ISSN-e: 2529-850X
Volumen 5 Numero 12 pp 1538-1557
Diciembre 2020
DOI: 10.19230/jonnpr.3983

ORIGINAL

Community pharmacy-based interventions with *Valeriana officinalis* or *Passiflora incarnata* together with sleep hygiene education improve climacteric symptoms and sleep problems in menopause

Las intervenciones farmacéuticas con Valeriana officinalis o Passiflora incarnata junto con la educación en la higiene del sueño mejoran los síntomas climatéricos y los problemas del sueño en la menopausia

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Received 5 September 2020; acepted 12 September 2019.

How to cite this paper:
Marcos E, Iglesias I, Vazquez-Velasco M, Benedi J. Community pharmacy-based interventions with *Valeriana officinalis* or *Passiflora incarnata* together with sleep hygiene education improve climacteric symptoms and sleep problems in menopause. JONNPR. 2020;5(12):1538-57. DOI: 10.19230/jonnpr.3983
Cómo citar este artículo:
Marcos E, Iglesias I, Vazquez-Velasco M, Benedi J. Las intervenciones farmacéuticas con *Valeriana officinalis* o *Passiflora incarnata* junto con la educación en la higiene del sueño mejoran los síntomas climatéricos y los problemas del sueño en la menopausia. JONNPR. 2020;5(12):1538-57. DOI: 10.19230/jonnpr.3983

Abstract

Introduction. Physiological and endocrine changes occur during menopause that can negatively affect the sleep-wake cycle and contribute to objective and subjective sleep problems.

ISSN-e: 2529-850X
Volumen 5 Numero 12 pp 1538-1557
Diciembre 2020
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Objective. To assess the effectiveness of a pharmaceutic intervention with two different complementary treatments and sleep hygiene education on climacteric symptoms and sleep domains in menopausal women with sleep disturbance.

Material and methods. A sample of 109 women (45-64 years) participated in a 3-month randomized study, 35 received sleep hygiene instructions (SHI), 36 received capsules containing *Passiflora incarnata* 3 times a day plus SHI (PI), and 38 received capsules containing *Valerian officinalis* 3 times a day plus SHI (VO). Participants were evaluated by a) the Menopause Quality of Life (MENQOL) instrument, b) Pittsburgh Sleep Quality Index (PSQI), c) Insomnia Severity Index, d) Epworth Sleepiness Scale, and e) Mental component of SF-12 health survey.

Results. MENQOL scores were similar at baseline in the three groups but were reduced (improved vasomotor domain and physical subscale) at the end of the study in the VO group when compared with PI and SHI counterparts (both, $p<0.05$). The SF-12 mental function showed improvement in the VO group ($p<0.05$). Global PSQI score was significantly improved by PI and VO treatments at the end of treatment ($p=0.046$ and $p=0.034$, respectively). VO group was more effective than PI in alleviating mild insomnia. Change in vasomotor symptoms positively and significantly correlated with changes in all items of PSQI components, except for sleep duration and the association was strongest with sleep latency. Most participants evaluated the pharmaceutical and educational interventions provided as satisfactory.

Conclusions. The *Valerian officinalis* was the preferable treatment for the climateric symptoms and sleep difficulties associated with menopause. This study provided evidence that community pharmacists can play a crucial role in referring menopausal women with symptoms of insomnia to potential medicinal plants therapy and sleep hygiene instructions.

Keywords

Valerian officinalis; Passiflora incarnate; community pharmacy; climacteric symptoms; sleep disturbance; menopause

Resumen

Introducción. Durante la menopausia se producen cambios fisiológicos y endocrinos que pueden afectar negativamente al ciclo sueño-vigilia y contribuir a problemas objetivos y subjetivos del sueño.

Objetivos. Evaluar la efectividad de la intervención farmacéutica con dos tratamientos complementarios diferentes y educación en la higiene del sueño sobre los síntomas climatéricos y los dominios del sueño en mujeres menopáusicas con trastornos del sueño.

Métodos. Una muestra de 109 mujeres (45-64 años) participaron en un estudio aleatorizado de 3 meses, 35 recibieron instrucciones de higiene del sueño (SHI), 36 recibieron cápsulas que contenían *Passiflora incarnata* 3 veces al día más SHI (PI), y 38 recibieron cápsulas que contenían *Valerian officinalis* 3 veces al día más SHI (VO). Las participantes completaron los cuestionarios de a) calidad de vida especifica de la menopausia (MENQOL), b) índice de calidad del sueño de Pittsburgh (PSQI), c) índice de gravedad del

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insomnio, d) escala de somnolencia de Epworth y e) dimensión salud mental del cuestionario de salud SF-12.

