腹刺痛

2.6. Head

眩晕	Vertigo	头晕目眩；头目眩晕；眩晕；目眩；【头晕、目眩】；【头晕，目眩】；头晕眼花；眼花
头晕	Dizziness	头晕；
头痛	Headache	头痛
头欲裂	Head hurting as if it was about to crack	头痛欲裂
头昏	Head confusion	头昏
头胀	Head pressure	头胀；脑胀

头重	Head heaviness	头重
头刺痛	Stabbing pain in head	头刺痛；头部刺痛；【阵发性头痛，痛如针刺】；头痛如刺；针刺样头痛

2.7. Thorax/body side

胸痛	Chest pain	胸痛；胸中隐痛
胸闷	Oppression in the chest	胸部憋闷；胸闷；胸闷不舒；胸翁不舒；胸膈满闷；憋气；胸中窒闷；胸中隐隐不适；胸痞闷；胸部的束带感；胸闷痞满；胸满；胸闷胀满
心胸热	Sensation of heat in the heart and chest	胸热（心心=>心）；心胸热
胸刺痛	Stabbing pain in the chest	胸刺痛；胸中隐作刺痛
善太息	Frequent sighs	善太息；擅叹息；喜叹息；善叹息；喜太息；太息（善善=>善）；喜欢叹息
胁痛	Hypochondriac pain	胁痛；两胁作痛；两胁隐痛；两胁肋隐痛
胁刺痛	Hypochondriac stabbing pain	胁肋刺痛；两胁刺痛；胁肋部刺痛
胁灼痛	Hypochondriac stabbing pain	胁肋灼痛
胁窜通	Hypochondriac running pain	两胁隐痛走窜不舒
胁胀	Hypochondriac distension	胁胀；胁肋不舒；两胁胀闷不舒； 两肋时胀；两胁胀满

2.8. Back

背痛	Back pain	背痛
背刺痛	Back stabbing pain	背刺痛
腰膝酸软	Sore and weak lower back and knees	腰脊酸软无力；腰酸腿软；腰膝酸软；腰酸膝软；腰酸骨软；腰腿无力；腰酸；骨软

腰痛	Lumbago	腰痛；腰脊痛
膝痛	Knee pain	膝痛
足跟痛	Heel pain	足跟痛

2.9. Lower belly

少腹刺痛	Lower abdomen stabbing pain	少腹刺痛
少腹胀	Lower abdomen distension	少腹胀
少腹疼痛	Lower abdomen pain	少腹痛

2.10. Limbs

肌肉酸	Muscle soreness	肌肉酸；肢体酸楚
肢体不适	Discomfort in limbs	肢体不适
肢体麻木	Numbness in limbs	肢体麻木
抽搐	Convulsions	抽搐
手足舞蹈	Chorea	手足舞蹈
活动不灵	Lack of flexibility	活动不灵

2.11. Cardio-respiratory

心悸	Palpitations	心悸；怔忡；心慌；忡怔
气短	Shortness of breath	短气；气短；少气;息短
喘气	Dyspnoea	喘；
动辄气喘	Frequent dyspnoea	动辄气喘
呼吸不利	Inhibited breathing	呼吸不利
咳嗽	Cough	咳嗽；咳（嗽嗽=>嗽）；
咳引胸痛	Cough-induced chest pain	咳嗽而引激胸痛
呛咳	Choking	呛咳阵作；呛咳；呛咳嗽

痰鸣	Wheezing	痰鸣
少痰	Scant phlegm	少痰
有痰	Phlegm	吐痰；痰涎
多痰	Abundant phlegm	痰多；多痰；
无痰	Absence of phlegm	无痰
痰稠	Thick phlegm	痰稠
痰色黄	Yellow phlegm	痰色黄
痰中丝	Threads in phlegm	痰中丝

