Australian Journal of Herbal Medicine **2014** 26(3)

The efficacy and safety of herbal medicine for insomnia in adults: an overview of recent research

Megan Taslaman
Endeavour College of Natural Health
815 George St, Sydney NSW 2000
Email: megantaslaman@optusnet.com.au

Abstract

Introduction: Insomnia disorder is prevalent throughout societies and places an immense burden on the individual and the wider community. Currently the main conventional treatment is with hypnotic/sedative drugs that may cause undesirable side effects and rebound insomnia. Consequently herbal medicine has become a popular alternative with some patients.

Methods: The search strategy sought the terms "insomnia" and "herbal medicine" and "clinical trials" across multiple databases with additional hand searches conducted from reference lists. Double-blind randomised controlled trials (RCT) with a placebo group, conducted between January 2003 and May 2014, were included for review if the participants were diagnosed with either primary insomnia or transient insomnia and used ingested Western herbal medicine to treat their insomnia.

Results: Nine RCTs matched the inclusion criteria of which five examined *Valeriana officinalis* with inconclusive results warranting further research. Two trials examined *Valeriana officinalis* in combination with *Humulus lupulus*, one of which reached statistical significance in subjective sleep parameters. Two individual trials examined *Matricaria chamomilla* and *Passiflora incarnata* indicating some promise for efficacy and safety, thus warranting further research.

Conclusion: Due to the multi-factorial causes attributed to insomnia disorder, it may be difficult to find a single herb for this treating this complex condition. Current research has not incorporated a broad and 'holistic' approach for the treatment of insomnia. Future research that focuses on this area, including the evidence for herbal medicine and further exploring the 'synergy' of herbs used in combination, may be advantageous proving a safe and viable treatment option.

Key Words: Insomnia, herbal medicine, complementary medicine, randomised controlled trials, whole systems research

Introduction

Insomnia is estimated to affect about one-third of all adults of whom 6-10% meet the criteria for insomnia disorder.[1] Common features include: difficulty falling asleep causing reduced sleep latency time (LT); several awakenings during the night and/or early morning awakening; all resulting in non-restorative and poor sleep quality (SQ).[2] Insomnia disorder is defined by these key features occurring at least three nights a week over the course of one month and causing significant impairment to daytime functioning.[1]

Insomnia is a sleep disorder previously diagnosed as independent from 'secondary' influences that are attributed to psychological, physiological, or environmental factors.[2] Recently, the diagnostic criteria for insomnia disorder acknowledge co-morbid conditions and 'secondary' influences on disease progression[1] (See Table 2). Chronic insomnia is highly co-morbid with anxiety, depression and heart disease both as a precipitating factor and effect of the condition.[3] Conventional treatment includes sedative/ hypnotic drugs that cause drug tolerance, drug dependence, and adverse effects with prolonged use, and are hence often not preferred by patients.[4] Examples of pharmacological treatments include benzodiazepine and non-benzodiazepine agonists, anti-depressants and antihistamines.[5] Herbal medicine has become a popular alternative for the treatment of insomnia,[6] believed by many to be a safe and moderate approach to healing.[7]

Methodology

The search strategy sought terms "insomnia" and "herbal medicine" and "clinical trials" across the following databases: Pub med, Cochrane Collaboration, CINAHL, EBSCO, Medline, Science direct, Scopus and Google Scholar. Additionally, hand searches were conducted from reference lists. The inclusion criteria consists of: insomnia disorder or primary insomnia diagnosis; transient insomnia; ingested herbs; Western herbal medicine; double-blind randomised controlled trials with a placebo group (RCTs); date range from 2003 to May 2014; population group adults.

A meta-analysis by Fernandez-San-Martin et al (2010)[8] and a systematic review by Taibi et al (2007)[9] conducted on valerian for the treatment of insomnia disorder were located. However upon detailed analysis both contained trials with methodological flaws such as poor double-blinding procedures and inadequate randomisation. The trials since 2003 had better methodologies, particularly in these key areas. Furthermore, the majority of more recent trials ranked the highest score of 5 using the Jadad scale that ascertains bias and thus is a reflection of improved

methodological rigour.[8] As such it was proposed that setting a date from 2003 ensured a review of 'better quality' RCTs in order to gain a clearer perspective on the efficacy of valerian as a treatment option for insomnia.

Results

Nine research articles were identified that matched the inclusion criteria. Of these five investigated the efficacy of valerian for insomnia in adults; two investigated a combination of valerian and hops; and one each explored the usefulness of German chamomile and passionflower for this condition. The evidence for the efficacy and safety of each herb is detailed below.

Valerian *(Valeriana officinalis)*

Five RCTs conducted on *Valeriana officinalis* for the treatment of insomnia disorder in adults met the inclusion criteria (see Table 1) and, of these, no single trial reached statistical significant scoring for either subjective or objective primary outcome measures.[10,11,12,13,14] Improvements in the valerian group were noted in some trials with the majority of evidence remaining either inconclusive or unsupportive for the efficacy of valerian for sleep disorders.

The largest RCT investigating the efficacy of valerian for insomnia recruited 434 adults with primary insomnia disorder (> 5, PSQI diagnosis) that were randomised to receive either placebo or Valeriana Forte ® (Cederroth International AB). The extract corresponded to 1200 mg *V. officinalis* (dried root) per tablet and the participants took 3 tablets per day for 2 weeks.[11] Primary measures did not reach statistical significance, although modest improvements favouring the valerian group for number of night awakenings and sleep duration were observed. The global self-assessment question for perceived 'better sleep' (a secondary measure) reached statistical significance (p=0.04). This RCT was relatively well conducted and included a baseline; adequate blinding procedures that masked the aroma of valerian; stratified randomisation; and stringent exclusion criteria of co-morbidities and some lifestyle factors. The second largest RCT that investigated the efficacy of valerian for insomnia was conducted over 4 weeks and recruited 270 adults that were randomised into three groups: Valerian (6.4mg valerenic acid); Kava (300mg kavalactones) and Placebo.[12] Primary objectives were to assess the efficacy of valerian for insomnia and kava for anxiety. Patients included were diagnosed with anxiety (State-Trait Anxiety Inventory State) and insomnia (Insomnia Severity Index). Primary outcomes measuring changes from baseline compared with placebo showed no major differences between the groups. Three other small RCTs were found with sample sizes of between 16 and 21 participants.[10,13,14] No statistical differences between the treatment group and placebo were found.