Resultados. Las puntuaciones del cuestionario de calidad de vida específico de la menopausia fueron similares en todos los grupos al inicio del estudio y se redujeron (dominio vasomotor y subescala física) al final del estudio en el grupo VO en comparación con PI y SHI (ambos, p <0.05). La función mental SF-12 mostró una mejoría en las mujeres del grupo VO (p <0.05). La puntuación global de PSQI mejoró significativamente con PI y VO al final del tratamiento (p = 0.046 y p = 0.034, respectivamente). El grupo VO fue más efectivo que PI para aliviar el insomnio leve. El cambio en los síntomas vasomotores mostró correlaciones significativas positivas con todos los ítems en los componentes del PSQI, excepto en la duración del sueño. La asociación fue más mayor con la latencia del sueño. La mayoría de las participantes evaluaron las intervenciones farmacéuticas y educativas prestadas como satisfactorias.

Conclusiones. La *Valeriana officinalis* asociada a la higiene del sueño fue el tratamiento preferible para los síntomas climáticos y las dificultades de sueño en la menopausia. Este estudio proporcionó evidencia de que los farmacéuticos comunitarios pueden desempeñar un papel importante derivando a las mujeres menopáusicas con síntomas de insomnio a la terapia potencial de plantas medicinales e higiene del sueño.

Palabras clave

Valerian officinalis; Passiflora incarnate; farmacia comunitaria; síntomas climatéricos; alteraciones del sueño; menopausia

Introduction

The menopausal period is characterized by a number of physiological and endocrine changes that may adversely affect the sleep-wake cycle, and contribute to both objective and subjective problems in sleep[(1)]. Approximately 90% of women experience menopausal symptoms, including sleep disorders[(1)], which may be related to the vasomotor domain as suggested by Lampio *et al.*[(2)], but still there is no extended consensus supporting this view.

Polo-Kantola[(3)] reported that 25% of women aged 50 to 64 years have sleep problems, and 15% of them state that severe sleep disturbance has a substantial effect on their quality of life. Thus, the presence of menopausal symptoms increases health care utilization and costs, as well as sick leave days[(4)]. Clinical guidelines recommend to start treating these symptoms, with non-pharmacological therapy[(5)], including medicinal plants, which are considered safe and available for most consumers[(6)].

Different studies indicate that phytoestrogens are particularly effective on vasomotor and psychosomatic symptoms of menopause[(7)]. In addition, there have been reported

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improvements on sleep and memory symptoms in menopausal women using herbal medicines [8]. Among them, *Valerian officinalis* and *Passiflora incarnata* has been reported to improve vasomotor symptoms, insomnia, and depression[8-10]. Commission E monographs recommend valerian root as a safe and effective treatment for the vasomotor symptoms of menopause, although little evidence support the use of valerian in treatment of hot flashes[11,12]. On the other hand, *Passiflora incarnata* has been recommended as a therapy for insomnia[11-13], anxiety[10-13] and hot flashes but not for the vasomotor symptoms[11].

Community pharmacists are in a suitable position to provide ongoing follow-up related to a range of health problems[14]. Several pharmacy-based studies evaluating the control of insomnia have been performed[15,16], but to the best of our knowledge, no interventions have been carried out to provide women information about medicinal plants and complementary therapies for menopause and sleep problems, which allow them to make an informed choice about how to relieve their symptoms.

We hypothesize that medicinal plants combined with sleep hygiene instructions could have a synergic effect on climacteric symptoms, sleep problems and women' s health. Thus, the aim of this study was to assess in a cohort of menopausal women with sleep disturbance attending to the Community Pharmacy Services, the effectiveness of a pharmacist-led intervention with medicinal plants combined with sleep hygiene instructions on sleep quality and climateric symptoms outcomes compared with sleep hygiene instructions alone over a 3 month period.

Material and methods

This is a community-based intervention, prospective, quasi-experimental with pre-test and post-test groups. Seven community pharmacies in Spain (three in Madrid, two in Toledo and two in Guadalajara) were invited to participate and express interest to join the study. The study period was January 2017 to September 2018.

Previous studies, based on the experience and suggestion of pharmacists who have participated in community research work, establish between 10 and 20 the reasonable number of volunteers by each pharmacist[17]. A total of 132 perimenopause women between 45-65 years with sleep problems, who had not received prior hypnotic or alternative treatments and who voluntarily requested sleep aid, were recruited consecutively in the participating pharmacies. Inclusion criteria were as described in Table 1. All woman with a history of hormone replacement therapy for the management of menopausal symptoms, were suffering

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from any kind of heart disease, hypertension and/or diabetes, if they were currently undergoing chemotherapy or had received any previous treatment for insomnia, were excluded from analysis. Finally, 109 women completed the study.

Table 1. Inclusion criteria

a) Menopausal women, aged 45 to 64 years
b) Subjective complaint of difficulties initiating (sleep latency >30 min) and/or maintaining sleep (time awake after sleep onset >30 min) for a minimum of 2 nights and a maximum of 5 nights per week and for at least a 1-month duration
c) General good health without evidence of clinical disease.