2.12. Heat, coldness and sweat

身热	Fever	身热；发热
畏热	Aversion to heat	恶热；喜冷
不欲覆被	Reluctance to be covered	不欲覆被
午后发热	Fever in the afternoon	午后发热
高热	High fever	高热
上半身热	Heat sensation in the upper body	上半身热；上半身很热
手足心热	Heat sensation in the palms and soles of feet	手心烦热；手心热；足心烦热；手足心热；手足心身热
潮热汗出	Hot flushes	潮热（汗出汗出=>汗出）；烘热汗出；烘热
骨蒸	Steaming bone	骨蒸
午后颧红	Red cheeks in the afternoon	午后颧红
畏寒	Aversion to coldness	畏寒；形寒；怕冷
背冷	Cold sensation in the back	背冷
胸背恶寒	Aversion to cold in the chest and back	胸背恶寒

腰腿寒冷	Cold sensation in the lower back and the legs	腰腿清冷畏寒；腰冷；膝盖是冷的
手足逆冷	Cold sensation in the hands and feet	足冷；肢冷；手足不温；四肢末端冷；四肢不温；肢体不温
时冷时热	Alternation of coldness and heat	寒热无常
恶风	Aversion to wind	怕风；畏风
自汗	Spontaneous sweating	汗多；自汗；动则汗出；易汗，时时汗出；自汗出
盗汗	Night sweating	盗汗；寐中盗汗；夜间盗汗；夜间汗出
出汗	Sweating	汗出（潮热出汗=>潮热汗出）
半身汗出	Half-body sweating	半身出汗
异常汗出	Abnormal sweating	异常出汗
时出冷汗	Frequent cold sweat	时出冷汗
手汗出	Sweating in hands	手汗出
易感冒	Susceptible to catching colds	易感冒

2.13. Fatigue

嗜睡	Somnolence	欲寐；昏昏欲睡；嗜睡；嗜卧；思睡
不困	Absence of sleepiness	数日毫无睡意
乏力	Fatigue	精神疲乏；乏力；体倦；神疲；倦怠；易疲乏；肢倦；精神不振；疲乏；肢困倦；神乏无力；四肢无力；困倦无力；身乏；不耐疲劳；易疲劳；疲劳感；四肢倦怠；疲惫；神困；神情疲惫；精神萎靡；神萎；神情乏力；身困重倦；无力；疲倦；神倦
不疲劳	No fatigue	不疲劳
晨起无力	Fatigue upon awakening	晨起乏力

懒言	Aversion to speak	懒言
少动	Lack of activity	少动；懒动
常哈欠	Frequent yawning	常哈欠

2.14. Skin

皮下紫癜	Purpura	皮下紫癜；紫斑
肤色黯淡	Dark pale skin	肤色黯淡
皮肤血缕	Visible capillaries	皮肤有血缕
皮肤甲错	Cracked skin	肌肤甲错；甲错；鳞屑；
皮肤干燥	Dry skin	皮肤干燥
面部油脂	Oily face	面部油脂

2.15. Miscellaneous symptoms

言謇语涩	Sluggish speech	言謇语涩
须发斑白	White hair	须发斑白；须发早白
脱发	Hair loss	脱发；发落

3. Psychological symptoms

3.1. Excitement

烦躁	Agitation	坐立不安；走坐不安；兴奋不已；心烦；虚烦；烦躁；噪扰；心中烦；懊恼；躁扰；燥扰；奔走不息；躁动；胸中懊；气躁；恶烦嚣而喜静；烦（躁躁）；心神烦躁；神情不宁；心神不安；神志不安；神魂不安
夜间烦	Agitation at night	夜间烦躁
入夜烦	Agitation at dawn	入夜烦躁
昼日烦	Agitation during the day	昼日烦躁
不烦	No agitation	不烦
急躁易怒	Stress and irritability	性情急躁；易躁，急躁（易怒易怒=>易怒）；脾气急；易急；急乱；性急；情绪易于激动；易怒（急躁