The RCT by Taibi et al (2008)[10] examined elderly adults (n=16) diagnosed with insomnia disorder (Pittsburgh Sleep Quality Index (PSQI) who were randomised to receive either placebo or valerian (300mg/day Nature's Resource ® valerian root extract standardised to contain 0.8% valerenic acid per 100mg soft gel capsule) for two treatment phases consisting of sleep laboratory (one night) and home (two weeks) before washout and cross-over. The outcome measures included both objective and subjective sleep parameters for the sleep laboratory: Polysomnography (PSG), sleep questionnaire and home recordings (wrist autography and sleep diaries). There were no major differences between the groups, with a decrease in LT reported for both groups indicating a placebo effect.[10] Increased nocturnal wakefulness was noted in the valerian group compared to placebo, indicating a negative outcome.[10]

The small RCT by Diaper & Hindmarch (2004)[13] (n=16) examined two different doses of valerian (300mg or 600mg), from a patented extract Li 156 Sedonium ® (Lichtwer Pharma) against placebo in a three way cross-over trial for a treatment duration of one night between six-day washout periods. Objective measures included sleep cycles and psychometric function the following morning. No statistical significance was observed between dosages and placebo, although appreciably more 'drowsiness' occurred with the 600mg valerian dosage.

The small RCT by Coxeter et al (2003)[14] (n=21) conducted a series of single patient trials for adult patients diagnosed with chronic insomnia (GP diagnosis), randomised into three treatment pairs of placebo or valerian at a dosage of 2 tablets taken half an hour before bed. Each tablet contained 225mg *V. officinalis* root/rhizome extract equivalent to 1g of dried root/rhizome standardised to contain 2.94 mg valerenic acids, 0.46 mg valerenal and 1.23 mg valtrates and supplied by Mediherb ® (Warwick, Australia). The dosage was taken for one treatment week before cross-over, taking six weeks to complete. The results did not show appreciable or significant sleep parameter improvements for the patients as individuals or as a group.

Valerian has a statistically significant safety profile when comparing all groups within the trials to date. Oxman et al (2007)[11] found the difference in the proportion of participants experiencing side effects in both the run-in period and treatment period for both groups to be statistically significant suggesting these effects (reduced concentration, drowsiness, tiredness, headache, dizziness, irritability and trembling) were more likely to be symptomatic of insomnia. Taibi et al (2008)[10] did not find any differences in side effects listed between the groups. Coxeter et al (2003)[14] reported a number of predominantly mild side effects, some moderate and a few severe, experienced by both groups such as headache, nervousness, restlessness, and some gastro-intestinal (nausea, diarrhoea) complaints. The authors postulated that some of these effects may be caused by concomitants unable to be screened out in the inclusion process.[14]

Furthermore valerian does not cause dependence and does not have additive effects with alcohol.[15] This is an important factor particularly in light strong evidence associating excessive alcohol consumption with insomnia disorders.[16] According to Bos et al (2002)[17] valepotriates (a minor constituent in *Valeriana officinalis)* are cytotoxic, mutagenic and carcinogenic in-vitro but the relevance of this is questionable since this constituent decomposes before absorption in the human digestive tract.

Evidence of valerian-drug interactions is limited with in-vitro evidence suggesting mild to moderate inhibition of drug metabolizing enzymes, while one in-vivo study showed no significant effect on circulating levels of medications with one valerian preparation.[9] Pharmacodynamic valerian-drug interactions have proven to be beneficial in cases of benzodiazepine withdrawal, with valerian lessening the side effects of drug withdrawal.[18] This is probably due to their similar GABA-mimetic mechanisms of action.[8] Interactions with phenobarbitals, CNS depressants, sedative-hypnotics, anticonvulsants, pre-anaesthetics or adrenergic antagonists theoretically warrant caution due to the uncertainty of these interacting substances.[18] In-vivo studies have demonstrated the ability of valerian to potentiate the effects of barbiturates on sleep.[19]

Valerian – hops combination

Two clinical trials conducted on hops (*Humulus lupulus*) in combination with *V. officinalis* met the inclusion criteria for this review (see Table 1).[20,21] The largest RCT (n=184) compared three groups: valerian-hops (374mg/ 82mg dried extracts 5-8:1 and 7-10:1 respectively from 45% methanol solventextraction); Pharmaceutical sedative (diphenhydramine) 50mg; and Placebo. It showed marked improvements in the valerian-hops group in quality of life measures after 14 days of treatment and further improvement after the 28-day treatment duration time.[20] Subsequently a RCT with a four-week duration testing a valerian-hops combination (500mg dried valerian extract /120mg dried hops extract Ze91019) found it was significantly superior to valerian (500mg dried extract) and placebo for sleep latency (primary measure), slow-wave sleep cycles and global impression scores.[21] The valerian group failed to reach statistical significance compared to placebo, though it improved sleep latency times.[21]

Hops can be responsible for allergic skin reactions, bronchial irritations, dry cough and dyspnoea which have been observed in hops processing workers.[22] Furthermore, women processing hops experienced menstrual changes which lead to the discovery of phytoestrogens such as 8-prenylnaringenin (8-PN) and isoxanthohumol.[22] Isoxanthohumul is a pro-oestrogen since it is metabolised into 8-PN by the intestinal microflora.[23] It is difficult to measure the safety profile of hops as an ingested herb, since no RCTs have been conducted on hops singularly. A valerian-hops combination reported no serious adverse effects or cases of rebound insomnia.[20,21]

German chamomile (*Chamomilla recutita* syn., *Matricaria chamomilla, M. recutita*)