Randomization was performed at the participating level in each pharmacy. All groups received sleep hygiene instructions (SHI) for improving insomnia (Table 2) based in studies on sleep disorders treatment in the elderly and non-pharmacological treatment of chronic insomnia [(18)]. The importance of the daily application of those instructions for three months was emphasized.

Table 2. Sleep hygiene instructions

Wake up at the same time and go to bed at the same time, every day.
Avoid naps, except for a brief 10- to 15-minute nap no later than 4 pm.
Take regular mild-to-moderate exercise terminating ≥4 hours before bedtime.
Do not smoke to get yourself back to sleep.
Limit caffeine use to ≤3 cups per day and not after 4 pm.
Limit alcohol consumption to light-to-moderate quantities.
Do not eat or drink heavily 3 hours before bedtime. A light bedtime snack may be helpful.
Use the bedroom only for sleep; do not work or do other activities that lead to prolonged arousal.
Do not stay in bed for more than 30 minutes without sleeping.
Get up and go to another room, try to engage in a relaxing activity (music, reading) and concentrate on pleasant feelings.
Use a bedtime ritual or read before lights out – this may be helpful if it is not work-related.

Adapted from Joshi[(18)]

The medicinal plant treatment groups received medicinal plant therapy: Group PI received capsules containing 300 mg of *Passiflora incarnata* 3 times a day for three months while group VO received capsules containing 350 mg of *Valerian officinalis* root 3 times a day for three months. Semi-structured face-to face interviews with participants and data collection were recorded by the researcher pharmacist in charge of the Pharmaceutical Care study, pre- and post-test, in order to guarantee rigor and homogeneity, for all participants.

Ethical principles were taken into consideration at all stages of the study. Ethical approval was obtained from the School of Pharmacy Ethics Committee, the Complutense

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University of Madrid (Reference number: PR016/05). Women were informed about the purpose and the course of the study and that they were free to withdraw at any stage. Women were assured about the confidentiality of the data and the absence of any constraints to participate.

Study Parameters

At baseline, the research obtained data pertaining to participants' socio-demographic and clinical characteristics. We evaluated menopausal-specific symptoms using the Menopause Quality of Life instrument (MENQOL), divided into four scales, assessing vasomotor (three items), psychosocial (seven items), physical (sixteen items) and sexual (three items) domains, with the score on each ranging from 1 (not experiencing a symptom) to 8 (extremely bothered). Thus, high scores in MENQOL subscales indicate low quality of life[19]. Different questionnaires were used for insomnia: a) The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire assessing sleep quality and disturbances over a 1-month time interval, with higher scores indicating worse sleep quality[20]; b) Insomnia Severity Index (ISI). The ISI is a brief, reliable, validated self-reporting instrument that yields a quantitative index of perceived insomnia severity, where higher scores reveal more severe insomnia (0–7, absence of insomnia; 8–14, mild insomnia; 15–21, moderate insomnia; 22–28, severe insomnia)[21]; c) Epworth Sleepiness Scale (ESS). The ESS was used to measure the severity of daytime sleepiness. Respondents rated eight items regarding the likelihood of dozing in sedentary situations on a scale from 0 (never) to 3 (high chance)[22]; d) The Mental Component Summary scale (MCS) from the 12-item short-form (SF-12) was used to assess the emotional role, vitality, social functioning, and mental health in menopausal women before and after treatment. Higher scores indicate a greater quality of life[23]. A satisfaction survey was performed based on the Treatment Satisfaction Questionnaire for Medication (TSQM version 1.4) to find out the participant´s acceptance grade of treatment[24]. Participants were instructed not to respond to the questions in the side effects dimension if they were not suffering from side effects. Pharmacists conducted follow-ups with included participants during the study period (start, one, three months) but only the first and latest was considered in this study to assess for resolution of symptoms, adherence to therapy and any adverse events.

Statistical analysis

The results were presented as mean and standard deviation (SD) for quantitative variables and percentages for categorical variables. Chi-square test and one way ANOVA followed by Tukey *post hoc* analysis were used to examine differences in the demographic

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variables among the three groups. Changes were evaluated as rate of change considering the following equation:

Rate of change (%) = 100* (Postintervention - Preintervention)/Preintervention

The rate of change in measured outcomes of climacteric symptoms and sleep problems were evaluated by univariate repeated measurement test considering the treatment groups (SHI, PI, and VO) followed by the GLM *post hoc* analysis and the significance of the intervention in each group evaluated. Spearman correlations were applied to assess the association between changes in menopausal symptom scores and mental component score (SF-12 MCS) with change in PSQI scores or other related parameters. A correlation coefficient ≥0.75 was considered good to excellent; 0.50–0.75, moderate to good; 0.25–0.50, fair; and 0.00–0.25, little to no relationship[25]. Satisfaction of the two treatment modalities and SHI group using TSQM scale were compared using the Wilcoxon test. The p-values were considered significant at $p < 0.05$.