		急躁=>急躁）；易生气；容易发脾气；容易恼怒；暴躁；性格急躁易怒；心情急躁易怒；言语急躁；易激惹
狂躁	Mania	狂躁
焦虑	Anxiety	焦虑；忧思；紧张；惕惕然如惊；惕惕；神情紧张；忧虑
易惊	Frequent panic	胆怯；易惊；遇事善惊；善惊；惊悸；恐惧；惊惕；惊恐；心惊；胆小；易受惊吓
思虑过度	Overthinking	多虑；思虑多；思虑；多思善虑；多思
强迫思维	Obsessive thinking	强迫思维
强迫行为	Compulsive behaviour	强迫行为
敏感	Sensitivity	敏感；性情敏感
情绪不稳定	Emotional instability	情绪不稳定；哭笑无常；喜怒无常；喜怒易哭；情绪变化；情绪突然变化；情志波动
情志诱发症状	Emotion-induced symptoms	每于情绪不好时加重；每于情绪变化时症状加重
惊恐加重失眠	Insomnia aggravated by panic	受惊恐后加重

3.2. Inhibition

抑郁	Depression	情绪抑郁；情志不舒；郁郁；悲伤；喜哭；情绪低落；抑郁；忧郁；情绪低沉；伤心；悲忧善哭；心情压抑；沮丧；神情抑郁不乐；精神抑郁；抑郁欲哭；悲怆欲哭
郁闷	Vexation	郁闷；心情郁闷；情志不畅
痛苦	Suffering	痛苦不堪
兴趣减少	Lack of interest	缺乏兴趣；兴趣索然；兴趣下降
迟钝	Slowness	迟钝；思维迟钝；反应迟滞；反应迟钝
少言	Lack of speech	不爱讲话；少言；不思言语；默默；不喜多言
自杀倾向	Suicidal tendency	自杀倾向

3.3. Cognitive symptoms

恍惚	Confusion	恍惚；神乱；意乱；
健忘	Forgetfulness	健忘；记忆力下降；记忆力减退；记忆减退；记忆力差；善忘；失忆；记忆力明显下降

智能减退	Mental decline	痴呆；智能减退；学习能力下降；
工作能力减退	Diminished ability to work	工作能力减退
注意力不集中	Lack of attention	注意力不集中；注意力不能集中

3.4. Psychotic symptoms

发狂	Delirium	狂；神志狂乱
乱语	Delirious speech	乱语；谵语；狂言妄语
欲狂	Being on the edge of delirium	欲狂
多疑	Excessive suspicion	疑神疑鬼；多疑；疑惑；性格多疑
癫	Depressive psychosis	癫
情感淡漠	Apathy	情感淡漠
精神失常	Mental abnormality	精神失常
怪僻	Peculiarity	性情怪僻

4. Signs

4.1. Complexion

暗	Dark	暗；不华；少华；萎；晦；少泽
青	Bluish	青
赤	Red	赤；红；面色如醉
苍白	Pale	白；苍白；苍；淡
赤丝	Red capillaries on the face	红丝
黑	Black	黑
颧红	Red cheeks	颧红，面部潮红
褐斑	Chloasma	褐斑

4.2. Appearance

无神	Absence of spirit	无神
目瞑倦卧	In a foetal position with eyes closed	目瞑倦卧

4.3. Body

体胖	Obese body	形体偏胖；形体肥胖
消瘦	Thin body	肌肉削瘦；形体偏瘦;形瘦；消瘦；体型较瘦；形体消瘦

4.4. Eyes

黑眼圈	Dark circles under the eyes	两目黯黑；黑眼圈；眼睑乌黑；眼周发黑

巩膜小黑点	Small scleral black spots	巩膜上出现静脉末梢小黑点
眼睑色淡	Pale eyelids	眼睑色淡

4.5. Nails

指甲色淡	Light-coloured nails	爪甲色淡；指甲白
指甲色暗	Dark-coloured nails	爪甲无华;爪甲不荣
指甲色青	Bluish nails	爪甲隐隐泛青;
指甲枯萎	Withered nails	指甲枯萎
反甲	Spoon nails	反甲

4.6. Lips

口唇紫	Purple lips	口唇紫；唇黯
口唇淡	Light-coloured lips	口唇淡
口唇红	Red lips	口唇红

4.7 Voice

语音高尖	High-pitched voice	语音高尖
声低	Low voice	声低
声音洪亮	Loud voice	声音洪亮

4.8 Miscellaneous

血压过高	High blood pressure	血压过高
容易过敏	Susceptible to allergies	易过敏