One recent RCT pilot study tested adult patients (n=34*)* diagnosed with chronic) primary insomnia (> 6 months - Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria), randomised to receive either placebo or German chamomile dried extract (540mg/day in a split dose of 2 x 3 tablets) for 28 days.[4] Each tablet contained 90mg of dried extract of flowering tops from solvent extraction (6:1) standardised to 2.5mg α-bisabolol and >/= 2.5mg apigenin supplied by Mediherb ®. The outcomes were measured using a combination of subjective sleep parameters. The differences between the groups were not statistically significant but generally favoured the German chamomile group.[4] Limitations to the study include the sample size, and patients on average experiencing milder insomnia compared to other drug studies.[4] Furthermore, no previous studies were available to compare the dosage and formulation, and outcomes were limited to subjective measures.[4]

German chamomile is part of the *Asteraceae* family which is commonly known to cause allergies in susceptible individuals.[24] Otherwise German chamomile has a good safety profile, with a long-standing history and is generally well tolerated amongst adults.[25] Mild and transient gastrointestinal complaints were experienced by both the active and placebo groups in the recent RCT by Zick et al (2011).[4]

Passiflora incarnata (passionflower)

One recent RCT tested healthy adults (n=41) with transient insomnia, randomised to receive either passionflower herbal tea bags (2g of dried *Passiflora incarnata* - leaves, stems, seeds and flowers) against a placebo parsley tea bag (2g of dried *Petroselinum crispum* – parsley) both manufactured by Hilde Hemmes' Herbal Supplies Pty Ltd, Australia.[26] Treatment was for one week separated by one week washout period before crossing over.[26] Six subjective outcomes were measured using a sleep diary; a Spielberger's state-trait anxiety inventory (completed day seven of treatment week); and an objective PSG measure for ten of the participants (one night only). The results were statistical significant ($p<0.01$) for SQ compared to placebo, suggesting a benefit for adults with mild sleep disorders. Double-blinding was confirmed with no statistical difference between the groups correctly identifying the passionflower tea. There were several limitations to the study that may decrease external validity such as: ill-defined sleep disorder inclusion criteria with participants noted to have only transient sleep problems; a strict exclusion criteria applied such as extreme sleep disorders (< 4 hours/night or > 10 hours/night); history/presence of sleep disorder; >/= three naps per week; and only ten participants were involved in the PSG objective measure thereby limiting statistical power. Overall, the results warrant

further research, particularly due to the external validity limitations although noting that *Passiflora incarnata* tea bags are an easy adjunct to a treatment plan tailored for mild sleep disorders.

Passionflower methanolic extract has a good safety profile classified by the US Food and Drug Administration as safe.[27] There have been few incidents of adverse reactions such as: a proposed 'additive' effect of *Passiflora incarnata* in combination with *Valeriana officinalis* interacting with the benzodiazepine drug (lorazepam) resulting in hand tremor, dizziness, throbbing and muscular fatigue.[27] Other idiosyncratic incidents have linked passionflower with cutaneous vasculitis and IgE-mediated asthma and rhinitis.[27] Passionflower contains cyanogenic constituents which thus do not rule out toxicity though humans are regarded as having the physiological functions to detoxify cyanide adequately.[28] Furthermore, an understanding of chemical constituent concentrations for passionflower and their exact mechanisms of action remains unclear, thus indicating the need for further research on safety as well as efficacy.[27]

Discussion

Overall the herbs included in this review were found to have a good safety profile but current research has failed to demonstrate the efficacy of these plants for the treatment of insomnia. Valerian is the most studied herb to date but discrepancies are apparent amongst the trials with highly variable research methodologies regarding dosage, sample size, treatment duration, preparation, and possible confounding factors due to various exclusion/inclusion criteria. As such, further research is warranted on valerian for the treatment of insomnia disorder.

Inadequate dosage may be one of the primary problems. According to Coxeter et al (2003)[14] the dosage intervention (450mg/day) was taken from the low end of the dosage scale used by clinically experienced Australian naturopathic practitioners, and as such may have hindered the results. Despite this finding a subsequent trial by Taibi et al (2008)[10] used an even lower dosage of 300mg/day. Oxman et al (2007)[11] used a higher dosage intervention of 600mg/day where results showed a promising trend toward benefiting sleep. This highlights the advantage and possible requirement of a higher dosage of valerian for effective treatment.

A major limitation to several trials was the small sample size (n<21) limiting the statistical power of results and thus impeding internal validity.[10,13,14] Furthermore, several trials had a sub-optimal treatment duration phase of two weeks or less. Various authors have suggested that valerian has an accumulative effect after two weeks of treatment.[14,29] Further research beyond this time frame is warranted to determine efficacy after a possible accumulative effect.

The inclusion and exclusion criteria amongst the trials ranged from moderate to stringent. Coxeter et al (2003)[14] noted that the GP diagnosis of insomnia disorder may have inadequately screened patients with various co-morbidities affecting sleep and as such may account as a confounding factor. Other confounders include stimulants taken throughout the day such as caffeine, sugar containing beverages or nicotine, all known to affect cortisol levels. Several trials failed to account for these stimulants.[11,13,14] Only one trial by Taibi et al (2008)[10] accounted for these effects, although the exclusion thresholds applied are arguably high such as >/= 3 alcoholic drinks per day; >/= 6 alcoholic drinks per week and >/= 3 caffeinated drinks per day. Caffeine is an adenosine antagonist which may contribute to nullifying the proposed mechanism of action of valerian.[30] The trial by Oxman et al (2007)[11] accounted only partially for stimulants such as excluding patients with a history of alcohol and drug abuse. Alcohol consumption is known to cause rebound wakening.[29] Furthermore, the RCTs by Oxman et al (2007)[11] and Coxeter et al (2003)[14] advised participants to avoid using other preparations for insomnia and to continue self-help strategies. This highlights the need for a RCT that accounts for all confounders evidenced to contribute to sleep benefit or deficit and by doing so create an even baseline for both groups.