Results

All analyses were limited to women who completed all assessments (n=109)[26]. The demographic characteristics of the study participants are shown in Table 3. Differences among the three groups were not significant.

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Table 3. Demographic and clinical characteristics of study participants

Variable	SHI (n=35)	PI (n=36)	VO (n=38)	Significance*
Age (years) Mean (SD)	59.6 (5.1)	58.2 (5.7)	59.1 (6.1)	0.75
Educational level (%)				0.96
Elementary (<10 years)	4.9	4.1	4.6	
High school (10-15 years)	43.8	42.1	44.7	
College graduate (>15 years)	51.3	50.2	52.5	
Marriage status (%)				0.26
Single	27.3	30.3	22.2	
Married	72.7	69.7	77.8	
Occupation status (%)				0.54
Employed	73.1	74.9	78.7	
Housewife	26.9	25.1	21.3	
BMI (kg/m^2) Mean (SD)	27.3 (2.8)	29.1 (4.5)	26.9 (3.1)	0.67
Smoking (%)				0.56
No	85.9	87.5	83.7	
Si	14.3	13.3	16.3	
Alcohol consumption (%)				0.33
No	89.1	87.8	90.7	
Yes (≥3 times/week)	10.9	12.1	9.3	
Caffeinated beverages (%)				0.41
None	76.3	73.9	73.2	
>3 serving per day	23.7	26.1	28.8	

BMI, body mass index; SHI, sleep hygiene instructions; PI, capsules containing 300 mg of *Passiflora incarnata*; VO, capsules containing 350 mg of *Valerian officinalis*; SD standard deviation; *Chi-square test or one-way ANOVA test were used to examine differences in percentage or absolute value, respectively, for demographic variables among groups.

Quality of life evaluation

Table 4 shows that the rate of changes of vasomotor and physical domains of MENQOL and SF-12 MCS score differ between groups according to GLM analysis ($p<0.05$). The study results revealed that vasomotor and physical subscale of the MENQOL score decreased (all $p<0.05$) follow after the intervention with VO over time. Following the VO ($p<0.01$) and PI ($p<0.05$) treatments, the SF-12 MCS score increases. The rate of changes of vasomotor and physical domains differed between the SHI and PI group versus VO group. The rate of changes of SF-12 MCS score differed between PI and VO group versus SHI group ($p<0.05$).

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Table 4. Effects of SHI, PI and VO therapy on the of MENQOL scores and mental health related quality of life (MCS SF-12) in menopausal women suffering from insomnia

		Groups			Rate of change (%)			
		SHI	**PI**	**VO**	**SHI**	**PI**	**VO**	**GML (p)**
MENQOL Score	Preintervention	11.9 (3.1)	11.3 (2.3)	11.4 (2.6)	-2.1 (-8.1, 4.9)	-1.1 (-4.6, 2.5)	-4.9 (-14.9, 5,2)	0.058
	Postintervention	11.6 (3.0)	11.1 (3.0)	10.6 (1.9)				
Vasomotor	Preintervention	3.0 (1.4)	2.9 (1.4)	2.9 (2.1)	1.8 (-5.7, 9.1)[a]	2.3 (-1.4, 5.8)[a]	-18.3 (-38.4, 0.6)[b]	0.009
	Postintervention	2.9 (2.2)	3.0 (1.2)	2.2 (1.1)*				
Psychosocial	Preintervention	2.8(1.3)	2.5 (1.3)	2.5 (1.9)	2.1 (-0.7, 4.9)	0.3 (-3.2, 3.7)	0.9 (-1.7, 3.4)	0.56
	Postintervention	2.9 (1.1)	2.5 (1.2)	2.5 (1.6)				
Physical	Preintervention	2.9 (1.6)	2.7(1.2)	2.9 (1.7)	-0.3 (-5.6, 6.2)[a]	2.6 (-1.9, 7.1)[a]	-18.6 (-28.1, -9.1)[b]	0.034
	Postintervention	2.8 (1.1)	2.8 (1.0)	2.4 (1.1)*				
Sexual	Preintervention	3.0 (1.1)	3.0 (1.3)	2.9 (1.3)	-2.1 (-5.2, 1.1)	-3,1 (-7.4, 1.3)	0.2 (-8.9, 9.4)	0.34
	Postintervention	2.9 (0.9)	2.8 (1.4)	2.9 (1.2)				
SF-12 MCS	Preintervention	49.6 (5.7)	49.8 (8.2)	49.9 (8.3)	2.1 (-5.4, 9.7)[a]	7.1 (-2.1, 16.2)[b]	24.2 (8.3, 40.2)[b]	0.017
	Postintervention	50.8 (7.6)	53.1 (7.7)*	61.0 (5.2)**				

Vales were mean (SD). SHI, sleep hygiene instructions group; PI, group with 300 mg of *Passiflora incarnate* capsules treatment together with SHI; VO, group with 350 mg of *Valerian officinalis* capsules treatment together with SHI. MENQOL, Menopause Quality of Life instrument; SF-12 MCS, SF-12 mental component score. Treatment effect was evaluated by Univariate repeated measurement followed by GLM test. *p<0.05, **p<0.01 with respect to its respective preintervention. Rate of change (%), 100 * (Postintervention - Preintervention)/Preintervention (CI 95%). Rate of change (%) values in same row bearing different letters were significantly different (a>b>c, at least p<0.05).