Chemical constituents of valerian vary depending on growing conditions and variety and are very sensitive to manufacturing, processing and storage.[31] These variances may have implications for the bioequivalence of manufactured valerian preparations. Furthermore, liquid extracts of valerian to date have not been utilised in an RCT, possibly due to the obvious problem of blinding with its strong odour.[10] It would be interesting to elucidate whether a liquid extract preparation may prove more efficacious, particularly in light of the apparent instability of valerian during processing and manufacturing.[31]

Valerian has a long history of use and was described by Ellingwood (1919)[32] as a minor nerve sedative and by Felter & Lloyd (1898)[33] as a "cerebral stimulant" to relieve irritability, pain, and "wakefulness". Primary constituents of valerian include valerenic acid (and derivatives), valerenol and the valepotriates. Valerenic acid is exclusive to *Valeriana officinalis* whilst valepotriates are more dominant in other valerian species. The mechanism of action of valerian is thought be similar to the drug class benzodiazepines, where it interacts with the delta-amino butyric acid (GABA) neurons in the brain.[8] In-vitro evidence suggests valerenic acid targets $GABA_A$ neuron receptors, and via their stimulation chloride channels open for neural inhibition.[34] In-vivo studies on wild mice demonstrated anxiolytic activity of valerenic acid and valerenol on the subunit β3 receptor of $GABA_A$ neurons.[35,36] Recent research by Felgentreff et al (2012)[37] suggests that whilst valerenic acid may enhance GABA neuron activity, its derivative acetoxyvalerenic acid inhibits this action on the same binding site – hence causing an opposing response. This may be a plausible reason for the idiosyncratic

Table 1: Methodological features of trials that meet the inclusion criteria such as (date range from 2003; insomnia disorder; transient insomnia; Western herbal medicine; RCTs: adult population group).

Trial	Sample size (n)	Diagnostic	Duration	Dosage	Species	Outcome measures
Valerian RCTs						
Coxeter et al, 2003[14]	21	GP diagnosis for chronic insomnia	1 week treatment, 6 weeks total (3 treatment pairs of valerian/placebo cross- over)	a) dried extract 450mg/ day (each 225mg tablet standardized to 2.94mg valerenic acid, 0.46mg valerenal, 1.23mg valtrates and equiv. 1g of dried root/ rhizome). (Mediherb ®) b) placebo	*V. officinalis*	Subjective: * † ‡ § II ¶
Diaper & Hindmarch, 2004[13]	16	Mild sleep complaints diagnosed by sleep researcher	1 night, 6 days washout, cross-over	a) 300mg/day dried extractand b) 600mg/day dried extract c) placebo	*V. officinalis*	Objective (11pm–7am): ** Subjective: ††
Jacobs et al, 2005[12]	270	Insomnia Severity Index (ISI) - self reported sleep problems for 2 weeks – LT and sleep maintenance	28 days	a) 6.4mg valerenic acid/day b) placebo	Valerenic acid constituent from *V. officinalis*	Subjective: * † ‡‡
Oxman et al, 2007[11]	434	Pittsburgh sleep quality index (PSQI) score >5; insomnia > 1 month	14 days baseline and 14 days treatment, 28 days total	a) 600mg/day dried extract equivalent to 3.6g valerian b) placebo	*V. officinalis*	Subjective: † ‡‡
Taibi et al, 2008[10]	16	> 5 PSQI index	One night treatment (sleep laboratory) + 2 weeks (home), washout and cross-over, 44 days total	a) 300mg (100mg each soft gel tablet equiv. to 0.8% valerenic acid) b) placebo	*V. officinalis*	Objective: §§ Subjective: * † ‡ II II
Valerian-hops combination RCTs						
Morin et al, 2005[20]	184	Self-assessment occasional insomnia	28 days	a) valerian-hops 374mg/84mg dried methanolic extracts b) Diphenhydramine 50mg c) placebo	*V. officinalis* and *Humulus lupulus*	Subjective: * † ‡ Objective: §§ (three separate days)
Koetter et al, 2007[21]	30	Standard International criteria for non-organic sleep disorder	28 days	a) valerian 500mg/day dried methanolic extract (Ze 911) b) valerian-hops 500mg/120mg dried methanolic extract (Ze 91019) c) placebo	*V. officinalis* and *Humulus lupulus*	Subjective: * † § Objective: §§ ¶¶
German chamomile RCT						
Zick et al, 2011[4]	34	DSM-IV criteria	28 days	540mg/day split doses 2x 3 tablets of 90mg dried extract standardised 2.5mg -bisabolol and >/= 2.5mg apigenin (Mediherb ®)	*Matricaria chamomilla*	Subjective: * † ‡ § II II (diary)

Table 1: Methodological features of trials that meet the inclusion criteria such as (date range from 2003; insomnia disorder; transient insomnia; Western herbal medicine; RCTs: adult population group). ***(cont.)***

Trial	Sample size (n)	Diagnostic	Duration	Dosage	Species	Outcome measures
Passionflower RCT						
Ngan & Conduit, 2011[26]	41	Sleep assessment questionnaire	1 week treatment, washout, cross-over with placebo	a) teabags – 2g of dried passionflower aerial parts b) placebo teabags parsley	*Passiflora incarnata*	Subjective: * † ‡ § II II *** Objective: §§ (only 10 participants)

Sleep parameters:

* Latency time (LT)
** EEG
*** Fatigue to refreshed scale
† Sleep quality (SQ)
†† Psychometric tests next morning
‡ Sleep duration (SD)
‡‡ Sleep quality measured on a visual analogue scale (SQS)
§ Number of night awakenings (NNA)
§§ Polysomnography (PSG)
II Refreshed next day
II II Wake after sleep onset (WASO)
¶ Energy previous day
¶¶ Transporter home recorder system (QUISI)

stimulatory effects that some people experience when taking valerian. Other proposed mechanisms of action involve the serotonergic pathways, namely the 5-HT_{5a} receptor subtype implicated in the sleep-wake cycle.[15] In-vitro studies by Dietz et al (2005)[15] suggest valerenic acid is a partial agonist of the 5-HT_{5a} receptor. Additional mechanisms of action include the adenosine receptors, where earlier in-vitro research has shown valerenic acid to agonise adenosine receptors.[30] Adenosine receptors are involved in the inhibitory central nervous system (CNS) pathways, which are typically antagonised by known stimulants such as caffeine and theophylline.[30]

Further research on the efficacy of valerian is warranted utilising a large sample sizes, higher dosage, longer duration (> three weeks) and inclusion/exclusion criteria that eliminate confounding factors such as caffeine and alcohol consumption for all participants. Due to the variable influences of sleep deficit the treatment of insomnia disorder may require a multi-faceted treatment approach..[29] As such, a 'naturopathic' approach that considers diet and lifestyle habits and other factors that hinder sleep in conjunction with herbal medicine treatment may be advantageous.

Aqueous passionflower extraction (tea bags) improved SQ (p=0.01) compared to placebo for mild sleep disorders in adults despite several limitations to the trial, as investigated by Ngan & Conduit (2011).[26] This is early emerging evidence that may justify a larger well-designed trial that improves external validity by narrowing the exclusion criteria for insomnia disorders in adults. Furthermore, research that examines passionflower as a methanolic extract may prove it to be a viable treatment option. Traditionally, passionflower is described by Ellingwood (1919)[38] as useful for "wakefulness", and symptoms of anxiety such as "mental worry" and "disturbed sleep". Passionflower has a long history of use in European traditional medicine, being prescribed for various conditions including anxiety, nervousness, and insomnia.[27] The mechanism of action suggests involvement of the $GABA_A$ receptors with a proposed agonist effect by the major constituent flavonoids (hispidulin, apigenin, and quercetin) and possibly the GABA content.[27,39] In-vitro and in-vivo studies on mice confirmed anticonvulsant effects.[39]

German chamomile is a popular herb and although there is limited research investigating its efficacy, it has a 'household' reputation for enhancing sleep. Future research is warranted using a large sample size of adults diagnosed with insomnia disorder, examining efficacy with a higher dosage of German chamomile. It is an ancient medicinal herb with a long history of traditional use treating a variety of conditions including insomnia and was described by Felter (1922)[40] as a "nerve sedative". The active constituents are present in the dried flowers, and include: terpenoid volatile oils (α-bisabolol and chamazulene); phenolic flavonoid compounds (apigenin, apigenin-7-*O*-glycoside, luteolin, patuletin, and quercetin); mucilage; and coumarins.[41] The major constituent is the flavonoid called apigenin present both as a glycoside and as a free constituent.[41] The exact mechanism of action as a sedative is unknown, but is thought to involve the interaction of the flavonoid apigenin with GABA receptors in the brain, thereby facilitating the GABA-ergic inhibitory pathway.[41]

There is a trend throughout the research to study synergistic use of valerian with other herbs for insomnia disorder. However the majority of these older trials did not meet the inclusion criteria of this review and also had methodological flaws. As such, there is scope for future research in this area. The results from the fixed valerian-hops combination Ze91019, may be the result of a particular 'synergy' or via a more broad and unknown mechanism of action of hops.[22] Historically, hops is described as having a hypnotic action to produce sleep and remove "restlessness".[42] The primary constituents are the volatile oils (terpenes) and bitter acids shown in animal

Table 2: Examples of co-morbidities and/ or secondary influences for insomnia disorder

Influencing factors	Examples
Psychological	Major depressive disorder [1] Anxiety [1] Cognitive arousal [1]
Physiological	Pain [1] Breathing-related sleep disorder [1] Neurological or somatic diseases [2]
Environmental	Maladaptive sleep habits and conditioning associated with the 'sleep' environment [1] Noise, light, temperature [1]

studies to produce sedative effects via their involvement in GABA-ergic pathways and adenosine receptors.[22] Herbal medicine combinations may be more efficacious when combined with 'sleep hygiene' techniques and with consideration to all factors contributing to insomnia.

The aetiology and pathophysiology of insomnia disorder may differ from one individual to another due to multi-factorial causes such as genetic, environmental, behavioural and physiological factors.[43,44] As such, a 'holistic' approach that utilises herbal medicine whilst considering other contributing factors may be advantageous and more realistic in a naturopathic setting.[45]

Whole systems research (WSR) is a relatively new phenomenon, which may be a useful tool for researching the treatment of complex health conditions by a system of medicine such as naturopathy as opposed to a single agent. The current evidence in this field is limited although promising, particularly with disorders with multi-factorial causes.[45,46,47] The current typical 'gold standard' RCT that attempts to align all independent variables may realistically not be the best vehicle for such research and may limit internal and external validity.[47] A WSR approach or insomnia disorder that examines holistic treatment and outcomes includes herbal medicines f may be more relevant.[45,47]

An example of a modified WSR approach was conducted by Cooley et al (2009)[48] in a RCT that examined the efficacy of *Withania officinalis* for the treatment of anxiety by including a 'naturopathic' baseline for placebo and intervention groups. Clearly the benefits of this clinical trial methodology would extend to disorders with multifactorial causes such as insomnia.

Conclusion

Based on the evidence to date, *V. officinalis* is the most researched herb for the treatment of insomnia disorder in adults but the results do not support its use as a sole treatment. There may, however, be questions about the adequacy of the dosage and quality of valerian used in the trials reviewed. RCTs investigating the efficacy of a valerian-hops combination have shown improvement on subjective sleep measures with statistical significance proving efficacy for the fixed standardised extract Ze91019. Recent RCTs show promise for both German chamomile and passionflower in improving insomnia disorder in adults, although further research is warranted to elucidate the dosage for German chamomile, and to explore safety and efficacy of methanol extraction processes for passionflower.

Current evidence of clinical trials is lacking in the field of WSR that utilises herbal medicine in synergy with a 'naturopathic' treatment approach for insomnia disorder. Due to the myriad of factors that cause insomnia, future research in this area is necessary. A 'holistic' approach to treatment that considers a wide range of factors and advises on dietary, lifestyle, and stress management techniques as well as utilising herbal medicine may be more efficacious. Future research that addresses this gap by utilising WSR or a modified version that incorporates a standardised 'naturopathic' treatment group and placebo baseline would be advantageous. Furthermore, evidence has demonstrated the safety of valerian, hops, German chamomile and passionflower which is reassuring, particularly in light of high utilisation.