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Table 5. Effects of SHI, PI and VO therapy on general sleep measures in menopausal women suffering from insomnia.

		Groups			Rate of change (%)			
		SHI	**PI**	**VO**	**SHI**	**PI**	**VO**	**GLM (p)**
Poor sleepers (%) (PSQI > 5)	Preintervention Postintervention	57.4 49.8	59.4 26.1*	61.2 21.4**	-9.8 (-24.8, 5.3)[a]	-49.1 (-74.2,-24.1)[b]	-63.7 (-82.1, -45.2)[b]	<0.01‡
Global PSQI	Preintervention Postintervention	10.2 (3.1) 9.4 (2.7)	10.8 (2.6) 8.8 (2.5)*	10.4 (2.9) 8.8 (1.2)*	-4.5 (-9.3, 0.3)[a]	-16.8 (-35.1, 1.4)[b]	-20.1 (-31.1, -9.2)[b]	0.046
Subjective sleep quality	Preintervention Postintervention	2.1 (1.2) 2.0 (1.5)	2.1 (0.9) 1.2 (0.8)*	2.0 (1.1) 1.1 (0.6) *	-5.9 (-11.9, 0.05)[a]	-12.4 (-21.1, -3.6)[a]	-34.5 (-45.2, -23.8)[b]	0.032
Sleep latency	Preintervention Postintervention	2.7 (0.6) 2.3 (0.7) *	2.7 (0.8) 1.9 (0.6)**	2.5 (0.6) 1.4 (0.3)***	-10.5 (-21.4, 0.3)[a]	-27.4 (-42.1, -12.6)[b]	-48.1 (-62.4, -34.1)[c]	0.003
Duration of sleep	Preintervention Postintervention	1.7 (0.7) 1.7 (0.8)	1.9 (0.7) 2.0 (0.8)	2.0 (0.5) 2.9 (0.6)***	-0.1 (-4.5, 4.2) [a]	4.1 (-3.2, 11.2)[a]	42.8 (34.2, 51.6)[b]	0.016
Sleep disturbance	Preintervention Postintervention	2.0 (0.7) 1.9 (0.4)	2.0 (0.9) 1.9 (0.6)	1.9 (0.6) 1.8 (0.7)	-3.9 (-8.2, 0.3)	-3.4 (-9.3, 2.6)	-4.2 (-15.3, 6.9)	0.78
ESS score	Preintervention Postintervention	6.3 (1.9) 6.1 (1.8)	6.9 (2.1) 5.3 (1.5)*	6.5 (2.7) 4.8 (2.3)**	-3.6 (-11.5, 4.3) [a]	-18.7 (-38.3, 0.8)[b]	-29.1 (-67.5, 9,4)[b]	0.014
ISI score	Preintervention Postintervention	12.4 (3.7) 10.3 (2.9)	12.3 (2.5) 9.4 (3.1) *	13.7 (3.4) 7.0 (2.8)**	-15.4 (-27.1, -3.7)[a]	-22.8 (-41.3, -4.3)[a]	-46.3 (-69.1, -23.5)[b]	0.015

Values were mean (SD). SHI, sleep hygiene instructions group; PI, group with 300 mg of *Passiflora incarnate* capsules treatment together with SHI; VO, group with 350 mg of *Valerian officinalis* capsules treatment together with SHI. ESS, Epworth Sleepiness Scale; ISI, Insomnia Severity Index. Treatment effect was evaluated by Univariate repeated measurement followed by GLM test. *p<0.05, **p<0.01, *** p<0.001 with respect to its respective preintervention. Rate of change (%), 100 * (Postintervention - Preintervention)/Preintervention (CI 95%). Rate of change (%) values in same row bearing different letters were significantly different (a>b>c, at least p<0.05). ‡Chi-square test.

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Subjective Sleep Quality

Table 5 shows that the rate of changes of percentage of menopausal woman with poor sleep habit differ between groups according to Chi-square analysis ($p<0.01$). It is observed after intervention with PI ($p<0.05$) and VO ($p<0.01$) a significant reduction in the prevalence of women with sleep problems. The rate of changes of poor sleepers (%) differed ($p<0.05$) between the PI and VO treatments versus SHI group.