References

1. American psychiatric Association 2013, Diagnostic and Statistical Manual of Mental Disorders, 5th edn, American Psychiatric Association, Arlington, VA.
2. Unbehaun T, Spiegelhalder K, Hirscher V, Riemann D. 2010. Management of insomnia: update and new approaches. *Nature and Science of Sleep* 2:127-138.
3. Pearson N, Johnson L, Nahin R. 2006. Insomnia, trouble sleeping, and complementary and alternative medicine: analysis of the 2002 national health interview survey data. *Arch Intern Med* 166(16):1775-1782.
4. Zick S, Wright B, Sen A, Arnedt T. 2011. Preliminary examination of the efficacy and safety of a standardized chamomile extract for chronic primary insomnia: A randomized placebo-controlled pilot study. *BMC Complementary and Alternative Medicine* 11(78):1-8.
5. Cho S, Shimizu M, Lee C, Han D, Jung C, Jo J, Kim Y. 2010. Hypnotic effects and binding studies for $GABA_A$ and $5\text{-}HT_{2C}$ receptors of traditional medicinal plants used in Asia for insomnia. *Journal of Ethnopharmacology* 132:225-232.
6. Antoniades J, Jones K, Hassed C, Piterman L. 2012. Sleep naturally: a review of the efficacy of herbal remedies for managing insomnia. *Alternative and complementary therapies* 18(3):136-140.
7. Ekor M. 2014. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in pharmacology* 4(177):1-10.
8. Fernandez-San-Martin M, Masa-Font R, Palacios-Soler L, Sancho-Gomez P, Calbo-Caldentey C, Flores-Mateo G. 2010. Effectiveness of Valerian on insomnia: A meta-analysis of randomized placebo-controlled trials. *Sleep Medicine*11:505-511.
9. Taibi D, Landis C, Petry H, Vitiello M. 2007. A systematic review of valerian as a sleep aid: Safe but not effective. *Sleep Medicine Reviews* 11(3):209-230.
10. Taibi D, Vitiello M, Barness S, Elmer G, Anderson G, Landis C. 2008. *Sleep Medicine* 10(3):319-328.
11. Oxman A, Flottorp S, Havelsrud K, Fretheim A, Odgaard-Jensen J, Austvoll-Dahlgren A, Carling C, Pallesen S, Bjorvatn B. 2007. A televised, web-based randomised trial of an herbal remedy (valerian) for insomnia. *PloS ONE* 2(10):1-10.
12. Jacobs B, Bent S, Tice J, Blackwell T, Cummings S. 2005. An internet-based randomized, placebo-controlled trial of kava and valerian for anxiety and insomnia. *Insomnia* 84(4):197-207.

13. Diaper A & Hindmarch I. 2004. A double-blind, placebo-controlled investigation of the effects of two doses of a valerian preparation on the sleep, cognitive and psychomotor function of sleep-disturbed older adults *Phytother. Res*.18(10):831-836.
14. Coxeter P, Schluter P, Eastwood H, Kikles C, Glasziou P. 2003. Valerian does not appear to reduce symptoms for patients with chronic insomnia in general practice using a series of randomised *n*-of-1 trials. *Complementary Therapies in Medicine* 11(4):215-222.
15. Dietz B, Mahady G, Pauli G, Farnworth N 2005. Valerian extract and valerenic acid are partial agonists of the 5-HT_{5a} receptor in vitro. *Molecular Brain Research* 138:191-197.
16. Vinson D, Manning B, Galliber J, Dickinson M, Pace W, Turner B. 2010. Alcohol and sleep problems in primary care patients: a report from the AAFP national research network. *Annals of Family Medicine* 8:484-492.
17. Bos R, Woerdenbag H, Pras N. 2002. Determination of valepotriates. *Journal of chromatography A* 967:131-146.
18. Stargrove M, Treasure J, McKee D. 2008. Herb, Nutrient, and Drug Interactions. St. Louis, Missouri: Mosby Elsevier.
19. Gutierrez S, Ang-Lee M, Walker D, Zacny J. 2004. Assessing subjective and psychomotor effects of the herbal medication valerian in healthy volunteers. *Pharmacology, Biochemistry and Behaviour* 78:57-64.
20. Morin C, Koetter U, Bastien C, Ware J, Wooten V. 2005. Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. *Sleep* 28(11):1465-1471.
21. Koetter U, Schrader E, Kaufeler R, Brattstrom A. 2007. A randomized, double blind, placebo-controlled, prospective clinical study to demonstrate clinical efficacy of a fixed valerian hops extract combination (Ze 91019) in patients suffering from non-organic sleep disorder. *Phytotherapy research* 21:847-851.
22. Zanoli P, Zavatti M. 2008. Pharmacognostic and pharmacological profile of *humulus lupulus L. Journal of Ethnopharmacology* 116:383-396.
23. Erkkola R, Vervarcke S, Vansteelandt S, Rompotti P, Keukeleire D, Heyerick A. 2010. A randomized, double-blind, placebo-controlled, cross-over pilot study on the use of a standardized hop extract to alleviate menopausal discomforts. *Phytomedicine* 17:389-396.
24. Lundh K, Hindsen M, Gruvberger B, Moller H, Svensson A, Bruze. 2006. Contact allergy to herbal teas derived from Asteraceae plants. *Contact Dermatitis* 54:196-201.
25. Dohil M. 2012. Natural ingredients in atopic dermatitis and other inflammatory skin diseases. *Journal of drugs in dermatology* 11(9):7-10.
26. Ngan A, Conduit R. 2011. A double-blind, placebo-controlled investigation of the effects of *Passiflora incarnata* (Passionflower) herbal tea on subjective sleep quality. *Phytother. Res*. 25:1153-1159.
27. Miroddi M, Calapai G, Navarra M, Minciullo P, Gangemi S. 2013. *Passiflora incarnata* L.: Ethnopharmacology, clinical application, safety and evaluation of clinical trials. *Journal of Ethnopharmacology* 150:791-804.
28. Dhawan K, Dhawan S, Sharma A. 2004. *Passiflora*: a review update. *Journal of Ethno-pharmacology* 94:1-23.
29. Wheatley D. 2005. Medicinal plants for insomnia: a review of their pharmacology, efficacy and tolerability. *Journal of Psychopharmacology* 19(4):414-421.
30. Muller C, Schumacher B, Brattstrom A, Abourashed E, Koetter U. 2002. Interactions of valerian extracts and a fixed valerian-hop extract combination with adenosine receptors. *Life Sciences* 71:1939-1949.
31. Wills R, Shohet D. 2009. Changes in valerenic acids content of valerian root (*Valeriana officinalis* L. *s.l.*) during long-term storage. *Food Chemistry* 115:250-253.
32. Ellingwood F. 1919. American Materia Medica. *Valeriana officinalis*. Therapeutics and Pharmacognosy. Portland: Eclectic Medical Publications.
33. Felter H, Lloyd J. 1898. King's American Dispensatory. *Valeriana officinalis*. Cincinnatti: Ohio Valley Co.
34. Khom S, Baburin I, Timin E, Hohaus A, Trauner G, Kopp B, Hering S. 2007. Valerenic acid potentiates and inhibits $GABA_A$ receptors: Molecular mechanism and subunit specificity. *Neuropharmacology* 53:178-187.
35. Benke D, Barberis A, Kopp S, Altmann K, Schubiger M, Vogt K, Rudolph U, Mohler H. 2009. $GABA_A$ receptors as *in vivo* substrate for the anxiolytic action of valerenic acid, a major constituent of valerian root extracts. *Neuropharmacology* 56:174-181.
36. Murphy K, Kubin Z, Shepherd J, Ettinger R. 2010. *Valeriana officinalis* root extracts have potent anxiolytic effects in laboratory rats 17:674-678.
37. Felgentreff F, Becker A, Meier B, Brattstrom A. 2012. Valerian extract characterized by high valerenic acid and low acetoxy valerenic acid contents demonstrates anxiolytic activity', *Phytomedicine* 19:1216-1222.
38. Ellingwood F. 1919. American Materia Medica. *Passiflora incarnata,* Therapeutics and Pharmacognosy. Portland: Eclectic Medical Publications.
39. Elsas S, Rossi D, Raber J, White G, Seeley C, Gregory W, Mohr C, Pfankuch T, Soumyanath A. 2010. *Passiflora incarnata* L. (passionflower) extracts elicit GABA currents in hippocampal neurons in vitro, and show anxiogenic and anticonvulsant effects in vivo, varying with extraction method. *Phytomedicine* 17(12):940-949.
40. Felter H, Lloyd J. 1898. King's American Dispensatory. *Matricaria recutita*. Cincinnatti: Ohio Valley Co.
41. Srivastava J, Shankar E, Gupta S. 2010. Chamomile: A herbal medicine of the past with bright future. *Mol Med Report* 3(6):895-901.
42. Felter H, Lloyd J. 1898. King's American Dispensatory. *Humulus lupulus.* Cincinnatti: Ohio Valley Co.
43. Buysse D. 2013. Insomnia. *JAMA* 309(7):706-716.