Table 5 also shows rates of change for global PSQI and PSQI subcomponents differ significantly among treatments in women according to GLM analysis (at least $p<0.05$). All variables but sleep disturbances were significantly affected. Both the PI and VO groups had significantly reduction in most of PSQI subscale scores at post-treatment. Global PSQI, sleep latency and subjective sleep quality decrease in VO and PI groups (at least $p<0.05$) while duration of sleep increase in VO group. The rate of changes of subjective sleep quality, sleep latency and duration of sleep differed ($p<0.05$) in the VO group versus PI and SHI groups.

The rates of change for ESS and ISI scores differ between treatments in women with sleep problems according to GLM analysis ($p<0.05$). A significant decrease in ESS and ISI scores was observed in the PI group ($p<0.05$) and VO group ($p<0.01$). At baseline menopausal women in all groups had a mean ISI total score of 13.5, which corresponds to “mild insomnia” but at the end of the study mean ISI score of the VO group changed from 13.7 (3.4) at baseline to 7.0 (2.8) and in the PI group, it altered from 14.3 (2.5) to 9.4 (3.1) after 3 months ($p<0.01$, $p<0.05$, respectively). The rate of changes of ISI score differed ($p<0.05$) between the VO group versus PI and SHI groups.

Figure 1 shows that after 3 months, the percentage of menopausal women who declare moderate insomnia reduction from baseline were larger in the VO group (25.4 vs 5.2%) than in the group that received PI (30.3 vs 17.5%). In addition, the VO treatment alleviated mild insomnia (70.vs 30.4%) more effectively than the PI counterpart (67.1 vs 49.8, respectively). Evaluation of the participants after the treatment showed that in the VO and PI groups 63.4 % and 31.4% respectively, of the menopausal women did not report any degree of insomnia whereas 18.1% in the SHI group (Figure 1).

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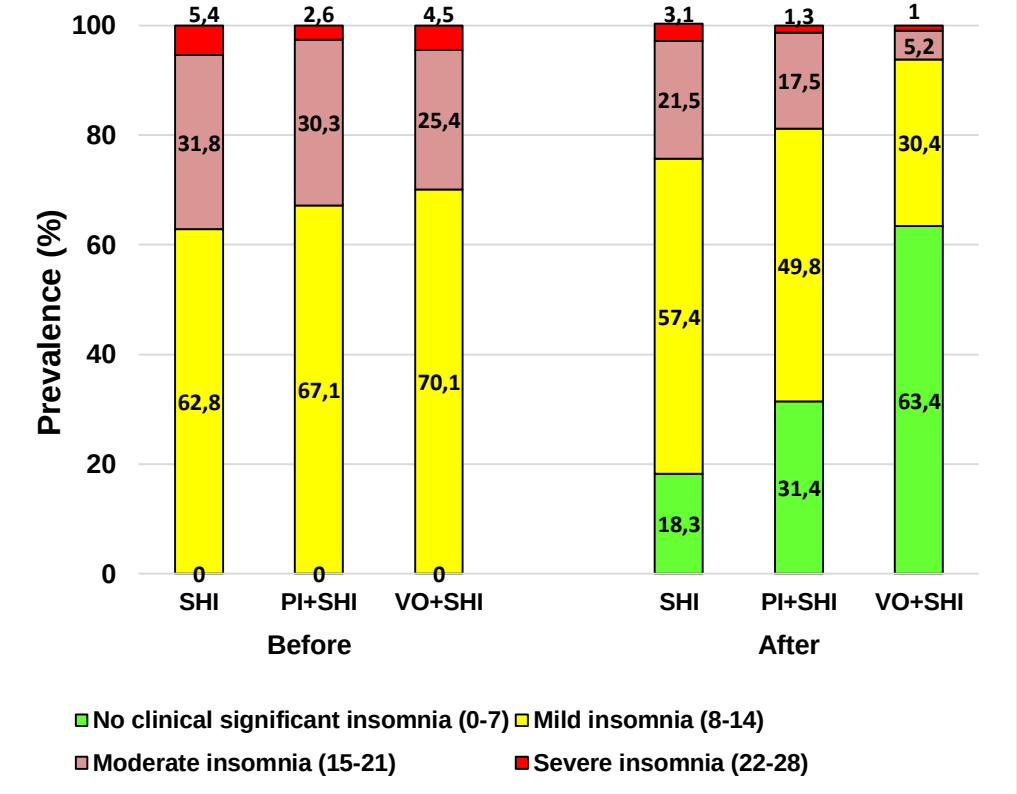

Figure 1. Percentage of menopausal women responders based on ISI scoring in control. PI (capsules containing 300 mg of *Passiflora incarnate*) and VO (capsules containing 350 mg of *Valerian officinalis*) groups, before and after treatment; SHI, sleep hygiene instructions.

The increase in "non-clinical significant insomnia" was mostly due to a reduction in the percentages of participants in the "severe insomnia" and "moderate insomnia" categories relative to baseline.