continued on page 99

a possible source of lead antiviral drug against poliomyelitis since it can selectively inhibit the virus without having much toxic effect on the host cells.

References

1. Siddhuraju P, Becker K. 2003. Antioxidant properties of various solvent extracts of total phenolic constituents from three different agro-climatic origins of drumstick tree (*Moringa oleifera* Lam.). *J Agric. Food Chem*. 15:2144-2155
2. Anwar F, Latif S, Ashraf M, Gilani AH. 2007. Moringa oleifera: a food plant with multiple medicinal uses. *Phytother Res*. 21(1):17-25.
3. Duke JA .2001. Handbook of Nuts. USA: CRC Press. 214- 217.
4. Nandave M, Ojha SK, Joshi S, Kumari S, Arya DS. 2009. *Moringa oleifera* leaf extract prevents isoproterenol-induced myocardial damage in rats: evidence for an antioxidant, antiperoxidative, and cardioprotective intervention. *J. Med. Food* 12:47-55.
5. Parvathy MVS, Umamaheshwari A. 2007. Cytotoxic effect of *Moringa oleifera* leaf extracts on human multiple myeloma cell lines. *Trends Med Res*. 2:44-50.
6. Muangnoi C, Chingsuwanrote P, Praengamthanachoti P, Svasti S, Tuntipopipat S .2012. *Moringa oleifera* pod inhibits inflammatory mediator production by lipopolysaccharide-stimulated RAW 264.7 murine macrophage cell line. *Inflammation* 35(2):445-55.
7. Rujjanawate C, Kanjanapothi D, Amornlerdpison D. 2004. The anti-gastric ulcer effect of *Moringa oleifera* Makino. *Phytomed* 11: 431-435
8. Debnath S, Guha D .2007. Role of *Moringa oleifera* on enterochromaffin cell count and serotonin content of experimental ulcer model. *Ind. J. Exp. Biol*. 45:726 731.
9. Gilani AH, Aftab K, Suria A, Siddiqui A, Salem R, Siddiqui BS, Faizi S. 1994. Pharmacological studies on hypotensive and spasmolytic activities of pure compounds from *Moringa oleifera*. *Phytother. Res*. 8:87-91.
10. Morton JF .1991. The horseradish tree, *Moringa pterygosperma* (Moringaceae)- A boon to arid lands? *Econ Bot*. 45:318-333.
11. Ghasi S, Nwobodo E, Ofili JO . 2000. Hypocholesterolemic effects of crude extract of leaf of *Moringa oleifera* Lam in high-fat diet fed wistar rats. *J. Ethnopharmacol*. 69:21-25.
12. Singh BN, Singh BR, Singh RL, Prakash D, Dhakarey R, Upadhyay G, Singh HB.2009. Oxidative DNA damage protective activity, antioxidant, and anti-quorum sensing potentials of *Moringa oleifera*. *Food Chem. Toxicol*. 47:1109-1116.
13. Ndong M, Uehara M, Katsumata S, Suzuki K. 2007. Effects of oral administration of *Moringa oleifera* Lam on glucose tolerance in gotokakizaki and wistar rats. *J. Clin. Biochem. Nutr.* 40:229-233.
14. Pari L, Kumar NA. 2002. Hepatoprotective activity of *Moringa oleifera* on antitubercular drug- induced liver damage in rats. *J Med Food* 5:171-177.
15. Chuang PH, Lee CW, Chou CY, Murugan M, Shieh BJ, Chen HM. 2007. Anti-fungal activity of crude extracts and essential oil of *Moringa oleifera* Lam. Bioresour. Technol. 98:232-236.
16. Saadabi AM, Abu ZAI. 2011. An in vitro antimicrobial activity of *Moringa oleifera* L. seed extracts against different groups of microorganisms. *Asian J. Basic Appl. Sci*. 5:129-134.
17. Kew O, Sutter R, de Gourville E, Dowdle W and Pallansch M. 2005. Vaccine-derived polioviruses and the endgame strategy for global polio eradication. *Ann Rev Microbiol* 59: 587–635.
18. Harborne JB .1998. Phytochemical Method, A Guide to Modern Technique of Plant Analysis. 3rd Edition, New York, Chapman and Hall. 1- 302.
19. Kinchington D, Kangro H, Jeffries DJ. 1995. Design and testing of antiviral compounds, in: Medical Virology: A practical approach, Desselberger, U. (ed.) New York, Oxford University Press, 147-171.
20. *WHO (2007)*:"WHO: Vaccines for routine use". *International travel and health.12*. http://www.who.int/ith/vaccines/2007_routine_use/en/index11.html.
21. Bennett RN, Mellon FA, Foidl N, Pratt JH, Dupont MS, Perkins L, Kroon PA. 2003. Profiling glucosinolates and phenolics in vegetative and reproductive tissues of the multi-purpose trees *Moringa oleifera* L. (Horseradish tree) and *Moringa stenopetala* L. *J. Agric. Food Chem*. 51:3546-3553.
22. Sabale V., Patel V., Paranjape A., Arya C., Sakarkar, S.N. and Sabele P.M. 2008. *Moringa Oleifera* (Drumstick): An overview. *Pharmacog Rev Suppl. 2;* 7 – 13.
23. Anwar F. and Bhangar M.I. 2003. Analytical characterization of M*oringa oleifera* seed oil growth in temperate regions of Pakistan. *J Agric food chem* 22:6558-63.
24. Dhar B. and Gupta O.P. 1982. Nutritional value of Shigru (*Moringa oleifera* Lam) *B.M.E. B.R* 3 (2-4): 280 – 288.
25. Fahey JW, Zalcmann AT, Talalay P .2001. The chemical diversity and distribution of glucosinolates and isothiocyanates among plants. *Phytochem* 56:5-51.
26. Serafini M, Ghiselli A, Ferro-Luzz A .1994. Red wine, tea and anti-oxidants. *Lancet* 344:626.
27. Nonaka GI, Nishioka I, Nishizawa M, Yamagishi T, Kashiwada Y, Dutschman GE, Bodner AJ, Kilkuskie RE, Cheng YC, Lee KH.1990. Anti-AIDS Agents 2: Inhibitory effects of tannins on HIV Reverse transcriptase and HIV Replication in H9 lymphocyte cells. *J Nat Prod* 53:587-595.
28. Li BQ, Fu T, Dongyan Y, Mikovits JA, Ruscetti FW, Wang JM .2000. Flavonoid baicalin inhibits HIV - I Infection at the level of viral entry. *Biochem. Biophys. Res. Commun*. 276: 534-538.
29. Li SF, Di YT, Luo RH, Zheng YT, Wang YH, Fang X, Zhang Y, Li L, He HP, Li SL, Hao XJ. 2012. Cycloartane triterpenoids from Cassia occidentalis. Planta Med. 78(8):821-7.
30. Murakami A, Kitazono Y, Jiwajinda S, Koshimizu K, Ohigashi H .1998. Niaziminin, a thiocarbamate from the leaves of *Moringa oleifera,* holds a strict structural requirement for inhibition of tumor-promoter- induced EpsteinBarr virus activation. *Planta Med* 64 (4):319-323
31. Lipipun V, Kurokawa M, Suttisri R, Taweechotipatr P, Pramyothin P, Hattori M, Shiraki K. 2003. Efficacy of Thai medicinal plant extracts against herpes simplex virus type infection *in vitro* and *in vivo*. *Antiviral Res*. 60:175-180.
32. Waiyaput W, Payungporn S, Issara-Amphorn J, Panjaworayan NT. 2012. Inhibitory effects of crude extracts from some edible Thai plants against replication of hepatitis B virus and human liver cancer cells. *BMC Complement. Altern. Med*. 12:246.

The efficacy and safety of herbal medicine for insomnia in adults: an overview of recent research

continued from page 93

44. Roth T, Roehrs R, Pies R. 2007. Insomnia: Pathophysiology and implications for treatment. *Sleep medicine reviews* 11:71-79.
45. Sarris J. 2011. Whole system research of naturopathy and medical herbalism for improving mood and reducing anxiety. *AJHM* 23(3):116-145.
46. Boon H, MacPherson H, Fleishman S, Grimsgaard S, Koithan M, Norheim A, Walach H. 2006. Evaluating complex healthcare systems: a critique of four approaches. *Advance Access Publication* 4(3):279-285.
47. Verhoef M, Lewith G, Ritenbaugh C, Boon H, Fleishman S, Leis A. 2005. Complementary and alternative medicine whole systems research: beyond identification of inadequacies of the RCT. *Complementary Therapies in Medicine* 13:206-212.
48. Cooley K, Szczurko O, Perri D, Mills E, Bernhardt B, Zhou Q, Seely D. 2009. Naturopathic Care for Anxiety: A Randomized Controlled Trial ISRCTN78958974 *Plos One* 4(8):1-10.