Table 6 shows the correlations of the average change in MENQOL (vasomotor and physical domains), MCS (SF-12) and PSQI scores with other parameter of sleep. Average change in vasomotor symptoms showed significant positive correlations with all items on the average changes the PSQI components except to duration of sleep, and the association was strongest with sleep latency (r=0.224; p=0.009). Also, there were significant and positive correlation between the average changes in the vasomotor symptoms, and the average changes in daytime sleepiness as assessed by the ESS (r=0.178; p=0.021). All average changes in PSQI items except the subjetive sleep quality were significantly associated with the

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average change in physical symptoms. Duration of sleep was significantly correlated with physical symptoms (r=0.127; p=0.024). The average changes insomnia severity as measured by ISI did not correlated with average changes in vasomotor and physical symptoms. Average change MCS (SF-12) was negatively and significantly correlated with average change in all PSQI scores (p<0.05) and average changes in ISI. ISI score was most highly correlated with mental SF-12 (r=-0.265; p<0.001).

Table 6. Spearman correlations between the average changes of vasomotor and physical symptoms and SF-12 (MCS) mental component score and the average changes of PSQI measures of Insomnia or related symptom severity

PSQI measure	**Vasomotor symptoms** r (p)	**Physical symptoms** r (p)	**SF-12 MCS** r (p)
Subjetive sleep quality	0.123 (0.003)	0.082 (0.245)	-0.171(0.041)
Sleep latency	0.224 (0.009)	0.075 (0.011)	-0.192 (<0.001)
Duration of sleep	0.087 (0.056)	0.127 (0.024)	-0.120 (0.024)
EES	0.178 (0.021)	0.109 (0.034)	-0.063 (0.63)
ISI	0.104 (0.89)	0.033 (0.44)	-0.265 (<0.001)

EES, Epworth Sleepiness Scale; ISI, Insomnia Severity Index; SF-12, 12-Item Short-Form Health Survey; MCS mean mental health related quality of life SF-12.

Global Satisfaction and tolerability

Treatments Users' satisfaction was calculated using the TSQM scoring algorithm. In the perception of efficacy, the average satisfaction of menopausal women was significantly higher with *Valerian officinalis* vs. with *Passiflora incarnate* (17.1/21 vs 14.7/21, respectively; p=0.03). In the second block of questions, 2 women described adverse effects (only with *Valerian officinalis*). These women detailed dyspepsia. Regarding to convenience, the assessment was 16.4/21 with *Valerian officinalis* vs. 16.1/21 with *Passiflora incarnata* (p=0.564). The global satisfaction level was 13.1/17 with *Valerian officinalis* and 12.8/17 with *Passiflora incarnata* (p=0.51). There were no statistically significant differences in the score obtained for these last two sections. Participants receiving SHI alone presented lower score values (effectiveness 10.1/21; global satisfaction 11.4/17) except in side-effects (not applicable) and convenience score (17.9/21).

Discussion

Present study evaluates the effectiveness of a community pharmacy medication support service for menopausal women with common insomnia. Although positive outcomes have been

ISSN-e: 2529-850X
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reported from clinical studies on herbal medicines, to the best of our knowledge this is the first report comparing capsules of *Passiflora incarnata* with capsules *Valerian officinalis* for relieving climateric symptoms in menopausal women with sleep problems in the frame of a community pharmacy intervention. In addition, the study demonstrates an improvement in the mental quality of life of menopausal women using the medicinal plants suggested with respect to the use of hygiene sleep techniques alone.

The results of our study showed that daily consumption of 350 mg of *Valerian officinalis* root 3 times a day for three months, in addition to SHI, significantly reduced the vasomotor and physical symptoms of menopausal women in comparison to only SHI. The reductions of climateric symptoms were modest, but similar in size to that found in other studies of phytoestrogen supplements[27, 28]. Mirabia and Mojab[29] suggest that the reduction in severity and frequency of hot flashes is merely due to the presence of phytoestrogens in valerian, which can be administered to women suffering from hot flashes in a simple and non-invasive manner. Furthermore, our study demonstrated the ability of *Valerian officinalis* supplement to also benefit physical symptoms. The changes in sleep quality correlated with changes in vasomotor and physical symptoms, in line with other studies[10]. In addition, a more positive change (greater improvement in mental health) was associated with lower somnolence values and greater subjective sleep quality. In particular, physical symptoms showed the strongest association with sleep quality. In comparison to *Passiflora incarnata*, we observed that *Valerian officinalis* produced a higher benefit on commonly coexisting climacteric symptoms for treatment of sleep disturbances. In contrast to our findings, *Passiflora incarnata* treatment has been associated with significant improvements in precocious menopause symptoms[10]. However, no clear consensus is able on bibliography[10,30]. The study criteria allowed us to select a population sample in which the onset of menopausal symptoms had preceded the development of insomnia, and no other reasons for the occurrence of co-morbid insomnia were detected. Treatment of insomnia with *Valerian officinalis* resulted in reduction of awakenings due to nocturnal hot flushes, with a positive impact on sleep quality and on the subsequent daytime function[29,31]. It could de hypothesized that the improvement in sleep duration with *Valerian officinalis* resulted in decreased awareness of the occurrence/severity of nocturnal hot flushes or increased threshold for awakenings caused by vasomotor symptoms. In addition, a longer restful night could have had a positive effect on daytime function and well-being and possibly influenced participants' ability to tolerate diurnal vasomotor symptoms, as noted by improvement in vasomotor sub-scores of the MENQOL questionnaire.

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The proportion of poor sleepers found at the beginning of our study (59.3%) was similar to that reported by others[32,33], confirming the high prevalence of poor sleeper among woman with climacteric symptoms. Present results demonstrated a decline of ISI, ESS and PSQI scores in the frame of both medicinal plant treatment groups. However, oral administration of *Valerian officinalis* and *Passiflora incarnata* significantly but differentially improved the subjective perception of sleep quality by PSQI. Thus, *Valerian officinalis* administration induced greater effect on sleep latency, and duration than did either *Passiflora incarnata* or the SHI protocol. A previous study demonstrated that sleep disorders could impact the daytime functioning and quality of life[33], which was confirmed by improved daytime dysfunction after treatment with *Valerian officinalis*. In the VO group, the mean ISI scores at 3 month were reduced by approximately 6-7 points as compared to its preintervention value. In the PI group, the reduction was approximately 4 points; however, this decrease was slightly smaller than the recommended reduction of 6 points for representing a clinically meaningful improvement in individuals with primary insomnia[21]. *Valerian officinalis* was more effective than *Passiflora incarnata* and the SHI in alleviating mild and moderate insomnia. The increase in "non-clinical significant insomnia" was mostly due to a reduction in the percentages of participants in the "severe insomnia" and "moderate insomnia" categories relative to baseline. In addition, more than double *Valerian officinalis*-treated women reported better sleep habits compared with those of the SHI group. Although in SHI has been found to exert positive impact on menopausal women life quality[34], present data suggest that SHI *per se* was not sufficient to induce significant changes in this postmenopausal population, and could be partially explained due to difficulties in producing and maintaining significant lifestyle changes, especially in adult or elder people. On the other hand, other studies assessing the impact of valerian on life quality of postmenopausal women reported a lack of change in response after 1-year treatment[35], suggesting that plants treatment without SHI were also not sufficient. Hence, it seems that the combination of SHI together with medicinal plants treatment could have a synergic effect allowing improvements in life quality[36] and climacteric symptoms[37]. As discussed, participants of our study were required in addition the the plant treatment to follow SHI daily during the 3-month treatment, which may have contributed to the improvements in sleep quality observed in both treatment groups.

In addition, study results clearly suggest that not all the medicinal plants labelled as "menopausal treatments" affected the different symptoms equally. Thus, the importance of the

ISSN-e: 2529-850X
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pharmacist assessment identifying the particular symptoms and choosing the most adequate plant for each person was capital in both interventions.

When comparing satisfaction of participants with insomnia and climacteric symptoms, a high satisfaction rate for the capsules of VO, followed by the capsules of PI was observed. The women of SHI group showed less satisfaction. These results are well in line with those of several studies and may be attributed to the efficacy and favorable risk-benefit profile[38]. Perceived convenience is also an important component of treatment satisfaction[23]. Medicinal plants play a central role not only as traditional medicines but also as trade commodities, meeting the demand of menopausal woman with insomnia.

In line with other consumer satisfaction surveys[19], this pharmacy based intervention was well received by menopausal women. Nevertheless, the present study has several limitations: 1) The intervention was applied by a limited number of pharmacies; 2) Multiple follow-up points and longer treatment would strengthen our results; 3) Absence of compliance monitoring; 4) Although we instructed the participants to avoid drinking caffeine and alcohol, there was no way to ascertain their compliance.

Conclusions

Valerian officinalis appear as the preferable treatment for the climateric symptoms and sleep difficulties associated with menopause. Both *Valerian officinalis* and *Passiflora incarnata* togheter with SHI ameliorated several sleep associated symptoms, while sleep hygiene instructions perse was unable to change women lifestyles enough to alleviate significantly those symptoms. This study provided evidence that community pharmacists can play a crucial role when addressing menopausal women with insomnia symptoms to the most fitting complementary treatment with a combination of medicinal plants and sleep hygiene instructions.

Acknowledgements

We thank the pharmacists that intervened in the study for their support and willingness in recruiting patients for this intervention. We also thank all volunteers for their time and participation in the study.

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Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Study concept and design: Juana Benedi; supervision and writing of manuscript: Miguel Vazquez and Juana Benedi; data acquisition, analysis and interpretation: Elena Marcos and Irene Iglesias; statistical analysis: Elena Marcos. We confirm that all listed authors meet the authorship criteria, and all authors agree with the content of the manuscript.

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